MEDPASS INTERNATIONAL	**STATISTICAL ANALYSIS PLAN**	REDUCE_FMR - SAP_V2 2018_08_06_CT **Sponsor :** CARDIAC DIMENSIONS **Device :** CARILLON **Protocol Nr:** CVP-1627-01 **MedPass Project Nr:** 319-01-14

The REDUCE FMR Trial:

Safety and Efficacy of the CARILLON Mitral Contour System® in Reducing Functional Mitral Regurgitation (FMR) Associated with Heart Failure

Statistical Analysis Plan

NCT: 02325830

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SIGNATURE PAGE

THE REDUCE FMR TRIAL:

SAFETY AND EFFICACY OF THE CARILLON MITRAL CONTOUR SYSTEM® IN REDUCING FUNCTIONAL MITRAL REGURGITATION (FMR) ASSOCIATED WITH HEART FAILURE

Version 0.1

CARDIAC DIMENSIONS PTY LTD

Name	Position	Date	Signature

MEDPASS INTERNATIONAL

Name	Position	Date	Signature

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AT	As Treated
CAD	Coronary Artery Disease
CBC	Complete Blood Count
CI	Confidence Interval
GCV	Great Cardiac Vein
CMCS	CARILLON Mitral Contour System®
CO	Cardiac Output
CRT	Cardiac Resynchronization Therapy
CS	Coronary Sinus
CXR (PA)	Chest X-Ray (Posteroanterior)
ECG	Electrocardiography
EROA	Effective Regurgitant Orifice Area
FMR	Functional Mitral Regurgitation
HF	Heart Failure
ITT	Intent-to-Treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LAA	Left Atrial Area
LOCF	Last observation carried forward
LVEF	Left Ventricular Ejection Fraction
LVEDD	Left Ventricular End Diastolic Diameter
LVESD	Left Ventricular End Systolic Diameter
MRJA	Mitral Regurgitation Jet Area
NT-BNP	N-Terminal prohormone of Brain Natriuretic Peptide
NYHA	New York Heart Association
PP	Per protocol
QoL	Quality of Life
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan

SF-12	Survey Form (12 questions)
TEE	Transesophagial Echocardiogram
TTE	Transthoracic Echocardiography
VC	Vena Contracta

1. OVERVIEW

This statistical analysis plan (SAP) describes the planned statistical analyses of the data collected in the course of the REDUCE FMR Trial: Safety and Efficacy of the CARILLON Mitral Contour System® in Reducing Functional Mitral Regurgitation (FMR) Associated with Heart Failure (HF).

This SAP provides additional details concerning the statistical analyses outlined in the protocol (Revision AA dated 27 October 2014). The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data.

1.1. Study Objective

The objective of this prospective, multi-center, randomized, double-blind trial is to assess the safety and efficacy of the CARILLON Mitral Contour System® (CMCS) in treating functional mitral regurgitation associated with Heart Failure (HF), compared to a randomized Control group which is medically managed according to HF guidelines.

1.2. Study Design

The REDUCE FMR Trial is a prospective, multi-center, randomized, double-blind clinical trial.

Subjects will be randomized between the Treatment Group and a Control Group. Subjects will be randomized in a 3:1 ratio (Treatment : Control). The Treatment group will be implanted with the CARILLON device. The Control group will be medically managed according to current HF guidelines.

As this is a double-blinded study, both the patients (Treatment and Control groups) and the assessors of the primary endpoint will be blinded for twelve months.

Subjects randomized to the Control or Treatment group will have safety and efficacy assessments performed at baseline, one (1), six (6), and twelve (12) months after randomization.

Subjects randomized to the Control group may be offered the CARILLON device once they have completed the protocol defined follow-up period (Cross-Over Registry).

1.3. Study Plan

1.3.1. Study population

Consent up to 180 subjects suffering from HF and presenting with FMR from up to 20 centers in Australia and Europe in order to randomize up to 120 subjects.

1.3.2. Study Device

The CARILLON Mitral Contour System® (XE2) is a Class III medical device and is manufactured by Cardiac Dimensions, Inc., in Kirkland, Washington, USA. The device received CE-Mark on 3rd August 2011. In Australia, the CARILLON device is intended “For Clinical Trial Use Only”.

The CMCS (XE2) consists of the following components:

- An implant intended for permanent placement in the coronary sinus (CS)/great cardiac vein (GCV);
- A delivery system which consists of a custom 9F delivery catheter and a handle assembly.

The implant is attached to the handle assembly and is delivered through the delivery catheter to the coronary vein along the posterolateral aspect of the mitral annulus.

The CMCS is indicated for use in patients with secondary (functional) mitral regurgitation.

The CMCS is contraindicated for use in:

- Patients with existing devices in the CS/GCV;

- Patients who have had a mitral valve replacement or a mitral annuloplasty ring implant.

1.3.3. Randomization

Randomization will occur in a 3:1 allocation to the Treatment (CARILLON) or Control group. Randomization has been stratified according to investigational center in a randomized permuted blocks design.

After all pre-randomization assessments are completed, each subject will be assigned sequentially to one of the two study groups (Treatment or Control), by means of a computer-generated random number scheme created by the Sponsor. The study coordinator and limited study personnel (e.g., implanting physician) will have also knowledge of the treatment assignment.

For subjects randomized to the Treatment group, the CMCS procedure will be performed.

1.3.4. Blinding

Subjects randomized to the Control group will experience an index procedure similar to the Treatment group, however, without device placement. To ensure that subjects randomized to the Control group will not be able to deduce the treatment assignment based on the type of intervention or time associated with the procedure, minimal interventional procedures, such as femoral arterial pressure monitoring and a jugular venous drip. If a recent (within the last 3 months for ischemic cardiomyopathy or 12 months for non-ischemic cardiomyopathy) coronary angiogram is available, this assessment may be precluded.

This will be a double-blind study in order to reduce the effect of bias and potential placebo effect on specific primary and/or secondary endpoint assessments. All study subjects and any study personnel responsible for primary efficacy and/or select secondary endpoint assessments will be blinded as to whether subjects are in the Treatment group or the Control group. Blinding will be maintained through the 12 month follow-up. All study personnel will be trained to follow study blinding procedures to ensure maintenance of the study blind. Subjects will be continually reminded that adhering to the blinding procedures is a critical part of their involvement in the study.

The assessors of the NYHA Class, six-minute walk test, echo corelab assessors, and Quality of Life Questionnaires (Kansas City Cardiomyopathy Questionnaire and SF-12) will not be aware of the treatment assignment.

1.3.5. Unblinding

The treatment assignment for a subject will be unblinded only in the following circumstances:

1) In the event of medical emergency where it is medically necessary to know if the subject received an implant

2) After all randomized study subjects have completed their 12-month visits, the treatment assignment will be unblinded for statistical analysis in readiness for submission to regulatory authorities

The DSMB and/or CEC, upon request, may be provided with the randomization assignment of a particular subject(s) or to assess safety trends between study groups. This can be provided by the study statistician and does not require unblinding of critical site and study personnel.

1.3.6. Patient's Follow-up

Subjects will be followed for 12 months from the time of randomization to meet primary and secondary endpoints in accordance with the follow-up periods.

6 visits are scheduled:

- Visit 1: Screening/Baseline*;
  *If 2 Sreening/Baseline visits are performed for a patient the latest Sreening/Baseline data will be considered for analyses.
- Visit 2: Index Procedure;
- Visit 3: Discharge;
- Visit 4: 1 Month Follow-up;
- Visit 5: 6 Months Follow-up;
- Visit 6: 12 Months Follow-up.

1.3.7. Study Assessments

The following flowchart applies to the study:

Study Task	Screening / Baseline		Index Procedure	Discharge	1 Month (±7 days)	6 Months (±14 days)	12 Months (±30 days)
Informed Consent	X	Randomization					
Inclusion/Exclusion Criteria	X						
Past Medical History & Physical Exam	X						
Serum Pregnancy Test	X						
TEE[1]	X						
Coronary Angiography	X[2]		X[2]				
Intraprocedure Echo (TTE or TEE)			X				
CHF Focused History & Physical Exam				X	X	X	X
Vital Signs	X		X	X	X	X	X
Coagulation Tests	X						
Cardiac Enzymes	X			X	X	X	X
Chemistries	X			X	X	X	X
CBC	X			X	X	X	X
12-Lead ECG	X			X	X	X	X
Complete TTE	X				X	X	X

Study Task	Screening / Baseline		Index Procedure	Discharge	1 Month (±7 days)	6 Months (±14 days)	12 Months (±30 days)
Exercise TTE[3]	X				X	X	X
Abbreviated TTE[4] (safety)				X			
CXR (PA & Lateral) or cine fluoroscopy				X	X	X	X
Six Minute Walk Test	X[5]				X	X	X
NYHA Classification	X				X	X	X
KCCQ	X				X	X	X
SF-12 QoL	X				X	X	X
Concomitant Medications	X		X	X	X	X	X
Adverse Events	X		X	X	X	X	X

1. To rule out LAA clot - only required for subjects with a prior history of atrial fibrillation
2. The eligibility angiography may occur immediately prior to randomization, unless a recent angiogram indicating no CAD requiring intervention is available. All Treatment group subjects undergo coronary angiography as part of the CMCS procedure.
3. Exercise TTE will be done only at pre-identified qualified sites with supine bicycle ergometry.
4. Abbreviated TTE safety assessment to rule out pericardial effusion.
5. Six-minute walk test will be undertaken for screening and baseline.

2. STATISTICAL METHODS

2.1. General Statistical Considerations

2.1.1. Handling Missing Data

If any subject does not have endpoint data available (12-month data), the primary analysis will assume that data as missing and that subject's data will not be included in the primary analysis.

Missing data will be imputed for all missing primary, secondary and observational endpoint parameters using a last observation carried forward (LOCF) methodology and will be presented as a sensitivity analysis to assess the robustness of results.

2.1.2. Descriptive Statistics in Summary Tables

- *Continuous variables* will be summarized using standard quantitative statistics: number of non-missing observations, mean, standard deviation, median, quartiles and range (minimum and maximum observed values). The number of missing observations will also be specified.
- *Categorical variables* will be summarized using classical frequency statistics: number of non-missing observations and percentages by categories. Percentages will be calculated on the number of non-missing observations, and will be displayed using one decimal. The number of missing observations will also be specified.

2.1.3. Inferential Analysis

Data will be compared between the two groups using bilateral tests at the type I error 5% level.

- *Continuous variables*: the appropriate test will be chosen depending on the data distribution.

  The normality of quantitative data will be tested using the Shapiro-Wilk test.

  - if the normality test pvalue is > 0.05, the data will be considered as normally distributed and the Student test will be used.
  - else, the data will be considered as not normally distributed and the Wilcoxon Rank Sum test will be used.

- *Categorical variables*: the appropriate test will be chosen depending on the expected cell frequencies:

  - If all expected cell frequencies are ≥ 5 then the Chi² test will be used.
  - Otherwise, the Fisher's exact test will be used.

The 95% confidence interval in regurgitant volume mean difference from baseline to 12 months will be presented by treatment group. If assumptions of normality are violated, the 95% confidence interval will be calculated using the Hodges-Lehmann estimate and distribution-free confidence interval based on a Wilcoxon Rank Sum test.

Further supportive analyses will be conducted which characterize the longitudinal effect of treatment on regurgitant volume in a repeated measures regression model, using a mixed effects model approach. Fixed effects will be treatment group and time effect. Site effect will be a random effect. Interaction between treatment group and site will also be studied.

2.1.4. Interim Analysis

Not applicable

2.1.5. Data Listings

Patients' data listings will be selected data supportive of summary statistical tables, including derived/calculated data from statistical process. These key data listings will be performed on selected analysis sets according to the focus of the listings and will be sorted as appropriate.

2.2. Sample size calculation

The primary endpoint of the study is to demonstrate a significantly greater improvement from baseline in Regurgitant Volume (assessed by echo CoreLab) associated with the CMCS at 12 months, relative to the Control group.

Parameter of Interest

The parameter of interest for each treatment group is the mean change from baseline in regurgitant volume, in milliliters, at 12 months.

Hypotheses

H0: $\mu_{CARILLON} = \mu_{CTL}$;

Ha: $\mu_{CARILLON} \neq \mu_{CTL}$;

where $\mu_{CARILLON}$ is the mean change in regurgitant volume for those randomized to the Treatment group, and μ_{CTL} is the mean change in regurgitant volume for those randomized to the Control group.

Sample Size Estimation

Sample size is calculated using a comparison of means (Student's t test). The minimum required sample size was calculated under the following assumptions:

- Significance level two-sided 0.05;
- Statistical power to detect design alternative hypothesis is 80%;
- Hypothesized mean regurgitant volume change (baseline to 12-month): Control group = -2.4ml; Treatment group = -12.4ml;
- Hypothesized standard deviation: Control group = 13ml; Treatment group = 13ml;
- 3:1 randomization allocation.

Under the assumptions outlined above, the estimated minimum required sample size is 76 subjects (57 Treatment, 19 Control).

A total of 120 subjects at up to 20 centers will be randomized, allowing for approximately 30% attrition (mortality, missing data and loss to follow-up) in the first 12 months of follow-up.

2.3. Analysis Sets

2.3.1. Databases

Core laboratory Excel databases will be used to analyze hemodynamic and echocardiographic assessments.

The CEC will be responsible for adjudicating complications reported during the study that are related to study endpoints (objectives), the procedure or the device. The CEC AE review Excel database will be used to analyze safety endpoints (MAE and HF-hospitalizations).

All other analysis will be done on the e-CRF clinical database.

2.3.2. Definition of patient populations

5 populations will be defined:

- The enrolled population will include all patients who consented to participate to the study.
- The screen failure population will include all enrolled patients who did not meet all eligibility criteria or randomized to treatment group but procedure discontinued before an implant attempt.

  Only a listing of these patients will be presented.
- The Intent-to-Treat (ITT) population will include all patients who fulfill all eligibility criteria and either underwent the procedure and on whom a device implant was attempted, or are considered as control patients.

  This population will therefore include all randomized patients except the patients for whom the procedure was discontinued before an implant attempt (see Fig 1 below).

  This population will be analyzed regardless of the treatment actually received: if there is an error in treatment (i.e. subject was not treated as randomized), the analysis will be performed according to the randomized group assignment, not the treatment actually received.
- The As -Treated (AT) population will include all ITT patients who left clinic with the randomized therapy administered (i.e., randomized to Treatment group and received a permanent implant, or randomized to Control group)

  This population will therefore include all randomized patients except the patients who underwent the procedure but were not implanted (see Fig 1 below).

  This population will be analyzed according to the treatment actually received: if there is an error in treatment (i.e. subject was not treated as randomized), the analysis will be performed according to the treatment actually received, not the randomized group assignment.
- The Per Protocol (PP) population will include all AT patients who received randomized therapy, assessors remained blinded, and who did not receive alternative or confounding therapies (e.g., CRT therapy, transplant, stenting, etc.) through the primary endpoint timeframe of the study, who did not met any major deviation (see 2.3.3).

Assignment of patients to populations will be reviewed and approved by the sponsor before the database lock.

2.3.3. Protocol Deviations

On a case-by-case basis, all protocol deviations will be reviewed and will be classified as “minor” or “major” according to the possible impact expected on primary results.

Patients meeting at least one of the following major deviations may be excluded from the PP population:

- At least one eligibility criterion not fulfilled;
- Treatment different from the randomized group assignment;
- Unblinded assessor(s);
- Unblinded subject(s);
- Patient who received alternative or confounding therapies (e.g., CRT, transplant, stenting, etc.);
- Study Windows not respected

All protocol deviations other than those defined in this section will be considered as minor and will not lead to patient exclusion from the PP population.

2.3.4. Treatment/device groups

2 treatment groups will be defined:

- Treatment group (CARILLON);
- Control group.

2.4. Statistical Analyses

2.4.1. Patient Disposition and Follow-up

2.4.1.1. Patient Populations, follow-ups and withdrawals

The number of patients present at each visit, as well as the reasons for study exit will be presented by population and treatment group as appropriate.

The corresponding average time of patients’ follow-up will also be presented by population and treatment group as appropriate.

The repartition by site will also be presented.

2.4.1.2. Protocol Deviations

The focus of protocol deviations description will be on major deviations as defined in section 2.3.3.

The total number of major deviations and the number of patients with at least one major protocol deviation and the corresponding percentages will be summarized on the ITT population and by deviation category.

Major as well as minor protocol deviations will be detailed in a patients’ data listing.

2.4.2. Baseline Patients’ Characteristics

The following parameters will be presented by treatment group on the ITT population as appropriate to draw up a recapitulation of the patients’ characteristics at the time of enrolment.

If 2 Sreening/Baseline visits are performed for a patient the latest Sreening/Baseline data will be considered for analyses.

- Age, gender and pregnancy test (Done, Result);

- Medical history(General:History of COPD and History of diabetes, Cardiovascular: History of hypertension, History of hyperlipidemia requiring medication, History of angina pectoris, History of myocardial infraction, History of heart failure, History of arrhythmias, History of ICD implant, History of permanent pacemaker implant, History of coronary artery disease, History of cardiovascular surgical intervention, if subject not treated with the CARILLON implant, which other heart failure therapy is the patient eligible for ?, History of cerebral vascular disease).
- Physical exam (Cardiovascular, Peripheral vascular, Pulmonary, Neurological, Allergies and Other), Vital signs (Height (cm), Weight (kg), BMI (kg/m^2), Resp (rr), SpO_2 (%), Temperature (°C), Systolic and Diastolic blood pressures (mmHg)),
- NYHA class
- ECG (12- Lead) (Done)
- Six minute walk test (Total distance walked (meters),
- Transthoracic Echo (TTE) (Heart rate (bpm), Systolic and Diastolic blood pressures (mmHg), MR Grade, LVEF (%), LVEDD (mm) or LVEDD/BSA (cm/ m^2))
- Exercise TTE results (Resting: Heart rate (bpm), Systolic and Diastolic blood pressures (mmHg), Symptoms and Intensity, Test conclusion: Work load (Watts), Heart rate (bpm), Systolic and Diastolic blood pressures (mmHg), Symptoms and Intensity)
- Transesophageal Echo (TEE) (Done);
- Hematology tests (Hemoglobin, Hematocrit, WBC, Platelets and other CBC results abnormal if any)
- Chemistries (Sodium, Potassium, Chloride, BUN, Creatinine or eGFR, Glucose, NT-BNP and other chemistry results abnormal if any)
- Pre-Procedure Chemistries (Creatinine or eGFR, Cardiac Troponin cT and other chemistry results if any)
- Pre-procedure Coagulation tests (Prothrombin Time (PT) and Partial Thromboplastin Time (PTT))
- Quality of life (KCCQ, SF-12).

Those baseline parameters will be compared in order to identify any imbalance following randomization using the Student (or Wilcoxon) test or Chi² (or Fisher) test as appropriate.

2.4.1. Procedure Characteristics

2.4.1.1. Pre-procedure

The following parameters will be presented by treatment group on the ITT population as appropriate to draw up a recapitulation of the pre-procedure characteristics.

- Type of sedation;
- Access site;
- Coronary Angiography: (Prior to implant RCA and LCX TIMI flows);
- Pre-implant pressures (LVEDP (mmHg), PAP (mmHg), Mean PAP (mmHg), PCWP (mmHg) and Mean PCWP (mmHg)),

The above parameters will be compared in order to identify any imbalance following randomization using the Student (or Wilcoxon) test or Chi² (or Fisher) test as appropriate

The following parameters will be descriptively presented based on attempts number instead of patients number:

- CS/GCV length (CS Ostium to GCV/AIV Junction)
- Presence of Coronary stent in implant zone;
- Average Great Cardiac Vein (GCV) diameter (mm)
- Average Coronary Sinus (CS) diameter (mm).

2.4.1.2. Device implant

The following parameters will be presented by population as appropriate to draw up a recapitulation of the CARILLON device implant characteristics:

- Number of attempts;

The following parameters will be presented based on CARILLON implant attempts number instead of patients number:

- CARILLON Implant size selection (Distal anchor size (mm), Proximal anchor size (mm), implant length (mm);
- Actual distal anchor location from CS ostium (cm), Actual proximal anchor location from CS Ostium (cm) and Proximal anchor displacement (prior decoupling);
- Post-implant pressures (LVEDP (mmHg), PAP (mmHg), Mean PAP (mmHg), PCWP (mmHg) and Mean PCWP (mmHg));
- Coronary Angiography (After proximal anchor locked Post-implant RCA and LCX TIMI flows (mm));
- Device successfully decoupled;

2.4.1.3. Procedure conclusion

The following parameters will be presented by treatment group on the ITT population as appropriate to draw up a recapitulation of the post-procedure characteristics.

They will be compared using the Student (or Wilcoxon) test or Chi² (or Fisher) test as appropriate.

- Procedure duration;
- Post implant Cine imaging protocol executed
- Equipment used to collect cine imaging
- Presence of change to coronary artery flow;
- Implant relationship to coronary artery;
- Number of arteries crossed;
- Total time of fluoroscopy (minutes), total heparin used (units), total contrast used (mL);

2.4.2. Primary Endpoint

The primary analysis will be performed on the Intent to treat (ITT) population.

The primary efficacy endpoint is to compare the change in regurgitant volume from baseline at 12 months between the treatment and control groups using a two-sided, two-sample t-test (or Wilcoxon Rank sum test as appropriate). The corresponding 95% confidence interval on the between-group difference will also be calculated and presented.

A sensitivity analysis of the primary efficacy endpoint analysis on the ITT population will be performed, using the last observation carried forward (LOCF) missing data imputation on the regurgitant volume at 12 months. The same comparison analysis as mentioned above for the primary efficacy endpoint will be performed.

Two other additional analyses will be performed on the primary efficacy endpoint on:

- As-treated population
- Per-protocol population

The same comparison analysis as for the primary efficacy endpoint mentioned above will be used

2.4.3. Secondary Endpoints

The secondary analysis will be performed on the ITT population. Secondary endpoints analyses will also be also performed on As-treated and Per-protocol populations as additional subgroup analyses.

The secondary endpoints are to determine the procedural safety of the device and the effect of the CMCS on hemodynamics, subject function and long-term safety.

2.4.3.1. Safety

The following secondary safety endpoints will measure the effect of the CMCS on safety parameters of interest, relative to the Control group.

- The rate of major adverse events, through 1 month (+7 days) and 12 months (+30 days) of follow-up.

  Major Adverse Events are defined as one of the following:

  - Death;
  - Myocardial Infarction;
  - Device Embolization;
  - Vessel Erosion, requiring percutaneous or surgical intervention;
  - Cardiac Perforation, requiring percutaneous or surgical intervention;
  - Occurrence of cardiac surgery or percutaneous coronary intervention associated with device failure.

- The HF-hospitalizations from the time of the index procedure through 12 months (+30 days) of follow-up:

  - Rate of HF-hospitalizations;
  - Number of admissions;
  - Total associated days in the hospital.

2.4.3.2. Efficacy

The following secondary efficacy endpoints will assess the effect of the CMCS on clinical parameters of interest, relative to the Control group:

- Change from baseline to 12 months in six-minute walk distance
- Change from baseline to 12 months in left ventricular volumes (end diastolic and end systolic)

2.4.4. Safety

The following secondary safety endpoints will be performed on the ITT population and compared between the treatment and control groups:

- Incidence of adverse events (AE) and the corresponding number and percentage of patient
- Incidence of serious adverse events (SAE) and the corresponding number and percentage of patient
- Incidence of device related adverse events (ADE) and the corresponding number and percentage of patient (based on CEC adjudication)
- Incidence of procedure related adverse events and the corresponding number and percentage of patient (based on CEC adjudication)
- Incidence of device related serious adverse events (SADE) and the corresponding number and percentage of patient (based on CEC adjudication)
- Incidence of unanticipated serious adverse device effects (USADE) and the corresponding number and percentage of patient (based on CEC adjudication)
- Incidence of anticipated device effects (AADE) and the corresponding number and percentage of patient (based on CEC adjudication)

- Event Severity
- Incidence of device deficiencies and the corresponding number and percentage of patient

2.4.5. Observational Data

The following analysis will be performed on the ITT population.

- Long-term safety (through 6 months (+14 days) and 12 months (+30 days) of follow-up):
  - Mortality;
  - Serious adverse events (SAE).
- NYHA classification at each visit
- Left ventricular hemodynamics:
  - Left ventricular end diastolic (LVEDD) and systolic (LVESD) dimensions;
  - Ejection fraction (LVEF);
  - Forward cardiac output (CO).
- Functional Mitral Regurgitation (FMR) echocardiographic assessments
  - Vena Contracta (VC)
  - Effective regurgitant orifice area (EROA)
  - Mitral regurgitation jet area / Left atrial area (MRJA/LAA)
  - Mitral regurgitation grade
- Left atrial size
- Mitral annular diameter and area
- Diuretic dose change from baseline to 6 months of follow-up and to 12 months of follow-up
- Pulmonary artery systolic pressure (echo derived at rest & during exercise)
- NT-BNP
- Kansas City Cardiomyopathy Questionnaire (KCCQ)
- Quality-of-Life Assessment (SF-12)

2.4.6. Supportive Analyses

In addition, a series of supportive, sensitivity analyses will be performed to assess the robustness of the primary analysis results:

- Primary endpoint analysis on ITT population according to etiology of cardiomyopathy (ischemic vs. non-ischemic) through the primary endpoint.
- Primary and secondary efficacy endpoints analysis using LOCF methodology.
- Primary and secondary efficacy endpoints analysis by MR Grade or MR Grade grouping
- Primary and secondary efficacy endpoints analysis using associated baseline characteristics
- Primary endpoint analysis using qualitative measure imputation of core lab derived values where quantification is technically challenging
- Calculation of treatment effect using mitral regurgitation volume and MR grade as parameters in responders and non-responders
- Assessment of treatment effects according to other important clinical subgroups such as:
  i. Atrial fibrillation vs normal sinus rhythm
  ii. Baseline MR grade

iii. Baseline LVEDD above or below 65mm
iv. Baseline EF (≤ 40% vs 41-50%)
v. Baseline left atrial dimension
vi. Baseline mitral annular diameter
vii. Gender

3. STATISTICAL SOFTWARE

All statistical outputs (summary tables and data listings) will be generated using SAS® version 9.4.

4. LAYOUT OF THE STATISTICAL TABLES

4.1. Quantitative variables

4.1.1. Type 3: by group

Variable	Group name	N	Missing	Mean	S.D.	Median	Min,Max	Q1-Q3	P-value
Variable name	Group 1	XX	XX	XX,X	XX,X	XX,X	XX,X , XX,X	XX,X - XX,X	0.XXX
	Group 2	XX	XX	XX,X	XX,X	XX,X	XX,X , XX,X	XX,X - XX,X	(Test)
	Total (*)	XX	XX	XX,X	XX,X	XX,X	XX,X , XX,X	XX,X - XX,X	

4.2. Qualitative variables

4.2.1. Type 2: by group

		Group name			
		Group 1 (N=XX)	Group 2 (N=XX)	Total (*) (N=XX)	P-value
Variable name	N	XX	XX	XX	
	1st Modality	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX
	2nd Modality	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	(Test)
	Missing	XX	XX	XX	

* if needed

4.2.2. Type 1: conditional variables

Var 1 / Var 2	Total (N=XX)	Group 1 (N=XX)	Group 2 (N=XX)	P-value
Var 1 mod 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)
Var 2 mod 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)
…	…	…	…	…
Var 2 mod n	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)
…	…	…	…	…

Var 1 / Var 2	Total (N=XX)	Group 1 (N=XX)	Group 2 (N=XX)	P-value
Var 1 mod n	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)
Var 2 mod 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)
…	…	…	…	…
Var 2 mod n	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)

4.2.3. Type 4: several variables by group and visit

			Group name			
			Group 1 (N=XX)	Group 2 (N=XX)	Total (*) (N=XX)	P-value
Visit 1	Var 1	N	XX	XX	0	
		1st Modality	XX (XX.X%)	XX (XX.X%)	0 (0.0%)	0.XXX
		2nd Modality	XX (XX.X%)	XX (XX.X%)	0 (0.0%)	(Test)
		Missing	XX	XX	0	
	…	…	…	…	…	…
	Var n	N	XX	XX	0	
		1st Modality	XX (XX.X%)	XX (XX.X%)	0 (0.0%)	0.XXX
		2nd Modality	XX (XX.X%)	XX (XX.X%)	0 (0.0%)	(Test)
		Missing	XX	XX	0	
…	…	…	…	…	…	…
Visit n	Var 1	N	XX	XX	0	
		1st Modality	XX (XX.X%)	XX (XX.X%)	0 (0.0%)	0.XXX
		2nd Modality	XX (XX.X%)	XX (XX.X%)	0 (0.0%)	(Test)
		Missing	XX	XX	0	
	…	…	…	…	…	…
	Var n	N	XX	XX	0	
		1st Modality	XX (XX.X%)	XX (XX.X%)	0 (0.0%)	0.XXX
		2nd Modality	XX (XX.X%)	XX (XX.X%)	0 (0.0%)	(Test)
		Missing	XX	XX	0	

* if needed

4.2.4. Type 5: conditional variables, by visit

Var 1 / Var 2	Var 1 / Var 2	Total (N=XX)	Group 1 (N=XX)	Group 2 (N=XX)	P-value
Visit 1	Var 1 mod 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)
	Var 2 mod 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)
	…	…	…	…	…
	Var 2 mod n	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)
	…	…	…	…	…
	Var 1 mod n	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)

Var 1 / Var 2	Var 1 / Var 2	Total (N=XX)	Group 1 (N=XX)	Group 2 (N=XX)	P-value
	Var 2 mod 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)
	…	…	…	…	…
	Var 2 mod n	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)
…	…	…	…	…	…
Visit n	Var 1 mod 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)
	Var 2 mod 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)
	…	…	…	…	…
	Var 2 mod n	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)
	…	…	…	…	…
	Var 1 mod n	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)
	Var 2 mod 1	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)
	…	…	…	…	…
	Var 2 mod n	XX (XX.X%)	XX (XX.X%)	XX (XX.X%)	0.XXX (Test)

* if needed

4.3. Other types

4.3.1. Type 6: AE/medications

	Population (N=XX)			Group 1 (*) (N=XX)			Group 2 (*) (N=XX)		
AE/Med/Deviation	YYY (1)	n (2)	% (3)	YYY (1)	n (2)	% (3)	YYY (1)	n (2)	% (3)
At least one (*)	XX	XX	XX.X	XX	XX	XX	XX.X	XX	XX
AE/Med/Dev description 1	XX	XX	XX.X	XX	XX	XX	XX.X	XX	XX
AE/Med/Dev description 2	XX	XX	XX.X	XX	XX	XX	XX.X	XX	XX
AE/Med/Dev description 3	XX	XX	XX.X	XX	XX	XX	XX.X	XX	XX

YYY=NAE/Nmed

(1): Number of adverse events/medication of a given type

(2): Number of patients with at least one adverse event/medication of a given type

(3): (n / N)*100 (N : total number of patients)

* if needed