Transcatheter Repair of Mitral Insufficiency with Cardioband System

REPAIR Post Market Study

Date: 31 January 2017

NCT: 02703311

Valtech

Cardioband

REPAIR

TranscatheteR REPair of MitrAl Insufficiency with CaRdioband System

Post Market Study

Protocol ID CB1-3

Rev. 01 - Date: 31 January 2017

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Confidentiality Statement

[redacted]

STATEMENT OF COMPLIANCE

The REPAIR Study will be conducted in accordance with the Declaration of Helsinki and ISO 14155:2011 (Clinical investigation of medical devices for human subjects - Good Clinical Practices). In addition, the study will comply with any applicable European or regional regulations.

The clinical investigation shall not begin until the required approval/favourable opinion from the EC or regulatory authority have been obtained, as appropriate.

SIGNATURES

Principal Investigator

I have read and understand the contents of the REPAIR PMS protocol. I agree to follow and abide by the recommendations set forth in this document.

Name	Title	Signature	Date
_____	_____	_____	_____

Sponsor Approval Signature

Name	Title	Signature	Date
_____	_____	_____	_____

PROTOCOL SYNOPSIS

Background	The Cardioband Transcatheter System (Cardioband) is indicated for the treatment of secondary (functional) mitral regurgitation (FMR). The Cardioband is a transcatheter system, deployed on the beating heart through a transseptal approach. The Cardioband is deployed along the posterior annulus of the mitral valve and is adjusted under trans-esophageal guidance on the beating heart. [redacted]
Hypothesis	1) The Cardioband will reduce the severity of MR acutely with durable performance at 6 months 2) The Cardioband will improve 6 minute walk test at 6 months 3) The Cardioband will improve heart failure associated quality of life at 6 months
Objectives	1) To test the efficacy of the Cardioband in improving MR and heart failure symptoms in patients with symptomatic (NYHA Class III-IVa), severe MR in the post-marketing setting 2) To evaluate the safety of the Cardioband system in the post-marketing setting
Study design	A multi-center (up to 20 sites) single arm open label study in n = 50 subjects. Subjects will be followed for up to 2 years.
Subject Population	Patients with secondary (functional) MR, symptomatic (NYHA Class III-IVa heart failure symptoms), with severe MR and to whom The Local Site Heart Team concur that surgery will not be offered as a treatment option and that medical therapy is the intended therapy.
Endpoints	Primary Endpoint (powered): Reduction in severity of MR at 30 days of at least one category on a 0-4 scale. Key Secondary Endpoint (powered): Change in 6 minute walk test at 6 months. Secondary Endpoints (all at 6, 12, and 24 months except as indicated) : 1) MR severity 2) 6 minute walk distance 3) Quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) (also at 30 days) 4) NYHA Class (also at 30 days) 5) Left Ventricular End Diastolic Volume (LVEDV) 6) Left Ventricular End Systolic Volume (LVESV) 7) Device success defined as deployment of the Cardioband, with MR reduction at hospital discharge. 8) Individual patient success (6 months and 1 year) defined as device success and the following:

[redacted]

	• Discharged from index hospitalization • NYHA class improvement by at least 1 level from baseline 9) Days alive and out of hospital (due to major cardiovascular events) at 1 year 10) Freedom from all-cause mortality and major adverse events defined as disabling stroke, myocardial infarction (peri-procedural or spontaneous), renal failure requiring dialysis, life-threatening bleeding, cardiac tamponade and device related cardiac surgical intervention at 30 days from the implant procedure or hospital discharge, whichever is later. (Individual components will also be evaluated). 11) Need for urgent/emergent surgical intervention
Sample Size Considerations	Based on the results of the Cardioband CE mark study (Protocol ID CB 1-2), the present study with a sample size of 50 subjects will have greater than 80% power to detect a reduction in MR severity of at least one grade (CE mark study showed improvement in MR severity of at least one grade in >80% of subjects in CE mark study). Based on the results of the Cardioband CE mark study (Protocol ID CB 1-2), the present study with a sample size of 50 subjects will have greater than 90% power to detect an improvement of 75 m in 6 minute walk test at 6 months (CE Mark study showed an improvement of 93.3 m ± 90.3 m).
Inclusion Criteria	1) Age ≥18 years 2) Severe (3+ to 4+) secondary Mitral Regurgitation 3) Symptomatic heart failure (NYHA Class III-IVa) despite guideline directed medical therapy including CRT if indicated 4) The Local Site Heart Team concur that surgery will not be offered as a treatment option and that medical therapy is the intended therapy. 5) Transfemoral access and transseptal deployment of the Cardioband is determined to be feasible 6) Subject is willing and able to provide informed consent and follow protocol
Exclusion Criteria	1) EF < 20% 2) LVEDD ≥ 70 mm 3) Heavily calcified annulus or leaflets 4) Significant CAD requiring revascularization 5) Active bacterial endocarditis 6) Any percutaneous coronary, carotid, endovascular intervention or carotid surgery within 30 days or any coronary or endovascular surgery within 3 months 7) Renal insufficiency requiring dialysis

	8) Life expectancy of less than twelve months 9) Subject is participating in concomitant research studies of investigational products that have not reached their primary endpoint 10) Pulmonary hypertension ≥ 70mmHg at rest 11) Mitral valve anatomy which may preclude proper device treatment 12) Right-sided congestive heart failure with echocardiographic evidence of severe right ventricular dysfunction and/or severe tricuspid regurgitation 13) Severe liver disease 14) Patient is pregnant or lactating 15) Hypersensitivity to Nickel or Chromium 16) Clinically significant bleeding diathesis or coagulopathy 17) History of mitral valve repair 18) TIA or CVA within 3 months 19) Subjects in whom transesophageal echocardiography is contraindicated 20) Patients who cannot tolerate anticoagulation/antiplatelet regimen 21) Patients with known severe reaction to contrast agents that cannot be adequately premedicated
Study Procedures	Key Pre-Implantation Procedures: 1. History and Physical 2. TTE , TEE and/or CT angiography 3. 6 minute walk test 4. KCCQ [redacted] Key Post-Procedure Procedures: 1. Serial AE assessment, history, and physical at 30 days, 6 months, 12 months, 24 months) 2. Serial TTEs (30 days, 6 months, 12 months, 24 months) 3. 6 minute walk tests (30 days, 6 months, 12 months, 24 months) 4. KCCQ (30 days, 6 months, 12 months, 24 months) [redacted]

ABBREVIATIONS

6MWT	6 minute walk test	ISO	International Standardization Organization
ADE	Adverse Device Effects	KCCQ	Kansas City Cardiomyopathy Questionnaire
AE	Adverse Event	LVEDD	Left Ventricle End-Diastolic Dimension
CABG	Coronary Artery Bypass Graft	LVEF	Left Ventricle Ejection Fraction
CDS	Cardioband Delivery System	MI	Myocardial infarction
CEC	Clinical Events Committee	MR	Mitral Regurgitation
CHF	Congestive Heart Failure	MSAE	Major Serious Adverse Event
COPD	Chronic obstructive pulmonary disease	NYHA	New York Heart Association
CRF	Case Report Form	QOL	Quality of Life
CRT	Cardiac Resynchronization Therapy	RO	Radiopaque
CT	Computerized Tomography	SADE	Serious Adverse Device Effect
CVA	CerebroVascular Accident	SAE	Serious Adverse Event
eCRF	Electronic Case Report forms	SAT	Size Adjustment Tool
EDC	Electronic Data Capture	SD	Standard Deviation
EF	Ejection Fraction	SOC	System Organ Class
FDA	Food and Drug Administration	SOP	Standard operating procedure
GC	Guide Catheter	TEE	Transesophageal Echocardiography
GCP	Good Clinical Practice	TF	Transfemoral
IC	Implant Catheter	TSS	Transseptal Steerable Sheath
ICD	Implantable Cardioverter-Defibrillator	TIA	Transient Ischemic Attack
IDS	Implant Delivery System	TTE	Transthoracic Echocardiography

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1. INTRODUCTION AND RATIONALE

Mitral regurgitation (MR) is a frequent disease associated with increased morbidity and mortality rates (1). Degenerative disease caused by damage to leaflets or other parts of the valve apparatus accounts for approximately one-third of the MR cases (DMR). The majority of patients suffer from functional mitral regurgitation (FMR) driven by adverse left ventricular remodeling due to ischemic or non-ischemic myocardial disease (2-4). Current guidelines are reluctant to advice isolated valve surgery of FMR since the prognostic benefit of surgical valve repair or replacement in typical high-risk heart failure patients is unclear (2, 5). Recent reports suggest that even patients in need for surgical coronary revascularization may not benefit from concomitant mitral valve surgery (6, 7). Therefore, surgical treatment of FMR is restricted to the small group of patients who require concomitant bypass surgery, or who are at considerably low risk for open- heart surgery with high-predicted surgical success rates. On the other hand, optimized medical therapy is ineffective in patients with significant FMR in order to control the progress of heart failure related morbidity and mortality (2, 5, 8-10). Consequently, reliable and predictable treatment for most patients with symptomatic FMR is lacking and there is an unmet need for alternative, catheter-based, minimal invasive interventional approaches. The edge-to-edge mitral valve repair with the MitraClip systems offers an effective and safe treatment option for non-surgical patients with either DMR or FMR (11). This direct approach on the mitral valve leaflets reduces MR severity and is associated with relief of heart failure related symptoms in up to 80% of treated patients (12). However, the MitraClip system has been developed for the treatment of DMR (13), and long-term outcome data on functional mitral valve disease are missing.

More importantly, an idealized interventional approach enables direct treatment of the underlying pathomechanism of FMR without interfering with the otherwise unaffected MV leaflets. To date, Cardioband is the only catheter-based direct mitral annuloplasty system (14). Other catheter-based, indirect approaches include the CE marked CARILLON, by Cardiac Dimensions, and the Mitraclip by Abbott. The Cardioband system uses a transvenous, transseptal route to implant a device on the posterior annulus from the antero-lateral to the posterior-medial MV commissure, which reduces the annular dimensions via controlled cinching of the implant.

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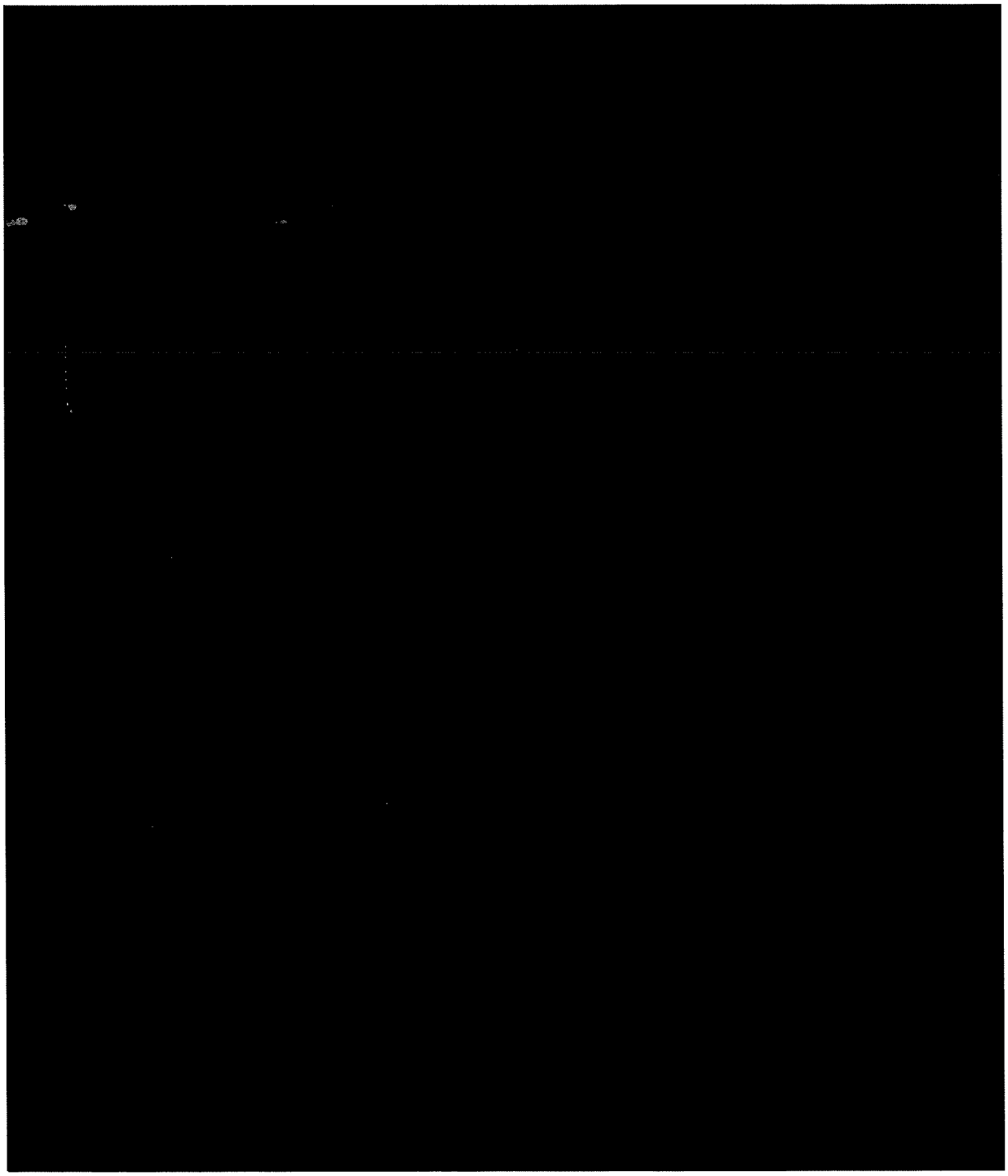
15.

2. DEVICE DESCRIPTION



[redacted]

[redacted]

2.3 Indication/Contraindication

Cardioband Mitral Reconstruction System is indicated for the reconstruction and/or remodelling of pathological mitral valves.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3. STUDY DESIGN

3.1. Overview

The purpose of this PMS is to collect patient data related to mitral valve performance and safety outcomes in patients with severe functional mitral regurgitation (MR) in whom Cardioband will be implanted.

Subjects will be followed for up to 2 years,

A multi-center (up to 20 sites), single arm, open label study in a minimum of 50 subjects. Patients must have provided written consent that their data can be used in the study. The patients will be followed up for 2 years with the primary endpoint being at 6 months.

The study will enrol Patients with secondary (functional) MR, symptomatic (NYHA Class III-IVa heart failure symptoms), with severe MR and to whom The Local Site Heart Team concur that surgery will not be offered as a treatment option. Anatomical feasibility is assessed by Echocardiography and/or other exams (such as CT and angiography) according to the site common practice. The subjects will be screened and enrolled according to the study inclusion and exclusion criteria.

Patients will undergo mitral valve repair with Cardioband implanted via transcatheter procedure under Transesophageal echocardiography (TEE) and fluoroscopy guidance. Post-procedure clinical care will be performed according to standard management of mitral valve repair and Transthoracic Echo (TTE) assessment of the degree of mitral regurgitation will be obtained at hospital discharge, 30 days, 6, 12 and 24 months post-index procedure.

[redacted]

Transthoracic Echocardiography (TTE) performed by the Study clinical sites will be used for sequential assessments of mitral regurgitation at baseline, at discharge and during follow-up. Guidelines for recording the echocardiographic examination of mitral regurgitation will be provided to the sites. An echocardiographic Core Lab will be involved in assessing echocardiographic examinations. [redacted]

[redacted]

3.2. Study Endpoints

3.2.1. Primary Endpoint (powered):

- Reduction in severity of MR at 30 days of at least one category on a 0-4 scale.

3.2.2. Key Secondary Endpoint (powered):

- Change in 6 minute walk test at 6 months

3.2.3. Secondary Endpoints (all at 6, 12, and 24 months except as indicated) :

- Key Secondary Endpoint (powered): Change in 6 minute walk test at 6 months.
- Secondary Endpoints (all at 6, 12, and 24 months except as indicated) :

1) MR severity
2) 6 minute walk distance
3) Quality of life as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) (also at 30 days)
4) NYHA Class (also at 30 days)
5) Left Ventricular End Diastolic Volume (LVEDV)
6) Left Ventricular End Systolic Volume (LVESV)
7) Device success defined as deployment of the Cardioband, with MR reduction at hospital discharge.
8) Individual patient success (6 months and 1 year) defined as device success and the following:
9) Discharged from index hospitalization
10) NYHA class improvement by at least 1 level from baseline
11) Days alive and out of hospital (due to major cardiovascular events) at 1 year
12) Freedom from all-cause mortality and major adverse events defined as disabling stroke, myocardial infarction (peri-procedural or spontaneous), renal failure requiring dialysis, life-threatening bleeding, cardiac tamponade, and device related cardiac surgical intervention

[redacted]

at 30 days from the implant procedure or hospital discharge, whichever is later. (Individual components will also be evaluated).

13) Need for urgent/emergent surgical intervention

3.3. Inclusion/Exclusion

The Principal Investigator will determine the patient's suitability for Cardioband implantation, based on the following inclusion/exclusion criteria:

3.3.1. Inclusion Criteria:

1) Age ≥18 years
2) Severe (3+ to 4+) secondary Mitral Regurgitation
3) Symptomatic heart failure (NYHA Class III-IVa) despite guideline directed medical therapy including CRT if indicated
4) The Local Site Heart Team concur that surgery will not be offered as a treatment option and that medical therapy is the intended therapy.
5) Transfemoral access and transseptal deployment of the Cardioband is determined to be feasible
6) Subject is willing and able to provide informed consent and follow protocol

3.3.2. Exclusion Criteria:

1) EF<20%
2) LVEDD ≥70 mm
3) Heavily calcified annulus or leaflets
4) Significant CAD requiring revascularization
5) Active bacterial endocarditis
6) Any percutaneous coronary, carotid, endovascular intervention or carotid surgery within 30 days or any coronary or endovascular surgery within 3 months
7) Renal insufficiency requiring dialysis
8) Life expectancy of less than twelve months
9) Subject is participating in concomitant research studies of investigational products that have not reached their primary endpoint
10) Pulmonary hypertension ≥70mmHg at rest
11) Mitral valve anatomy which may preclude proper device treatment
12) Right-sided congestive heart failure with echocardiographic evidence of severe right ventricular dysfunction and/or severe tricuspid regurgitation
13) Severe liver disease
14) Patient is pregnant or lactating
15) Hypersensitivity to Nickel or Chromium
16) Clinically significant bleeding diathesis or coagulopathy

[redacted]

17) History of mitral valve repair
18) TIA or CVA within the past 3 months
19) Subjects in whom transesophageal echocardiography is contraindicated
20) Patients who cannot tolerate anticoagulation/antiplatelet regimen
21) Patients with known severe reaction to contrast agents that cannot be adequately premedicated

4. Data collection

Patients will be recruited from the pool of patients who are referred for transcatheter mitral valve repair.

4.1. Key Pre-Implantation Procedures:

1. History and Physical
2. TTE , TEE and/or CT
3. 6 minute walk test
4. KCCQ

[redacted]

4.2. Key Post-Procedure Procedures:

1. Serial AE assessment, history, and physical at 30 days, 6 months, 12 months, 24 months)
2. Serial TTEs (30 days, 6 months, 12 months, 24 months)
3. 6 minute walk tests (30 days, 6 months, 12 months, 24 months)
4. KCCQ (30 days, 6 months, 12 months, 24 months)

[redacted]

5. STUDY VISITS AND PROCEDURES

The study will commence following institutional medical ethics committee

Screening of patients will be performed according to the hospital standard screening for transcatheter mitral valve repair and replacement. Patients will give a written consent for health information release prior to screening process. The treatment procedure will be performed according to the instructions outlined in the current approved IFU. The clinical assessments will be done as per routine practice at the participating sites.

Data will be collected at the following time points (as expected in the course of a normal treatment): baseline, procedure, discharge, clinical follow-up at 30 days, 6 months, 12 months, and 24 months from the index procedure. Data from any other additional time points may be collected and analyzed if available.

[redacted]

The procedures associated with each study visit are outlined and summarized in Table 1.

[redacted]

Table 1. Variables captured in the REPAIR database at various time points.

Procedure	Screening	Baseline	Implantation	Discharge	30 days	6 months	12 months	24 months
Visit Number	-1	1	2	3	4	5	6	8
Range	- 1 month	- 1 month	0	NA	-1 wk/+ 2 wks	+/- 1 month	+/- 1 month	+/- 1 month
Data release Consent	X							
Study informed consent		X						
Demographics		X						
Wearable data watch		X	X	X	X	X	X	X
Medical History		X						
Routine Blood tests		X		X	X	X	X	X
General Clinical State		X		X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
Medication Profile		X		X	X	X	X	X
Mitral Regurgitation Assessment by TTE	X	X		X	X	X	X	X
Mitral Regurgitation Assessment by TEE		X	X					
Mitral valve anatomy (by Echo and/or CT)	X							
Coronary Angiography (within the past 12 months, optional)	X							
6-minute walk test		X			X	X	X	X
QoL questionnaire (KCCQ)		X			X	X	X	X
NYHA Functional Class		X			X	X	X	X
Cardioband Implantation			X					

[redacted]

5.1. Echocardiographic imaging

Echocardiographic data will be collected from the TEE and TTE images for the corelab interpretation of the degree of MR reduction and adverse events, if any. A physician or sonographer familiar with valvular heart disease and experienced in performing echocardiograms should perform each assessment. [redacted]

5.2. Unscheduled Visits

An unscheduled visit will be any visit to the clinical site other than the specific visits requested in the protocol. The Investigator or trained and qualified staff will perform all procedures necessary to evaluate the study participant at these visits, and record the visit in the subject's chart. The Principal Investigator must be notified by the subject immediately of any unscheduled visits to any medical facilities during the study period. (Subjects will be instructed to report).

6. STATISTICAL ANALYSIS & DATA MANAGEMENT

6.1 Number of patients (sample-size)

Based on the results of the Cardioband CE mark study (Protocol ID CB 1-2), the present study with a sample size of 50 subjects will have greater than 80% power to detect a reduction in MR severity of at least one grade (CE mark study showed improvement in MR severity of at least one grade in >80% of subjects in CE mark study).

Based on the results of the Cardioband CE mark study (Protocol ID CB 1-2), the present study with a sample size of 50 subjects will have greater than 90% power to detect an improvement of 75 m in 6 minute walk test at 6 months [redacted]

The PMS population may be expanded to collect additional experience from market introduction. This will also allow avoiding the potential influence of patients lost to follow-up or withdrawn.

[redacted]

6.2 Statistical rationale

6.2.1 Population: All patients Per Protocol

Endpoint: MR Reduction at 30 days

Estimates:

- Power: 80%, 90%
- Change in MR at 30 Days: 81.48%
- Two-tailed Alpha = 0.05
- Test: Exact Test
- Drop-out rate = 5%

[redacted]

6.2.2 Population: All patients Per Protocol

Endpoint: Mean 6MW at 6 Months

Estimates:

- Power: 80%, 90%
- Mean 6Mw at 6 months: 50, 75 meters
- Standard Deviation = 139
- Treatment arms = 1
- Two-tailed Alpha = 0.05
- Test: One-sample t-test
- Drop-out rate = 10%

[redacted]

[redacted]

6.3 Subject withdrawal

6.3.1 Withdrawal

Subjects may withdraw from the study at any time for any reason, according to the terms of the Informed Consent document, which includes continuation of clinical study follow-up whenever possible, and ongoing medical care as appropriate. Subjects may also be withdrawn from the study at any time at the discretion of the investigator.

It should be understood that an excessive rate of withdrawals could render the study difficult to interpret. Hence, unnecessary withdrawal of subjects should be avoided. Should a subject withdraw or is withdrawn, every effort must be made to complete and report the observations as thoroughly as possible. If possible, in case of withdrawal, permission for yearly study telephone follow up to assess long-term outcomes and safety will be obtained from the subject.

6.3.2 Procedures for handling withdrawal

Subjects who withdraw or are withdrawn from the study should:

- Have the reason(s) for their withdrawal recorded (if possible).
- May be seen by an investigator and all final assessments should be performed and recorded.
- Be asked about the presence of any AEs. If an ongoing AE if present, the patient should be followed up until satisfactory clinical resolution of the event is achieved.

If a subject is withdrawn, Valtech monitor should be informed as soon as possible by the site. One additional subject will be enrolled for each subject withdrawn (or died) for any reason before the primary endpoint period completed.

6.3.3 Lost to follow up

If a subject does not appear for a follow-up visit and cannot be contacted for collecting follow-up information the primary physician will be contacted and will be asked about the subject's health condition. At least 3 attempts should be made to contact the subject through all available routes attempt to contact the patient should be recorded. If there is no contact with the patients and/or primary physician - he/she will be considered 'lost to follow up'. One additional subject will be enrolled for each lost to follow up before the primary endpoint period completed.

6.3.4 Referral for alternative treatments

Subjects may be referred, at the discretion of the investigator, for an additional structural heart treatment. In such cases, the subject will be followed according to the follow up plan to assess long-term safety. The follow up may be performed by telephone, to collect safety information

(occurrence of adverse events), and if possible information regarding clinical status, and changes in medications. One additional subject will be enrolled for each patient if treated before completing the primary endpoint period.

6.4 Information collected in the Case Report Forms (CRFs)

The study physician or his designee at each clinical site will perform primary data collection. The CRFs will be collected in an electronic version. Only the study physician or other pre-designated study personnel will be authorized to enter data (from source documents).

Only anonymous data will be collected after the patient has consented that personal data can be used.

6.5 Source Documents

Source documents are original hospital records, clinical charts, screening log, patient identification list/enrolment log, original laboratory report, recorded data from automated instruments, imaging data, subject's files, and records kept at the laboratories and medico-technical departments involved in the study. The investigator must maintain source documents for each patient in the study. All information recorded on the eCRFs must be traceable to these source documents.

6.6 Site Documentation

Each clinical site will maintain a Regulatory Binder that includes all the required document (per ISO 14155:2011 - Clinical investigation of medical devices for human subjects), the laws and regulations of the countries where the PMS will take place, and indemnity / insurance requirements.

6.7 Data Retention

All study records and reports must remain on file for at least the number of years required by the local regulations after the completion or termination of the study. Study records are to be discarded only upon notification by Valtech. If audits are required, the Principal Investigator shall allow access to the original medical records and provide all requested information.

The study physicians should contact Valtech before the destruction of any records and reports pertaining to the study to ensure they no longer need to be retained. In addition, Valtech should be notified if the study physician plans to leave the institution.

6.8 Study Monitoring

Valtech or its designees will conduct investigational site monitoring to ensure that all investigators are in compliance with the investigational plan and the Investigator's Agreement. The monitors will verify source documentation against completed eCRF's according to a risk based monitoring approach.

[redacted]

Each site will be visited regularly, according to the monitoring plan, to ensure that the study is conducted in full compliance with all applicable regulations and the investigational plan.

6.9 Investigational Site Initiation and Training Requirements

Prior to investigation site activation, Valtech will provide study training relevant and pertinent to the involvement of personnel conducting study activities, investigator responsibilities, as well as device training.

[redacted]

6.10 Study Closeout

Upon completion of the study (when all subjects enrolled have been followed at 2 years and the eCRFs and queries have been completed), a close-out visit will be performed. All unused study materials and equipment will be collected and returned to Valtech or designee. The Monitor will ensure that the study physician's regulatory files are up to date and complete and that any outstanding issues from previous visits have been resolved. Other issues which will be reviewed at this visit include: discussing retention of study files, possibility of site audits, publication policy, and to ensure that the study physician will notify the local ethics committee and/or competent authority regarding study closure, if needed.

[redacted]

7 SAFETY EVALUATION AND REPORTING

7.1 Adverse event definitions

For purposes of this protocol cardiac adverse event definitions are provided in Appendix 2; Definitions of Adverse Events according to *The Mitral Valve Academic Research Consortium*

[redacted]

(MVARC) Guidelines: Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement (JACC 2015;66(3):278-307). Reporting procedures

Appendix 1 of this protocol provides detailed information on investigator responsibilities for assessing and reporting adverse events. All adverse events will be reported and recorded throughout the clinical investigation; each event will be followed until adequately resolved or explained. *A list of expected AEs, which may result from the study procedure, is included as part of the IFU.*

The Principal Investigator must determine whether the adverse event meet the definition of "serious" (Appendix 1). The investigator(s) will report any serious adverse event to the Valtech's Clinical Research department without unjustified delay.

Valtech or its designee will determine reportability of applicable adverse events according to its responsibilities for vigilance reporting.

7.2 Clinical Events Committee

All Serious adverse events will be reviewed by an independent Clinical event Committee (CEC) for adjudication of the event relation to the study device or procedure. [redacted]

7.3 Subject deaths

In the event of subject death, every effort should be made to obtain a copy of the autopsy report and/or death summary. Information on the cause of death and its relationship to the device used in this clinical investigation will be determined by the principal investigator. Copies of an autopsy report, if available, and/or a death summary are to be sent to the Investigation Sponsor.

If a device is explanted during autopsy, the device should be returned to the Sponsor for investigation and analysis. Return kits for devices will be provided upon request by the clinical monitor.

7.4 Termination criteria

The sponsor may suspend or prematurely terminate either a clinical investigation in an individual investigation site or the entire clinical investigation for significant and documented reasons. If suspicion that the disadvantages of participation may be significantly greater than those foreseen, the sponsor shall suspend the Study while the risk is assessed. The Principal Investigator shall promptly inform the enrolled subjects at his/her investigation site, if appropriate.

8 STUDY CONDUCT AND RESPONSIBILITIES

8.1 Regulatory compliance

This study will be conducted in conformity with the ethical principles set forth by the Declaration of Helsinki, Good Clinical Practice (GCP) principles, international harmonized standards for clinical investigation of medical devices (ISO 14155:2011, Clinical investigation of medical devices for human subjects), the laws and regulations of the countries where the study will take place, and indemnity / insurance requirements.

8.2 Informed consent procedure

Patient authorization and written informed consent must be obtained prior to the patient's enrolment into the Study and in accordance with GCPs, the Medical Devices Directive and all other applicable standards, regulations (local and national), guidelines and institutional policies.

The patient will also give his written consent for health information release, i.e. screening informed consent, in order to determine if the patient is a potential candidate for the device.

8.3 Confidentiality

Patient confidentiality must be maintained in accordance with GCPs, the Medical Devices Directive and all other applicable standards, regulations (local and national), guidelines and institutional policies. Study physicians will comply with the applicable provisions of the study agreement with regard to nondisclosure and confidentiality.

[redacted]

8.4 Device Accountability

The Investigator shall document in the procedure reports and eCRFs the serial/lot number of all devices used during procedures.

8.5 Protocol Changes/Amendments

The investigators will not deviate from the protocol except in emergency circumstances to protect the rights, safety and well-being of the patients. Deviations shall be documented and reported to the sponsor and the EC, if applicable, as soon as possible. Valtech or its designee will evaluate circumstances where an investigator deviates from the investigational plan.

Amendments to the protocol or any study documents already approved by the EC must be submitted and approved before the changes are implemented. For non-substantial changes [e.g.

minor logistical or administrative changes, change of monitor(s), telephone numbers, renewal of insurance], a simple notification to the EC and, where appropriate, regulatory authorities may be sufficient.

[redacted]

[redacted]

9 Appendices

9.1 Appendix 1 – Adverse Events

9.1.1 Definitions

AE – Averse Event - Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device.

SAE – Serious Adverse Event - Event that leads to death, to a life-threatening illness or injury, or a permanent impairment of a body structure or a body function, or in-patient or prolonged hospitalization, or medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, foetal distress, death or a congenital abnormality.

ADE – Adverse Device Effect - Includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device or use errors and intentional misuse.

Device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. A device deficiency should be reported as AE or SAE according to the AE and SAE definitions.

SADE – Serious Adverse Device Effect - Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

ASADE – Anticipated Serious Device Effect - An effect which by its nature, incidence, severity or outcome has been identified in the current version of the risk analysis report.

USADE – Unanticipated Serious Device Effect - An effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.2 Appendix 2 – Reportable Events - by MVARC

The following is a list of events defined by MVARC as clinical endpoints to be collected in all trials of mitral valve therapies. The different events should be reviewed and reported in light of the following definitions.

Mortality	1. Cardiovascular vs. non-cardiovascular mortality a. Cardiovascular mortality - Any of the following contributing conditions: • Heart failure (subclassified into left ventricular vs. right ventricular dysfunction) • Myocardial infarction • Major bleeding • Thromboembolism • Stroke • Arrhythmia and conduction system disturbance • Cardiovascular infection and sepsis (e.g., mediastinitis • and endocarditis) • Tamponade • Sudden, unexpected death • Other cardiovascular • Device failure • Death of unknown cause (adjudicated as cardiovascular) b. Non-cardiovascular mortality - Any death in which the primary cause of death is clearly related to another condition: • Non-cardiovascular infection and sepsis (e.g., pneumonia) • Renal failure • Liver failure • Cancer • Trauma • Homicide • Suicide • Other non-cardiovascular 2. Periprocedural vs. non-periprocedural mortality: Death is considered periprocedural if occurring within 30 days of the intervention or beyond 30 days in the patient not yet discharged
Hospitalization	Hospitalization is defined as admission to an inpatient unit or ward in the hospital for ≥24 h, including an emergency department stay. Hospitalizations planned for pre-existing conditions are excluded unless there is worsening of the baseline condition. Hospitalization is Further Sub-classified as: 1. Heart failure hospitalization: Both of the following additional criteria are present: • Symptoms, signs and/or laboratory evidence of worsening heart failure • Administration of intravenous or mechanical heart failure therapies • Patients hospitalized with heart failure are further subclassified as: o Primary (cardiac related) heart failure hospitalization o Secondary (non-cardiac related) heart failure hospitalization 2. Other cardiovascular hospitalization: such as for coronary artery disease, acute myocardial infarction, hypertension, cardiac arrhythmias, cardiomegaly, pericardial effusion, atherosclerosis, stroke, or peripheral vascular disease without qualifying heart

	failure 3. Non-cardiovascular hospitalization: not due to heart failure or other cardiovascular causes, as defined above
Neurologic events	Stroke and transient ischemic attack Diagnostic criteria: 1. Acute episode of a focal or global neurological deficit with at least 1 of the following: • Change in the level of consciousness • Hemiplegia, hemiparesis, numbness, or sensory loss affecting 1 side of the body • Dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke 2. In addition, there is no other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumour, trauma, infection, hypoglycaemia, peripheral lesion, pharmacological influences) as determined by or in conjunction with the designated neurologist The neurological event type classification 1. Stroke: duration of a focal or global neurological deficit ≥24 h OR ,24 h if available neuroimaging documents a new intracranial or subarachnoid haemorrhage (haemorrhagic stroke) or central nervous system infarction (ischaemic stroke) OR the neurological deficit results in death 2. TIA: duration of a focal or global neurological deficit ,24 h and neuroimaging does not demonstrate a new haemorrhage or infarct Confirmation of the diagnosis of stroke or TIA requires at least 1 of the following: 1. Neurologist or neurosurgical specialist, or 2. Neuroimaging procedure (CT scan or brain MRI) Stroke/TIA timing classification 1. Periprocedural if it occurs within 30 days of the intervention, or if beyond 30 days in the patient not yet discharged. A periprocedural stroke/TIA may be further considered immediate if it occurs within 24 h of the procedure or within 24 h of awakening from general anaesthesia if beyond 24 h. 2. Nonperiprocedural if it occurs beyond 30 days after the intervention and after the patient has been discharged. Stroke/TIA aetiology classification 1. Ischaemic: an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue 2. Haemorrhagic: an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid haemorrhage 3. Undetermined: if there is insufficient information to allow categorization as ischaemic or haemorrhagic Stroke severity is further classified as 1. Disabling stroke: an mRS score ≥2 at 90 days plus an increase in ≥1 mRS category from the pre-stroke baseline 2. Non-disabling stroke: an mRS score ,2 at 90 days or without an increase ≥1 mRS category from the pre-stroke baseline
Myocardial infarction	Definition of MI after transcatheter and surgical mitral valve replacement: 1. Periprocedural MI (≤ 48 h after the index procedure) • In patients with normal baseline CK-MB (or cTn): The peak CK-MB measured within 48 h of the procedure rises to ≥10x the local laboratory ULN plus new ST-segment elevation or depression of ≥1 mm in ≥2 contiguous leads (measured 80 ms after the J-point), or to ≥5x ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the PCI rises to ≥70x the local laboratory ULN plus new ST-segment elevation or depression of ≥1 mm in ≥2

	contiguous leads (measured 80 ms after the J-point), or ≥35x ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB. • In patients with elevated baseline CK-MB (or cTn): The CK-MB (or cTn) rises by an absolute increment equal to those levels recommended above from the most recent pre-procedure level plus, new ECG changes as described. 2. Spontaneous MI (.48 h after the index procedure) - Detection of rise and/or fall of cardiac biomarkers (preferably cTn) with at least 1 value above the 99th percentile URL (or ULN in the absence of URL) together with at least 1 of the following: • Symptoms of ischaemia • ECG changes indicative of new ischaemia (new ST-segment or T-wave changes or new LBBB) or new pathological Q waves in ≥2 contiguous leads • Imaging evidence of a new loss of viable myocardium or new wall motion abnormality 3. MI associated with sudden, unexpected cardiac death: Sudden cardiac death or cardiac arrest, often with symptoms suggestive of myocardial by presumably new ST-segment elevation or new LBBB and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurs before blood samples could be obtained or at a time before the appearance of cardiac biomarkers in ischaemia, and accompanied the blood. 4. Pathological findings of an acute myocardial infarction
Access and vascular complications	Vascular complications: 1. Major access site vascular complications, including: • Aortic dissection or aortic rupture, or • Access site-related arterial or venous injury (dissection, stenosis, ischaemia, arterial, or venous thrombosis including pulmonary emboli, perforation, rupture, arteriovenous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, atrial septal defect‡), irreversible nerve injury, or compartment syndrome resulting in death; hemodynamic compromise; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischaemia; or neurological impairment, or • Distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage, or • Unplanned endovascular or surgical interventions resulting in death; life-threatening, extensive, or major bleeding (MVARC bleeding scale); visceral ischaemia; or neurological impairment 2. Minor access site vascular complications, including: • Access site arterial or venous injury (dissection, stenosis, arterial, or venous thrombosis including pulmonary emboli, ischaemia, perforation, rupture, arterio-venous fistula, pseudoaneurysm, haematoma, retroperitoneal haematoma, atrial septal defect‡) not resulting in death; • life-threatening, extensive, or major bleeding (MVARC scale); visceral ischaemia; or neurological impairment, or • Distal embolization treated with embolectomy and/or thrombectomy not resulting in amputation or irreversible end-organ damage, or • Any unplanned endovascular stenting or unplanned surgical intervention not meeting the criteria for a major vascular complication, or • Vascular repair (via surgery, ultrasound-guided compression, transcatheter embolization, or stent-graft) Cardiac structural complications due to access-related issues 1. Major cardiac structural complications, including: • Cardiac perforation* or pseudoaneurysm resulting in death, life-threatening bleeding, hemodynamic compromise, or tamponade, or requiring unplanned

	surgical or percutaneous intervention 2. Minor cardiac structural complications, including: • Cardiac perforation* or pseudoaneurysm not meeting major criteria *Including the left ventricle, left atrium, coronary sinus, right atrium, and right ventricle. †May arise from the access procedure per se or complications from vascular closure devices. ‡Meeting pre-specified criteria for a hemodynamically significant shunt, or requiring unplanned percutaneous or surgical closure.
Bleeding complications	MVARC Primary Bleeding Scale* 1. Minor Any overt,† actionable sign of haemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that meets ≥1 of the following: requiring nonsurgical medical intervention by a health care professional; leading to hospitalization or increased level of care; prompting evaluation; or requires 1 or 2 U of whole blood or packed RBC transfusion and otherwise does not meet criteria for major, extensive, or life-threatening bleeding. 2. Major Overt bleeding either associated with a drop in the haemoglobin of ≥3.0 g/dl‡ or requiring transfusion of ≥3 U of whole blood or packed RBCs AND does not meet criteria of life-threatening or extensive bleeding. 3. Extensive Overt source of bleeding with drop in haemoglobin of ≥4 g/dl‡ or whole blood or packed RBC transfusion ≥4 U within any 24-h period, or bleeding with drop in haemoglobin of ≥6 g/dl‡ or whole blood or packed RBC transfusion ≥4 U (BARC type 3b) within 30 days of the procedure. 4. Life-threatening Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating surgery or intervention, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or hypotension (systolic blood pressure ,90 mm Hg lasting .30 min and not responding to volume resuscitation) or requiring significant doses of vasopressors or surgery. 5. Fatal Bleeding adjudicated as being a proximate cause of death. Severe bleeding adjudicated as being a major contributing cause of a subsequent fatal complication, such as MI or cardiac arrest, is also considered fatal bleeding. *Modified with permission from VARC-2.5 †"Overt" bleeding is defined by any of the following criteria being met: Reoperation after closure of sternotomy for the purpose of controlling bleeding; chest tube output .2 l within any 24-h period, .350 ml within the first post-operative hour, ≥250 ml within the second post-operative hour, or 150 ml within the third post-operative hour; or visible bleeding from the vascular system either at or remote from the access/surgical site. ‡Adjusted for the number of units of blood transfused (1 U packed red blood cells or whole blood is equivalent to 1 g/dl haemoglobin). §Modified from BARC.6 BARC, bleeding academic research consortium; IV, intravenous; MVARC, Mitral Valve Academic Research Consortium; RBC, red blood cells; VARC, valve academic research consortium.
Acute kidney injury	Definition and stages of acute kidney injury: Maximal change in sCr from baseline to 7 days post-procedure Stages • Stage 1 Increase in sCr to 150%–199% (1.50–1.99x increase vs. baseline), increase of ≥0.3 mg/dl (≥26.4 mmol/l) within 48 h, or urine output ,0.5 ml/kg/h for ≥6 h but ,12 h • Stage 2 Increase in sCr to 200%–299% (2.00–2.99x increase vs. baseline) or urine output ,0.5 ml/kg/h for ≥12 h but, 24 h • Stage 3 Increase in sCr to ≥300% (.3.0x increase vs. baseline), sCr of ≥4.0 mg/dl,

	(≥354 mmol/l) with an acute increase of ≥0.5 mg/dl (44 mmol/l), urine output ,0.3 ml/kg/h for ≥24 h, or anuria for ≥12 h; patients receiving renal replacement therapy are considered stage 3 irrespective of other criteria
Arrhythmias and conduction system disturbances	Arrhythmias and conduction system disturbances 1. Procedure-related new or worsened cardiac conduction disturbance (including first-, second- [Mobitz I or Mobitz II], or third-degree AV block; incomplete and complete right bundle branch block; intraventricular conduction delay; left bundle branch block; left anterior fascicular block; or left posterior fascicular block, including heart block) requiring a permanent pacemaker implant; each subclassified as persistent or transient 2. New-onset atrial fibrillation (or flutter)† 3. New-onset ventricular tachycardia or fibrillation 4. Pacemaker or defibrillator lead dislodgement Arrhythmias and conduction system disturbances are subclassified according to: 1. The occurrence of hemodynamic instability 2. Need for therapy including electrical/pharmacological cardioversion or initiation of a new medication (oral anticoagulation, rhythm, or rate control therapy) 3. Need for new permanent pacemaker and/or defibrillator implantation, including the indication(s) and the number of days post-implant. For patients with defibrillators, the number of appropriate and inappropriate shocks should be recorded. *The type of permanent pacemaker should be recorded (e.g., single vs. dual chamber, biventricular). †Which lasts sufficiently long to be recorded on a 12-lead electrocardiogram, or at least 30 s on a rhythm strip. AV, atrioventricular.
Specific device-related technical failure issues and complications	Technical failure (measured at exit from the catheterization laboratory): 1. Procedural mortality; 2. Failure in access, delivery, or retrieval of the device delivery system; 3. Failure in deployment and correct positioning of the first intended device; 4. Emergency surgery or reintervention related to the device or access procedure. Device failure (measured at 30 days and at all later post-procedural intervals) 1. procedural mortality or stroke; or 2. failure in placement and positioning of the device; or 3. unplanned surgical or interventional procedures related to the device or access procedure; or 4. lack of safety and performance of the device, including: • evidence of structural or functional failure • device-related technical failure issues and complications • significant mitral stenosis Procedural Failure (measured at 30 days) 1. Device failure 2. major device or procedure related serious adverse events, including: • Death • Stroke • Life-threatening bleeding (MVARC scale) • Major vascular complications • Major cardiac structural complications • Stage 2 or 3 acute kidney injury (includes new dialysis) • Myocardial infarction or coronary ischaemia requiring PCI or CABG • Severe hypotension, heart failure, or respiratory failure requiring intravenous pressors or invasive or mechanical heart failure treatments such as ultrafiltration or hemodynamic assist devices, including intra-aortic balloon pumps or left ventricular or biventricular assist devices, or prolonged intubation for ≥48 h. • Any valve-related dysfunction, migration, thrombosis, or other complication requiring surgery or repeat intervention

[redacted]

	Patient failure (measured at 1 year) 1. Device failure 2. Patient returned to the pre-procedural setting 3. rehospitalizations or reinterventions for the underlying condition (e.g., mitral regurgitation, heart failure); 4. No Improvement from baseline in symptoms (e.g., no NYHA improvement by ≥1 functional class); and 5. No Improvement from baseline in functional status (e.g., 6-min walk test did not improvement by ≥50 m); and 6. No Improvement from baseline in quality-of-life (e.g., on improvement in Kansas City Cardiomyopathy Questionnaire by at least ≥10) *MR reduction is considered optimal when post-procedure MR is reduced to trace or absent. MR reduction is considered acceptable when post-procedure MR is reduced by at least 1 class or grade from baseline and to no more than moderate (2+) in severity. For clinical trials and registry studies, assessment of baseline and post-procedure MR must be made by an echocardiographic core laboratory. For large observational databases, baseline and post-procedure MR may be assessed by physicians trained in echocardiography evaluation.

Mortality, Hospitalization, Neurological events and Myocardial Infarction are events which should be adjudicated by an independent central adjudication committee.

For further details for each event, please refer to The Mitral Valve Academic Research Consortium (MVARC) Guidelines: Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement (JACC 2015;66(3):278-307).

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