CS0005-P
MAC Feasibility Study
Feasibility study of the Tendyne Mitral Valve System in Mitral Annular Calcification

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Study Type	Prospective, single-arm, multicenter feasibility clinical study of the Tendyne Mitral Valve System
Sponsor	Tendyne Holdings, Inc. (a subsidiary of Abbott Vascular, Inc.) 177 County Road B East St. Paul, MN 55117
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TENDYNE

Mitral Valve System

CLINICAL INVESTIGATION PLAN SIGNATURE PAGE

Feasibility study of the Tendyne Mitral Valve System in Mitral Annular Calcification

Clinical Investigation Plan No. CS0005-P

Version A

25APR2018

I have read this Clinical Investigation Plan (CIP) and agree to adhere to conduct the investigation in accordance with the agreement, the CIP, applicable regulations, and any conditions of approval imposed by the Institutional Review Board (IRB). I will provide copies of this CIP and all pertinent information to the study personnel under my supervision and my hospital IRB. I will discuss this material with them and ensure they are fully informed regarding the Tendyne Mitral Valve System and the conduct of the study according to this CIP, applicable laws and regulatory regulations, including hospital IRB requirements.

Investigational Site Name

_____

Site Investigator Signature Date

_____

Site Investigator Printed Name

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COMPLIANCE STATEMENT

This study will be conducted in accordance with this Protocol, the Declaration of Helsinki and US Good Clinical Practice and the applicable regulatory requirements (such as, 21 CFR Part 50, 21 CFR Part 56,21 CFR Part 812, 21 CFR Part 54, and 21 CFR Part 11and 45 CFR part 46). The conduct of the study will be approved by the Food and Drug Administration (FDA) and the appropriate Institutional Review Board (IRB) of the respective investigational site.

CLINICAL INVESTIGATION PLAN SUMMARY

Study Name and Number	MAC Feasibility Study (CS0005-P)
Title	Feasibility study of the Tendyne Mitral Valve System for use in subjects with Mitral Annular Calcification
Objectives	To evaluate the feasibility of using the Tendyne Mitral Valve System in the treatment of mitral valve regurgitation in patients with severe mitral annular calcification.
Investigational Device	Tendyne Mitral Valve System
Clinical Study / Investigation Design	This study is a prospective, single-arm, multicenter feasibility clinical study of the Tendyne Mitral Valve System for the treatment of eligible subjects with symptomatic, severe mitral regurgitation and severe mitral annular calcification. Subjects satisfying the study inclusion/exclusion will undergo a procedure to implant the Tendyne device.
Planned Sample Size / Investigational Sites	Up to 30 subjects will be registered in the study to receive the Tendyne device at up to 10 sites in the United States.
Primary Safety Endpoint	Composite endpoint of Device Success **and** freedom from device or procedure related serious adverse events (SAEs) at 30 days post implant, as classified by the Clinical Events Committee (CEC). **Definition of Device Success**: All of the following must be present: 1) Absence of procedural mortality or stroke; and 2) Proper placement and positioning of the device; and 3) Freedom from unplanned surgical or interventional procedures related to the device or access procedure; and 4) Continued intended safety and performance of the device, including: a) No evidence of structural or functional failure b) No specific device-related technical failure issues or complications c) Reduction of MR to either optimal or acceptable levels without significant structural valve dysfunction and with no greater than mild (1+) paravalvular MR (and without associated hemolysis)

Clinical Endpoints	The following clinical endpoints will be assessed as part of this feasibility study 1) Technical Success as measured at exit from the procedure **Definition of Technical success:** a) Absence of procedural mortality; and b) Successful access, delivery and retrieval of the device delivery system; and c) Successful deployment and correct positioning of the intended device; and d) Freedom from emergency surgery or re-intervention related to the device or access procedure 2) Patient Success at 1, 2, 3, 4, and 5 years post index procedure **Definition of Patient Success:** a) Device Success (either optimal or acceptable); and b) Subject returned to the pre-procedural setting (e.g. home, assisted living facility); and c) No transcatheter or surgical re-interventions for mitral valvular disease (modified from MVARC guidelines); and d) Improvement from baseline symptoms (NYHA improvement by ≥ 1 Functional Classification); and e) Improvement from baseline in functional status (6MWD improvement by ≥ 50 meters); and f) Improvement from baseline in Quality of Life (KCCQ improvement by ≥ 10 points) 3) Device Success as measured at 30 days and at all post-procedural intervals 4) Freedom from all-cause mortality at 3 months, 6 months, 1 year and then annually through 5 years post index procedure 5) Change from baseline in distanced walked on the 6MWT at each follow-up visit 6) Change from baseline in QoL, as measured by the KCCQ at each follow-up visit 7) NYHA Functional Classification at each follow-up visit

Subject Follow-up	Subjects will be seen at the following study intervals: **Visit 1** – Screening / Baseline **Visit 2** – Procedure **Visit 3** – Pre-discharge **Visit 4** – Follow up 30 days post procedure **Visit 5** – Follow-up 90 days post procedure **Visit 6** – Follow-up 182 days post procedure **Visit 7** – Follow-up 365 days post procedure **Visit 8** – Follow-up 731 days post procedure **Visit 9** – Follow-up 1096 days post procedure **Visit 10** – Follow-up 1461 days post procedure **Visit 11** – Follow-up 1826 days post procedure
Planned Duration of Study	Approximately 76 months. This includes a 16-month subject enrollment phase period, with subject follow-up continuing for an additional 60 months. Study reports will be completed annually with a final report estimated for completion within 3 months of the last subject visit.
Eligibility Criteria	
Inclusion Criteria	1. Heart Team determines subject is not a suitable candidate for conventional surgical treatment due to degree of MAC present and, the subject will likely benefit from transcatheter valve implantation 2. Severe, symptomatic mitral regurgitation (as defined in the 2017 ACC expert Consensus Decision Pathway on the Management of MR) 3. NYHA Functional Classification ≥ II (if Class IV, patient must be ambulatory) 4. Age 18 years or older at time of consent 5. Not a member of a vulnerable population per the investigator's judgment 6. The subject or the subject's legal representative has been informed of the nature of the study and agrees to its provisions, including complying with study required testing and follow-up visits, and has provided written informed consent
Exclusion Criteria	1. Presence of Left Ventricle or Left Atrium thrombus 2. Subject has a chest condition that prevents transapical access

	3. Left Ventricular Ejection Fraction (LVEF) less than 25% assessed by echocardiogram 4. Left Ventricular End Diastolic Dimension (LVEDD) > 7.0 cm 5. Severe mitral stenosis not amenable to balloon valvuloplasty or transcatheter therapy 6. Prior intervention with permanently implanted mitral device (e.g. MitraClip) 7. Mitral pathoanatomy and Left Ventricular Outflow tract (LVOT) anatomy deemed not suitable for Tendyne mitral valve implantation 8. Any planned cardiac surgery or intervention that is 30 days prior and 30 days post that is not concomitant with the Tendyne procedure 9. Cardiac resynchronization therapy (CRT) device or implantable pulse generator (IPG) implanted within three months of planned implant procedure 10. Myocardial Infarction (MI) within 30 days prior to the planned implant procedure 11. Symptomatic, or ischemia-associated coronary artery disease (e.g., active ischemia) amenable to revascularization and thus requiring stenting or Coronary Artery Bypass Grafting (CABG) 12. Cerebrovascular accident (CVA) within six months prior to the planned implant procedure 13. Unresolved severe symptomatic carotid stenosis (>70% by ultrasound) 14. Cardiogenic shock or hemodynamic instability requiring inotropes or mechanical support devices within 1 month prior to planned implant procedure 15. Severe tricuspid regurgitation or severe right ventricular dysfunction 16. Hypertrophic or restrictive cardiomyopathy, constrictive pericarditis or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non-ischemic etiology 17. Any of the following: leukopenia, acute anemia, thrombocytopenia, history of bleeding diathesis, or coagulopathy if cannot be adequately treated

	18. History of endocarditis within 6 months of planned implant procedure 19. Active systemic infection requiring antibiotic therapy 20. Known hypersensitivity or contraindication to procedural or post-procedural medications (e.g., contrast solution, anti-coagulation therapy) which cannot be adequately managed medically 21. Subject unable or unwilling to take anticoagulation with warfarin for a minimum of 6 months following Tendyne valve implantation 22. Known hypersensitivity to nickel or titanium 23. Subject is undergoing hemodialysis due to chronic renal failure (≥ Stage 4 CKD) 24. Subject has pulmonary arterial hypertension (fixed PAS >70mmHg) **Note:** If PAS > 70mmHg, site must provide documentation PAS is not fixed in order to be eligible 25. FEV1 < 50% of predicted **or** < 1L 26. Subject refuses blood transfusions 27. Subject has COPD requiring continuous home oxygen therapy or chronic outpatient oral steroid use 28. Pregnant, lactating, or planning pregnancy within next 12 months **Note:** Female subjects of childbearing age should be instructed to use safe contraception (e.g. intrauterine devices, hormonal contraceptives: contraceptive pills, implants, transdermal patches hormonal vaginal devices, injections with prolonged release) 29. Currently participating in an investigational drug or another device trial that has not reached its primary endpoint **Note:** Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials 30. Subjects with non-cardiac co-morbidities that are likely to result in a life expectancy of less than 12 months

1 INTRODUCTION

The objective of this feasibility study is to provide preliminary information on the safety and effectiveness of the Tendyne Mitral Valve System for the treatment of symptomatic, severe mitral regurgitation in patients with severe mitral annular calcification (MAC).

As the Sponsor, Tendyne Holdings, Inc. ("Tendyne") has the overall responsibility for the conduct of the study including assurance that the study will be performed according to this CIP as per the U.S. Food and Drug Administration (FDA) and any other applicable regulations. Tendyne will have direct responsibilities for day-to-day study management, and may delegate responsibilities for some study management activities to a Contract Research Organization (CRO), if needed.

2 BACKGROUND INFORMATION

2.1 Mitral Valve Disease

2.1.1 Mitral Regurgitation

Two population-based studies in the US showed that mitral regurgitation (MR) is the most common heart valve disease [1,2]. The Framingham Offspring Study used color Doppler echocardiography to assess for MR, which was detected in 90% of the subjects, albeit trace or mild in severity (not clinically significant) in the majority of cases. However, 1.6% of subjects had moderate to severe MR [2]. The most common factors associated with the presence of MR were older age, lower body mass index, heart failure, myocardial infarction (MI) and hypertension.

Similarly, a population-based study by Nkomo et al. found moderate to severe MR occurring in approximately 1.7% of the US population with increasing prevalence among older individuals (7.3% of those ≥65 years of age). The authors estimated that in the year 2000 approximately 2 to 2.5 million people were affected by moderate to severe MR. With current US demographic trends toward increasing population growth and increasing numbers of older Americans, the number of people with MR is expected to double by 2030 [1].

Referral and treatment patterns for valvular heart disease were evaluated in the Euro Heart Survey of 92 centers over a 3 month period in 2001 [3,4]. Mitral regurgitation was identified as the second most common form of valvular heart disease after aortic stenosis. The authors noted that the difference compared to the US studies may have been due to the nature of the survey, in which only those patients referred for at least moderate valve disease to tertiary centers were included [4]. This suggests that patients with moderate or severe MR are not being properly referred for treatment, and important interventions are being delayed.

2.1.2 Mitral Annular Calcification

Mitral annular calcification is a chronic degenerative process in the fibrous base of the mitral valve which can result in either MS or MR, or a combination of both disorders. The prevalence of MAC is age-dependent, with 15% to 30% of those older than 70 years affected. MAC is more common in patients with kidney disease, fibrous skeletal abnormalities (e.g., Marfan syndrome), atherosclerosis, hypertension, and chronic inflammatory disorders. MAC causes significant mitral stenosis or regurgitation by impairing diastolic annular dilation and restriction of mitral leaflet

motion. These changes typically progress over time with secondary calcification of the valvular apparatus.

The pathophysiology of the disease is variable depending on the severity of the valve lesion, and whether the lesion is predominantly stenosis, regurgitation, or both. In predominant MR, there is a volume overload of the left ventricle that results in (LV) hypertrophy to compensate for both the metabolic demands of the body (forward stroke volume) and regurgitant volume with each heartbeat. There is also a compensatory gradual enlargement of the left atrium (LA) and increase in LA compliance. The chronic, compensated phase of the disease may consist of asymptomatic patients with normal exercise tolerances.

Compensated MR may persist for many years. At some point, however, the LV myocardium is no longer able to contract adequately to overcome the volume overload caused by MR. The reduced ability of the LV to contract results in a decreased stroke volume, which leads to decreased cardiac output, an increase in end systolic volume, increased LV filling pressures and increased pulmonary congestion. In this stage, the patient displays signs of heart failure and exercise intolerance. In an attempt to increase cardiac output, there is further dilatation of the LV, which leads to increasing dilatation of the MV annulus and increasingly more severe MR.

2.2 Treatment of Mitral Valve Disease

2.2.1 Current Guidelines

The American College of Cardiology/American Heart Association (ACC/AHA) and the European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) have published guidelines for the management of mitral disease [5,6]. In summary, the guidelines advise surgical treatment of primary MR when the lesion is severe and with symptoms, left ventricular dysfunction, or when cardiac surgery is being undertaken for other indications. Surgical intervention also should be considered when patients have secondary, severe MR and are undergoing coronary artery bypass grafting. For mitral stenosis (MS), percutaneous mitral balloon commissurotomy is recommended for symptomatic patients with severe MS (valve area <1.5 cm^2) and favorable valve morphology. Characteristics of valve morphology that are favorable include pliability of the leaflets and sub-chordal apparatus, and the absence of grade 3 or 4 MR. When the valve morphology is not favorable for percutaneous mitral balloon commissurotomy, surgery for severe MS is advised when the patient has severe symptoms (class III or IV). Some reports indicated that medical therapies directed at the underlying heart failure and LV dysfunction may have a beneficial effect on secondary MR in some patients. Specifically, maximal therapy beta adrenergic blockers or angiotensin-converting enzyme inhibitors and cardiac resynchronization therapy have been shown to reduce MR severity [7-11]. The general belief has been that early reperfusion with percutaneous coronary intervention (PCI) or coronary artery bypass grafts (CABG) would reduce ischemic damage to the heart muscle and retard the process of LV remodeling, thereby preventing the development of MR [12]. However, treatment of the ischemia with PCI or CABG did not improve survival or result in the short-term or long-term improvement in the IMR severity [11-13]. Some data suggest that MV repair or reduction of annular diameter with an annuloplasty ring concomitant with a CABG procedure may provide benefit [14-17]. It should be noted; however, that surgical treatment of secondary MR is evolving such that many patients will not receive repair or replacement unless the patient has concomitant surgical indications for revascularization or aortic valve replacement.

2.2.2 Treatment of Mitral Annular Calcification

Patients with MAC are a unique subgroup of patients due to their marked surgical risk. In these patients, there is a high risk of atrioventricular groove disruption, a complication that is nearly universally fatal [18,19]. Other potential complications that can occur with open surgical treatment of MAC include ventricular rupture and injury to the left circumflex coronary artery. The presence of MAC is associated with increased intraoperative conversion from valve repair to replacement [20]. In addition, MAC will be accompanied by severe morbidities that significantly increase surgical risk, such as coronary atherosclerosis, vascular disease, and renal failure. Thus, mitral valve surgery for treatment of MAC is reserved only for select patients.

In order to avoid or minimize the risk of surgical complications with treatment of MAC, several approaches have been developed. Mitral valve replacement without debridement of the mitral annulus has been utilized, though paravalvular regurgitation may occur due to the non-uniform sewing borders. In other instances, an edge-to-edge repair has been employed; the main limitation with this approach is worsening of pre-existing mitral stenosis that is common in these patients. Success with surgical dissection and reconstruction of the calcified annulus with suturing, a pericardial patch, or an atrial flap, followed by mitral repair or replacement also has been reported [21-23].

Transcatheter techniques for treatment of MAC have been developed to obviate the need for open surgical correction and minimize the procedural risk. These off-label techniques have utilized direct atrial access, transseptal puncture, and transapical approaches for implanting transcatheter valves that were initially designed for treatment of calcific aortic stenosis. In the largest registry of transcatheter implantation of valve prostheses for the treatment of MAC (n=64), initial technical success was achieved in 46 patients (or 72%); additional valves were needed in 11 patients, leading to an overall procedural success rate of 89.2% [24]. Complications included left ventricular outflow tract obstruction with hemodynamic compromise (9.3%) and valve embolization (6.5%). Periprocedural death, owing to technical failures as well as high patient co-morbidity, occurred in 19 of 64 cases (29.7%). Importantly, there were no incidences of annular rupture. All patients had mild or no residual MR after transcatheter valve implantation. These results, which mirror what has also been described multiple case reports and series, are important advances as 1) the operators had utilized circular valve prostheses (Sapien, Sapien XT, Sapien 3, Inovare) in off-label fashion for the treatment of rigid, irregularly shaped annuli; 2) the high success rates occurred among operators who were new to the procedure with very limited experience (64 patients treated at 32 sites); and 3) the valve prostheses utilized were neither retrievable nor repositionable, and thus create challenges for instances where there is device malpositioning.

2.3 Therapeutic Need

2.3.1 Mitral Regurgitation

Although the guidelines for management of valvular heart disease suggest that surgical repair of symptomatic MR is preferred over surgical replacement, more recent evidence indicates that replacement is not inferior and represents a viable first line treatment option for many patients. Additionally, there is a large patient population that has limited treatment options. Specific populations of patients with limited options include those who are not suitable surgical candidates,

because they considered high risk for peri-procedural morbidity and mortality and those with secondary MR.

These populations could benefit from a less invasive approach that does not require an open-heart procedure nor cardiopulmonary bypass. Therefore, transcatheter mitral valve implantation has the potential to be a viable alternative to traditional mitral valve surgery.

2.3.2 Mitral Annular Calcification

Although the practice guidelines for the management of valvular heart disease recommend treatment of symptomatic mitral disease, patients with MAC have limited surgical and transcatheter options. The surgical risk is markedly elevated in these patients due to technical challenges, as well as the severe morbidities (e.g., renal failure, atherosclerosis, inflammatory disorders) that frequently are present in patients with MAC. While transcatheter therapy is routinely employed for the treatment of valvular disease in high or prohibitive risk patients, no technology has been designed specifically for patients with mitral disease due to MAC. The use of available transcatheter therapy, while feasible in these patients, remains technically challenging with complications that, in part, are attributable to the off-label nature of employed devices. Thus, patients with MAC who are at high or prohibitive surgical risk could benefit from a less invasive approach designed for the mitral valve that does not require an open-heart procedure or cardiopulmonary bypass. If successful, transcatheter mitral valve implantation with such devices would help to address a large unmet clinical need.

2.4 Compassionate Use Experience with the Tendyne Mitral Valve System

The Tendyne Mitral Valve System is only available for use under clinical investigational settings. For patients who do not meet entry criteria for the current ongoing clinical study (ClinialTrials.gov identifier: NCT02321514 Expanded Clinical Study of the Tendyne Mitral Valve System), they may receive the device under expanded access mechanisms such as compassionate use. As of February 12, 2018, the Tendyne valve has been successfully implanted in twenty patients under compassionate use including six patients with MAC (**Table 1**).

Table 1. MAC Compassionate Use Implants

Site Name	City, State	Implanted
Abbott Northwestern Hospital	Minneapolis, MN	5
Emory University Hospital	Atlanta, GA	1

2.4.1 Rationale for Conducting this Clinical Study / Investigation

This feasibility study is designed to capture clinical and outcomes data to investigate whether the Tendyne Mitral Valve System holds promise for the treatment of patients suffering from the debilitating symptoms of symptomatic, severe mitral regurgitation associated with severe MAC. Information garnered from this study may be used to refine the patient population for whom the device is intended and/or form the basis for the development of subsequent clinical protocols.

Patients who are not appropriate for MV surgery due to the increased procedural risk associated with the presence of MAC and history of comorbidities will undergo the Tendyne procedure.

Potential benefits of the use of the Tendyne device include, but may not be limited to, the following:

- Improved symptomatic status and quality of life
- Reduced mortality
- Avoidance of procedural risks such as: cardiopulmonary bypass (CPB); atrioventricular groove disruption; ventricular rupture; and injury to the left circumflex coronary artery

Early data obtained from the compassionate use experiences with the Tendyne device in patients with severe MR and severe MAC demonstrate that the Tendyne device can be successfully implanted. Patients experience post-procedure improvement in NYHA functional status and the device remains in place without paravalvular leak. In consideration of the potential benefits and the favorable risk profile of the Tendyne device, this feasibility study is clinically justified.

2.5 Summary of Investigational Device

2.5.1 Name of the Investigational Device

The investigational device to be used in this study is the Tendyne Mitral Valve System, which consists of the Tendyne Mitral Valve and an instrument to facilitate placement of the valve. In this CIP, the investigational device is referred to as the "Tendyne Mitral Valve System" or the "Tendyne device".

2.5.2 Intended Use

The Tendyne Mitral Valve System is intended for transapical, beating heart, mitral valve replacement in patients with a diseased, damaged, or malfunctioning mitral valve.

2.5.3 Indications for Use

The Tendyne Mitral Valve System is indicated for transapical delivery via a sheath in patients with symptomatic, severe mitral valve regurgitation with severe mitral annular calcification, who are not suitable for surgical treatment and in whom existing co-morbidities would not preclude the expected benefit from reduction of the mitral regurgitation.

2.5.4 Description of the Investigational Device (Tendyne Mitral Valve System)

The Tendyne Mitral Valve is a bioprosthetic valve, which consists of a porcine pericardial tri-leaflet valve attached to an inner frame. This inner valve is then attached to an outer frame and a tether. During the implantation procedure, the tether is secured to an apical pad on the epicardial surface of the heart.

The inner valve is comprised of three (3) identical, porcine leaflets assembled onto a circular, self-expanding inner frame. The outer valve assembly is intended to provide sealing and conform to the native mitral annulus. It is made from the same super-elastic nickel-titanium alloy (Nitinol) as the inner frame. The outer surface of the outer-frame is covered with a porous polyester material. The atrial surface of the outer-frame is covered in fixed porcine pericardial tissue. The inner porcine and outer polyester materials are sutured to the outer frame with braided ultra-high molecular weight polyethylene suture.

A radiopaque marker at A1 can be visualized under fluoroscopy to confirm orientation of the valve. The outer-frame cuff is raised along the straight leg of the D-shape frame and is referred to as the A2 region or the "proud cuff" as it is the tallest section of the outer frame. The proud cuff of the outer-frame is also used to orient the prosthesis inside the native mitral valve.

The valve is fully repositionable and retrievable intraoperatively. Repositioning allows optimization of the valve position following deployment, and retrieval allows use of an alternative valve size if the initial valve does not have adequate performance.

The inner valve is assembled into various sizes of outer frames to give the valve the ability to conform to a wide range of patient geometries. The size of the valve is defined by the anterior-posterior (AP) length, inter-commissural diameter (IC), the perimeter (PER) of the outer-frame and the effective orifice area (EOA). Imaging techniques are used to determine valve size based on the subject's mitral annulus dimensions. The valve size is chosen to provide the proper fit for paravalvular sealing and device stability. The decision regarding which valve size to implant may be influenced by the simulated area of the LVOT created following implantation of the valve. This modeling is performed using software (Circle cardiovascular imaging software, www.circlecvi.com; and Mimics medical image segmentation for engineering on anatomy, biomedical.materialise.com/mimics).

The Instrument Set used in the transapical implantation of the valve includes the following components: 1) Tendyne Loading System, 2) Tendyne Delivery System and 3) Tendyne Pad Positioning System. An additional instrument 4) Tendyne Retrieval System, is also available, which can be used to retrieve the valve intraoperatively, should the valve implant be suboptimal. All of the components of these systems are provided sterile via ethylene oxide (EO) sterilization. All components of these systems that come in contact with the subject are also provided non-pyrogenic.

For a more detailed description of the Tendyne Mitral Valve System refer to the Instructions for Use (IFU).

2.5.5 Procedures Involved in the Use of the Device

The procedures outlined in the approved Tendyne Mitral Valve System IFU must be followed in the use of this device under this CIP.

2.5.6 Training Required for the Use of the Device

Investigators will be trained in accordance with the approved Tendyne Mitral Valve System IFU. Investigator training will include, but will not be limited to, the use of a bench top model and demonstration unit to ensure that investigators understand the mechanics and characteristics of the Tendyne Mitral Valve System. Sponsor staff will conduct this training and a training log will be used for documentation. Only physicians who receive all required device training and have documentation that training was completed can perform the Tendyne procedure under this CIP.

2.5.7 Investigational Device Accountability

The Sponsor is responsible for the availability and distribution of all investigational products. Product will only be distributed to study sites when the Sponsor has provided written documentation of investigational site readiness. The Sponsor will ship and/or hand-carry devices

(the Tendyne System) to the Principal Investigator or his/her designee at each site. The Tendyne System must be stored in a secured location separate from market-released products.

The investigator, or designee, will maintain adequate records of the receipt and disposition of the investigational device system, including reference/serial/lot numbers (as appropriate), date of use, subject number and implanting physician(s). A Device Accountability Log supplied by the Sponsor will be used. All unused investigational devices must be returned to the Sponsor when study registration is complete (completed device accountability reports will be generated for the site) or as otherwise deemed necessary (e.g., expired devices).

Any investigational devices that are associated with a device failure or device deficiency (and were not successfully implanted) should be returned immediately to the Sponsor.

3 STUDY OBJECTIVES / ENDPOINTS

The objective of this study is to capture preliminary information regarding the safety and effectiveness of the Tendyne Mitral Valve System. There are no pre-defined pass or fail criteria for evaluating the study objectives. Endpoints were selected to help determine the feasibility of the Tendyne Mitral Valve System in the treatment for mitral regurgitation in subjects with MAC.

3.1 Primary Safety Endpoint

The primary safety endpoint will evaluate the procedural and device safety of the Tendyne Mitral Valve System. The composite endpoint is: Device Success (defined below) and freedom from device or procedure related serious adverse events (SAEs) at 30 days post implant, as classified by the Clinical Events Committee (CEC).

Definition of Device Success:

All of the following must be present:

1) Absence of procedural mortality or stroke; and
2) Proper placement and positioning of the device, and
3) Freedom from unplanned surgical or interventional procedures related to the device or access procedure; and
4) Continued intended safety and performance of the device, including:
   a) No evidence of structural or functional failure
   b) No specific device-related technical failure issues or complications
   c) Reduction of MR to either optimal or acceptable levels without significant structural valve dysfunction and with no greater than mild (1+) paravalvular MR (and without associated hemolysis).

Structural failure is when the valve fails to perform as intended due to a complication related the valve, such as: fracture, migration or embolization. Functional failure is when the valve performs as intended without complication but does not adequately reduce the degree of MR or results in new, significant mitral stenosis.

Post-procedure MR reduction is considered optimal when reduced to trace or absent and acceptable when reduced by at least 1 class or grade from baseline and to no more than moderate (2+) residual MR in severity [25].

Note: Criterion #4c above has been modified from the MVARC guidelines [25], to align with the structural valve dysfunction definition used in this CIP.

3.2 Clinical Endpoints

The following clinical endpoints will be evaluated:

- Technical success evaluated upon exit from procedure room, defined as:
    1) Absence of procedural mortality; and
    2) Successful access, delivery and retrieval of the device delivery system; and
    3) Successful deployment and correct positioning of the intended device; and
    4) Freedom from emergency surgery or re-intervention related to the device or access procedure
- Patient Success evaluated at 1, 2, 3, 4, and 5 years post index procedure, defined as:
    1) Device Success (either optimal or acceptable); and
    2) Subject returned to the pre-procedural setting (e.g. home, assisted living facility); and
    3) No transcatheter or surgical re-interventions for mitral valvular disease (modified from MVARC guidelines); and
    4) Improvement from baseline symptoms (NYHA improvement by ≥ 1 Functional Classification); and
    5) Improvement from baseline in functional status (6MWD improvement by ≥ 50 meters); and
    6) Improvement from baseline in Quality of Life (KCCQ improvement by ≥ 10 points)
- Device Success as measured at 30 days and at all post-procedural intervals
- Freedom from all-cause mortality at 3 months, 6 months, 1 year, and then annually through 5 years post index procedure
- Distance walked on the 6MWT at baseline, 30 days, 3 months, 6 months, 1 year, and then annually through 5 years post index procedure (change from baseline to follow-up)
- KCCQ QoL scores at baseline, 30 days, 3 months, 6 months, 1 year, and then annually through 5 years post index procedure (change from baseline to follow-up)
- NYHA Functional Classification at baseline, 30 days, 3 months, 6 months, 1 year, and then annually through 5 years post index procedure

4 STUDY DESIGN, SCOPE AND DURATION

4.1 Study Design

This study is a prospective, single-arm, multicenter feasibility clinical study of the Tendyne Mitral Valve System for the treatment of eligible subjects with symptomatic, severe mitral regurgitation and severe mitral annular calcification (MAC).

Subjects whom the local site heart team determines: (a) are not suitable candidates for conventional mitral valve surgery due to the degree of MAC present; (b) will likely benefit from transcatheter valve implantation; and (c) meet study entrance criteria will receive the Tendyne device.

4.2 Number of Subjects to be Registered

This study will enroll male and female subjects who satisfy the inclusion and exclusion criteria and provide written informed consent. This study will register up to 30 subjects at up to 10 investigational sites in the U.S.

Subjects are enrolled in the study upon signing the informed consent form. Subjects are considered registered in the study upon attempt of the implant procedure.

There is no minimum number of subjects to be registered at any site.

4.3 Total Expected Duration of the Clinical Investigation

The total duration of the study is estimated as 76 months. This includes a 16-month subject enrollment phase period, with subject follow-up continuing for an additional 60 months.

Subjects will have required follow-up evaluations at pre-discharge, 30 days, 3 months, 6 months, 1 year, and then annually through 5 years post index procedure (see **Table 2** for visit windows). When all registered subjects have been followed for 5 years, or have exited the study, the study will be closed.

5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Screening and Informed Consent

All subjects must be screened by the site's investigator and clinical research staff, who have been trained to the CIP, to determine if the potential subject is eligible for study registration. Potential subjects will be assigned a unique subject identifier through the electronic Case Report Form (eCRF) database.

Patients are enrolled (i.e., become "subjects") after they sign the Informed Consent Form (ICF). During the informed consent process, the investigator or designee, who has been trained on the CIP, will explain the nature and scope of the study, potential risks and benefits of participation, and answer questions from potential subjects. All subjects (or subjects' legally authorized representatives, if applicable) must sign and date the IRB approved informed consent form prior to any clinical study-specific procedures. No subjects belonging to a vulnerable population (see **Appendix II: Definitions**) will be enrolled.

Obtaining the consent, and provision of a copy of the consent to the subject, along with date and time must be documented in the subject's medical records. The informed consent form must be signed by the investigator (or designee). In addition, the signed informed consent must be kept in the subjects medical records. The investigator, or designee, is responsible for advising the subject of any new information about the investigation or the Tendyne device that may become known during the study.

If a specific test required to determine a subject's eligibility is not standard of care, the test must be performed after written informed consent has been obtained. If any of the required screening assessments are conducted as part of standard of care prior to obtaining written informed consent, it is acceptable to provide the results of these previously performed tests for purposes of screening after the subject (or subject's legally authorized representative) has provided informed consent.

An authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), must be obtained from the subject or the subject's legally authorized representative.

For live cases at congresses, subjects need to sign a specific Live Case ICF, approved by the IRB and by Tendyne Holdings, Inc., as well as by the regulatory authorities (e.g. FDA), as applicable. The investigator must request Tendyne Holdings, Inc. approval prior to performing a Live Case.

5.1.1 Enrollment of Medicare Beneficiaries

This clinical investigation will enroll appropriate Medicare beneficiaries that qualify based on the inclusion and exclusion criteria set forth in the study. The investigational device exemption (IDE) clinical trial adheres to all standards of Medicare coverage requirements set forth by CMS's IDE and clinical trial coverage policies. The Risk Analysis section of this CIP (see **Section 16)** describes how all enrolled subjects, including Medicare beneficiaries, may be affected by the device under investigation.

Subjects enrolled in the clinical investigation are expected to be consistent with the Medicare population based on demographic characteristics and cardiovascular risk factors, therefore, the clinical investigation results are expected to be generalizable to the Medicare population.

5.2 Eligibility Criteria

5.2.1 General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records at the site and interview with a potential subject. Clinical and laboratory tests used to assess eligibility shall be per site standard. If a specific test required to determine subject's eligibility is not included in a site's standard tests, the test must be performed after written informed consent has been obtained from the subject (or the subject's legally authorized representative, if applicable).

If any of the required screening assessments are conducted as part of standard of care prior to obtaining written informed consent, it is acceptable to provide the results of these previously performed tests for purposes of screening after the subject (or subject's legally authorized representative) has consented to participate in the study. Subjects must meet all of the inclusion criteria to be considered for the clinical study. If any of the exclusion criteria are met, the subject is excluded from the clinical study and cannot be registered.

5.2.2 Inclusion Criteria

Patients must meet all of the following inclusion criteria to participate in the study:

1. Heart Team determines subject is not a suitable candidate for conventional surgical treatment due to degree of MAC present and the subject will likely benefit from transcatheter valve implantation
2. Symptomatic, severe mitral regurgitation, as defined in the 2017 ACC expert Consensus Decision Pathway on the Management of MR (see **Figure 1** in the Appendix II)
3. NYHA Functional Classification ≥ II (if Class IV, patient must be ambulatory)
4. Age 18 years or older at time of consent
5. Not a member of a vulnerable population per the investigator's judgment
6. The subject or the subject's legal representative has been informed of the nature of the study and agrees to its provisions, including complying with study required testing and follow-up visits, and has provided written informed consent

5.2.3 Exclusion Criteria

Subjects must not meet any of the following exclusion criteria to participate in the study:

1. Presence of Left Ventricle or Left Atrium thrombus
2. Chest condition that prevents transapical access
3. Left Ventricular Ejection Fraction (LVEF) less than 25% assessed by echocardiogram
4. Left Ventricular End Diastolic Dimension (LVEDD) > 7.0 cm
5. Severe mitral stenosis not amenable to balloon valvuloplasty or transcatheter therapy
6. Prior intervention with permanently implanted mitral device (e.g. MitraClip)
7. Mitral pathoanatomy and Left Ventricular Outflow tract (LVOT) anatomy deemed not suitable for Tendyne mitral valve implantation
8. Any planned cardiac surgery or intervention that is 30 days prior and 30 days post that is not concomitant with the Tendyne procedure
9. Cardiac resynchronization therapy (CRT) device or implantable pulse generator (IPG) implanted within three months of planned implant procedure
10. Myocardial Infarction (MI) within 30 days of the planned implant procedure
11. Symptomatic, or ischemia-associated coronary artery disease (e.g., active ischemia) amenable to revascularization and thus requiring stenting or CABG
12. Cerebrovascular accident (CVA) within six months of planned implant procedure
13. Unresolved severe symptomatic carotid stenosis (> 70% by ultrasound)
14. Cardiogenic shock or hemodynamic instability requiring inotropes or mechanical support devices within 1 month prior to planned implant procedure
15. Severe tricuspid regurgitation or severe right ventricular dysfunction
16. Hypertrophic or restrictive cardiomyopathy, constrictive pericarditis or any other structural heart disease causing heart failure other than dilated cardiomyopathy of either ischemic or non-ischemic etiology
17. Any of the following: leukopenia, acute anemia, thrombocytopenia, history of bleeding diathesis, or coagulopathy if cannot be adequately treated
18. History of endocarditis within 6 months of planned implant procedure
19. Active systemic infection requiring antibiotic therapy
20. Known hypersensitivity or contraindication to procedural or post-procedural medications (e.g., contrast solution, anti-coagulation therapy) which cannot be adequately managed medically
21. Subject unable or unwilling to take anticoagulation with warfarin for a minimum of 6 months following Tendyne valve implantation
22. Known hypersensitivity to nickel or titanium

23. Subject is undergoing hemodialysis due to chronic renal failure (≥ Stage 4 CKD)
24. Subject has pulmonary arterial hypertension (fixed PAS >70mmHg)
    a. **Note:** If PAS > 70mmHg, site must provide documentation PAS is not fixed in order to be eligible
25. FEV1 < 50% of predicted **or** < 1L
26. Subject refuses blood transfusions
27. Subject has COPD requiring continuous home oxygen therapy or chronic outpatient oral steroid use
28. Pregnant, lactating, or planning pregnancy within next 12 months
    a. **Note:** Female subjects of childbearing age should be instructed to use safe contraception (e.g. intrauterine devices, hormonal contraceptives: contraceptive pills, implants, transdermal patches hormonal vaginal devices, injections with prolonged release).
29. Currently participating in an investigational drug or another device trial that has not reached its primary endpoint
    a. **Note:** Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.
30. Subjects with non-cardiac co-morbidities that are likely to result in a life expectancy of less than 12 months

5.3 Subject Discontinuation

Each registered subject shall remain in the study until completion of the required follow-up period, however, a subject's participation in any clinical study is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but not be limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Subject lost-to-follow-up as described below
- Subject's follow-up is terminated according to **Section 5.4 - Early Termination of the Clinical**

The Sponsor must be notified of the reason(s) for subject discontinuation. The site will provide this information to the Sponsor. Investigators must also report this to their respective IRB as defined by their institution's procedure(s).

No additional follow–up will be required or data recorded from subjects once withdrawn from the study, except for the status (deceased/alive), which will be obtained from the Social Security Death Index.

However, if a subject withdraws from the study due to problems related to the safety or performance of the investigational device, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical investigation.

5.3.1 Subject Lost-to-Follow-up

If a subject misses two consecutive required follow up visits and attempts to contact the subject as detailed below are unsuccessful, then the subject is considered lost to follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following:

- A minimum of two (2) telephone calls, or e-mails, on different days over the specified follow-up window to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, a certified letter should be sent to the subject.
- If a subject misses one or more non-consecutive follow-up visits it will be considered a missed visit. The subject may then return for subsequent visits. If the subject misses two consecutive time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

Note: Contact with a general practitioner, non-study cardiologist or relative without presence of subject, or indirect documentation obtained via discharge letters will not be considered subject contact.

5.4 Early Termination of the Clinical Study

No formal statistical rule for early termination of the study for insufficient effectiveness of the investigational device is defined.

The Sponsor reserves the right to discontinue the clinical study/investigation at any stage or reduce the follow up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- Unanticipated adverse device effect (UADE) occurs and it presents an unreasonable risk to the participating subjects
- Recommendation from the Data Safety Monitoring Board (DSMB) and Steering Committee decision to terminate the study
- Further product development is cancelled
- Decision by a regulatory body

Should the clinical study be discontinued by the Sponsor, subjects will be followed per routine hospital practice, with device-related AEs being reported to the Sponsor. The investigator shall return all clinical study/investigational materials (including devices) to the Sponsor, and provide written notification to the overseeing IRB (if applicable) regarding reasons for premature termination. All applicable Clinical Investigation documents shall be subject to the same retention policy as detailed in **Section 13 – Data Handling and Record Keeping**.

5.5 Study Completion

The study will be completed when all registered subjects have either completed a 5 year follow-up visit, have reached a clinical outcome or have withdrawn from the study. Upon study completion, the Sponsor and/or its designees will notify the sites and perform study closeout visits.

All unused devices and any unused study materials and equipment will be collected and returned to the Sponsor and/or its designees. The Sponsor and/or its designees will ensure that the investigator's regulatory files are up to date and complete, that database queries are resolved, and that any outstanding issues from previous monitoring visits have been resolved.

Other items that will be reviewed during the study closeout visit may include: discussing record retention requirements, device accountability, the possibility of site audits, publication policy, and notifying the IRB of study closure.

6 SUBJECT SCREENING

6.1 Screening and Baseline Assessments

Once a patient has signed the IRB approved informed consent form, screening of a subject for possible inclusion in the study may commence. The subject's general medical eligibility must be assessed via interview and medical record review prior to subject registration, all screening and baseline assessments shall be within the windows stipulated in **Table 2**. Standard of care tests that are performed prior to obtaining informed consent can be used to determine eligibility if those tests meet the requirements of this study and are within the screening window.

The following screening/baseline imaging and assessments are to be completed prior to registration:

Images must be captured per the core lab imaging protocols for TEE, TTE, and Cardiac CT. If any imaging is not standard of care, the subject (or subject's legally authorized representative) must provide informed consent prior to obtaining any study imaging.

- TEE and TTE images to be obtained and submitted to the Sponsor **within 60 days prior to registration**. The Echocardiography Core Laboratory will review the images and confirm the subject's MR etiology, MR severity, and LVEF.
- Cardiac CT images to be obtained and submitted to Sponsor **within 120 days prior to registration**. Both the CT core laboratory and the Sponsor will review the cardiac CT images and assess annular calcification, assess subject's anatomical suitability relevant to valve sizing, and to perform procedural planning.
- Subject's coronary artery disease status should be assessed via a routine diagnostic coronary angiogram, if clinically indicated. Any revascularization treatment should be administered prior to subject registration as outlined in the subject eligibility criteria in **Section 5.2.**

Screening/Baseline Assessments within 90 Days Prior to Registration

- Medical history must be obtained, including review of subject's medical records. This review will include history of co-morbidities and co-existing medical conditions; previous cardiovascular and peripheral vascular interventions; symptoms and diagnosis of mitral insufficiency.
- A physical exam including an assessment of subject's cardiac status and sitting vital signs.

- Blood tests performed, including: BNP or NT-proBNP, plasma free hemoglobin, serum creatinine, International Normalized Ratio (INR), Creatine kinase-MB (CK-MB) and Troponin (Type I or T)
- A 12-lead electrocardiogram (ECG)
- Concomitant cardiovascular medications must be documented and may include the following: anticoagulants, antiplatelet agents, ACE inhibitors, angiotensin II receptor blockers or inhibitors, angiotensin receptor-neprilysin inhibitor, I_f channel inhibitor, beta blockers, calcium channel blockers, diuretics, digitalis preparations, and any medication that may increase the risk of bleeding
- Modified Rankin Scale must be assessed
- NYHA Functional Classification must be assessed
- Canadian Cardiovascular Society (CCS) grading of angina pectoris must be assessed
- KCCQ questionnaire must be completed by the subject;
    - **Note:** To minimize bias and undue influence, the QoL questionnaire will be completed by the subject, unless the subject is unable to complete the questionnaire on their own (in such cases a note to file must be completed to document the inability of subject to complete the questionnaire on their own).
- Administer the 6MWT
- Subject is evaluated by the local site heart team to confirm they have been adequately treated per applicable standards, including for coronary artery disease (e.g., revascularization), left ventricular dysfunction (e.g., cardiac resynchronization therapy)
- Surgical risk assessment - the local site heart team shall review subject's medical information to determine if subject is not a suitable candidate for conventional surgical treatment due to degree of MAC present and will likely benefit from transcatheter valve implantation

6.2 Notification by Sponsor of Subject Screening Pass or Fail

Prior to subject being scheduled for the procedure, the Sponsor will review submitted screening and baseline medical information, TTE, TEE, and CT images to confirm anatomic and procedural suitability of the subject for the Tendyne device. Sponsor will notify Investigator when subject passes or fails the screening review.

7 TREATMENT AND PRE-DISCHARGE VISITS

Subjects that pass the screening review will undergo a procedure to implant the Tendyne device.

7.1 Concomitant Procedures

Pre-procedural planning and assessment of MAC may determine that concomitant mitral annulus valvuloplasty is required to ensure mobility of calcification prior to Tendyne valve implantation. In such cases, standard institutional techniques may be used.

7.2 Tendyne Procedure

The valve should be implanted with sterile techniques using primarily TEE guidance. In addition, TTE and fluoroscopic imaging modalities may be used.

Implantation of the valve will be performed by the local site heart team, with an experienced cardiac surgeon trained to perform transapical procedures and jointly with an experienced interventional cardiologist and echocardiographer. Sponsor personnel will be available for procedural support for all Tendyne cases. For a comprehensive description of the Tendyne procedure, refer to the Tendyne Mitral Valve System IFU.

Note: Prior to performing the procedure, all investigators must undergo training by the Sponsor on the Tendyne System and on the CIP. In addition, all investigators must read and understand the IFU that accompanies the device.

Subjects will be prepared for the procedure as per the institution's standard practice for a transapical therapeutic intervention and TEE.

The subject must be on anticoagulant/antiplatelet therapy appropriate for transapical therapeutic interventions. Activated clotting time (ACT) is to be maintained at >300 seconds for the duration of the procedure.

7.2.1 Tendyne Procedure - Access

An 8 Fr. sheath is placed in the apex at the orthogonal access location determined by CT. A 7 Fr. Fogarty catheter is then inserted, leading with the balloon until the mitral annulus is crossed. A 0.035 standard J wire is then advanced into either a pulmonary vein or coiled in the atrium.

Once the J wire is in place, the Fogarty catheter is used to determine a chord-free path has been achieved by retracting/advancing over the wire. Once an entanglement free pathway has been achieved, the Fogarty balloon is deflated and removed. The 8 Fr. sheath is also removed and the Tendyne sheath is inserted.

7.2.2 Tendyne Procedure - Device Delivery

The delivery system is inserted into the Tendyne sheath and aligned for pre-planned rotation of the valve. Both the sheath side port and the delivery system are de-aired and the flush is open until the valve is advanced to the tip of the delivery sheath.

Clocking is performed in the 3D enface view. The valve is then incrementally advanced until the A2 portion of the Tendyne valve is clocked to the center of the "D" shape of the mitral annulus. Using an X-plane echo image, the Tendyne valve is seated intra-annularly and the deployment of the valve is completed.

When the valve is fully deployed, a full echo assessment is made to evaluate PVL, LVOT obstruction and MR resolution. At this point, the valve can be recaptured and can be adjusted if needed. When valve position has been optimized, the delivery system is removed.

7.2.3 Tendyne Procedure - Tensioning

Tension is adjusted using the apical pad tool to attain proper seating of the valve for mechanical stability and optimal paravalvular sealing. Once stability is achieved and valve function is determined to be acceptable, the instrument is removed and the apical pad is fastened to the tether.

Note: The valve can be retrieved at any point during delivery and tensioning up to the point when the tether is cut just prior to surgical site closure.

7.2.4 Tendyne Implant Identification Card

At discharge, each subject implanted with a Tendyne device must be provided with an Implant Identification Card. An Implant Identification Card is included in the package with each Tendyne Mitral Valve System. The subject should be instructed to keep this Implant Identification Card on their person at all times. The serial number of the implanted Tendyne device should be recorded on the Implant Identification Card.

7.3 Procedural Data Requirements

The following procedural information should be recorded on the appropriate eCRF(s) after implant or attempted implant of the Tendyne device.

7.3.1 12-Lead ECG

A 12-lead ECG will be performed pre- and post-valve implant. If prolonged hospitalization occurs after the procedure, the ECG may be collected within 10 days after the index procedure.

7.3.2 Intraoperative Hemodynamic Measurement

During the procedure to implant the Tendyne device, subjects will undergo right-heart catheterization to measure hemodynamics intraoperatively. Cardiac output (CO), pulmonary arterial (PA), aortic and right arterial (RA) pressures will be measured before and after the valve placement via the right heart catheter. LV pressures should be measured via a pigtail catheter.

7.3.3 Intraoperative Angiography

Per investigator discretion, subjects may undergo left-heart catheterization with radiographic imaging before and after the Tendyne valve placement to assess the LV and mitral valve competence. Care must be taken to minimize the amount of contrast media injected into subjects with compromised renal function. Therefore, left ventriculogram procedures described in this protocol are optional.

Tendyne will provide specific instruction on intraoperative imaging requirements as part of investigator training.

7.3.4 Additional Procedural Data Collection

In addition to the intraoperative imaging and hemodynamic measurements, the following procedural information should be recorded:

- General procedure information
- Treatment and Control group implant information
- Laboratory and clinical tests
- Antiplatelet/Anticoagulation medications
- Concomitant cardiovascular medications
- Fluoroscopy duration
- Adverse events, if applicable

- Protocol deviations, if applicable
- Device deficiency, if applicable

7.3.5 Immediate Post-Operative Care

Blood pressure is to be closely monitored and maintained below 135 mmHg systolic during the immediate post-operative period, if possible. The subject's ACT should also be monitored in accordance with hospital protocols.

Subjects will receive standard post-cardiac transapical care as judged appropriate by the investigator.

7.3.6 Anticoagulation Regimen

Subjects receiving the Tendyne device are required to be on anticoagulation therapy, warfarin, with a target INR range of 2.5 to 3.5, for a minimum of six months. A single antiplatelet therapy (aspirin or alternate agent) should also be administered immediately after the procedure and may be continued indefinitely.

Notes:

- During the period of required anticoagulation as stated above, a subject's anticoagulation regimen may be altered or stopped only if medically indicated, however, it should be restarted as soon as possible per physician's discretion.
- For subjects who receive the Tendyne device, a TTE must be performed between 60 and 120 days after anticoagulation stoppage.
    - If the TTE indicates increased gradients (e.g. mitral valve gradient > 6mmHg) or leaflet mobility concerns are identified, a gated CT (4D with contrast) must be performed to evaluate leaflet thrombosis resulting in hypoattenuated leaflet thickening or motion.
        - For subjects with renal insufficiency, a TEE must be performed

7.3.7 Pre-Discharge

Pre-discharge data collection is to be performed within 72 hours prior to discharge from implanting hospital. Pre-discharge data requirements include:

- A physical exam including an assessment of subject's cardiac status and sitting vital signs
- Concomitant cardiovascular medications
- 12-lead ECG
- Laboratory and clinical tests
- Adverse events, if applicable
- Protocol deviations, if applicable
- Device deficiency, if applicable

8 FOLLOW-UP FOR EVALUATION OF SAFETY AND EFFECTIVENESS

8.1 Clinical Follow-up

Follow-up visits are required at 30 days, 3 months, 6 months, 1 year, and then annually through 5 years (**Table 2**); visits will be calculated from the date of the index procedure. Follow-up assessments can be performed at any point in the window, and should be conducted, whenever possible, by the same individual who performed the baseline tests. For a complete schedule of study assessments occurring at each visit, refer to **Appendix III: STUDY Assessment and Follow-up Schedule**.

Subjects should be followed at the investigational site where the subject was registered, and may be followed at another investigational site only with prior agreement from both the new site's Principal Investigator and approval from the Sponsor.

All registered subjects should continue to be monitored and treated per applicable standards of care consistent with the subject's condition. Subjects should be followed by the site investigators at all scheduled follow-up visits and be evaluated for device function.

Note: If a subject has an unsuccessful Tendyne device implant, they should remain in the study and continue to be followed per the study follow-up schedule.

8.2 30 Day, 3 Month, 6 Month, and Annual Visits

Subjects should continue to take baseline medications as clinically (medically) necessary. Required tests and procedures outlined below must be completed. All visits and tests must be completed within the visit window specified in **Table 2**, even if the subject is in hospital.

- A physical exam including an assessment of subject's cardiac status and sitting vital signs
- Concomitant cardiovascular medications assessment
- NYHA Functional Classification assessment
- Blood tests performed, including: BNP or NT-proBNP, plasma free hemoglobin, serum creatinine, INR, CK-MB and Troponin (Type I or T)
- TTE
- 12-lead ECG
- Cardiac CT (**Note:** Required at 30 day visit – an additional CT may be required if anticoagulation regime is stopped, refer to **Section 7.3.5 - Immediate Post-Operative Care**)
- KCCQ questionnaire
- 6-Minute Walk Test
- Modified Rankin Scale (Assessment to be completed after onset of stroke)
- Assess and record adverse events
- Assess and record protocol deviations

Echocardiography images (TTE) obtained at each follow-up visit should be submitted in a timely manner. Throughout the course of the study, the Echocardiography Core Lab may provide feedback to sites regarding quality of images obtained.

During the follow-up period, if a subject requires a cardiac procedure (e.g. MV surgery, permanent LVAD, heart transplant) which may or may not result in explant of the Tendyne device, the subject will remain in the study and continue to be followed.

Every attempt must be made to ensure study subjects do not miss a scheduled follow-up visit. If a subject is unable to complete a visit, the site may attempt to contact them remotely to document their status (e.g., alive) and to administer study questionnaire (KCCQ). This should only be performed in rare instances and the Sponsor should be notified of such instances in advance.

Subjects who do not complete a required follow-up visit will be documented as having a missed visit and a protocol deviation (refer to **Section 12.5 - Deviations from Clinical Investigation Plan**) will be completed. The investigator will keep a record of documented follow-up attempts in the subject's file.

Table 2. Follow-up Schedule and Windows for Study Subjects

Follow-Up Visit	Window Start Day	Target Day	Window Close Day	Follow up Method
Pre-Discharge	Within 72 hours of discharge	Discharge date	N/A	In hospital or Site visit
30 Days (-3 /+14 days)	27	30	44	Site visit
3 Months (±30 days)	60	90	120	Site visit
6 Months (±30 days)	152	182	212	Site visit
1 year (±30 days)	335	365	395	Site visit
2 years (±30 days)	701	731	761	Site visit
3 years (±45 days)	1051	1096	1506	Site visit
4 years (±45 days)	1416	1461	1506	Site visit
5 years (±45 days)	1781	1826	1871	Site visit
Follow-up visit dates are calculated from the date of the index procedure				

9 ADVERSE EVENTS

9.1 Definitions / Types of Events

9.1.1 Adverse Event

An adverse event (AE) is 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.

This definition includes events related to the investigational medical device and the procedures involved. For users or other persons, this definition is restricted to events related to the investigational medical device.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Note: Unchanged, chronic conditions are not adverse events and should not be recorded on the eCRF Adverse Event form. Pre-existing conditions that have not worsened are not considered AEs.

9.1.2 Serious Adverse Event

If the AE meets any of the criteria below, it is regarded as a serious adverse event (SAE).

a) Death,

b) Serious deterioration in health that either:

1) Resulted in a life-threatening illness or injury, or

2) Resulted in a permanent impairment of a body structure or a body function, or

3) Required in-patient hospitalization or prolongation of existing hospitalization, or

4) Resulted in medical or surgical intervention to prevent life threatening illness or Injury or permanent impairment to a body structure or a body function

c) Fetal distress, fetal death or a congenital abnormality or birth defect

Note 1: This includes device deficiencies that might have led to a serious adverse event if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

Note 2: A planned hospitalization for pre-existing condition, or a procedure required by the CIP, without a serious deterioration in health, is not considered to be a SAE. Such events will not count toward the primary endpoint.

9.1.3 Anticipated Adverse Events

Table 3 summarizes the anticipated events that have been identified as possible complications from the Tendyne Mitral Valve System. Please also refer to the list of anticipated events in the Tendyne Mitral Valve System IFU.

Table 3. Anticipated Adverse Events

Adverse foreign body response	Foreign body response
Adverse reaction to anesthesia	Heart Failure, new or worsening
Allergic reaction	Hematoma
Anemia	Hemolysis
Annular dissection	Hypotension
Aortic insufficiency	Infection / Sepsis
Atrial or ventricular injury	Leaflet, chordal, papillary or ventricular rupture (resulting from mitral valvuloplasty, if performed)

Atrial Septal Defect (resulting from mitral valvuloplasty, if performed)	Liver failure
Bioprosthetic valve dysfunction	Mitral valve injury
Bleeding complications	Mitral valve prolapse / stenosis
Blood loss which may require transfusion	Myocardial infarction
Cardiac arrest	Obstruction
Cardiac arrhythmia, atrial or ventricular	Paravalvular leak
Cardiac perforation	Pain
Conduction defect with or without need for pacemaker	Pericardial effusion / tamponade
Damage to cardiac tissue and/or structures	Pleural effusion
Death	Pulmonary embolism
Decreased LV function and/or cardiac output	Pulmonary hypertension
Device embolism	Renal insufficiency or failure
Device erosion, migration or malposition	Respiratory difficulty, insufficiency, or failure
Device thrombosis	Stroke or transient ischemic attack
Embolism (air, blood clot, tissue, calcium, etc.)	Tear or damage to device
Endocarditis	Vascular and access-related complications
Esophageal irritation, stricture, or perforation	Worsening of mitral regurgitation
Fever	

Normal post-operative sequelae or expected post-operative events do not need to be recorded as AEs unless they require physician prescribed pharmacologic and/or surgical intervention outside of the acute peri-operative period. A few common examples of normal post-operative sequelae or expected post-operative events include access-site pain, bruising, and events related to general anesthesia.

9.1.4 Unanticipated Adverse Device Effect (UADE)

Unanticipated Adverse Device Effect (UADE) refers to any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, the Tendyne System, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the CIP, or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

9.2 Device Deficiency

Device deficiency (DD) is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, safety or performance, such as malfunction, misuse or use error and inadequate labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended.

9.3 Device / Procedure Relationship

Determination of whether there is a reasonable possibility that the device, the implant procedure, or the patient condition (pre-existing condition) caused or contributed to an AE is to be **assessed by the investigator** and recorded on the appropriate eCRF. Additionally, the probability of relationship to the device or procedure should also be categorized. This determination should be based on assessment of temporal relationships, evidence of alternative etiology and

medical/biologic plausibility. Definitions for the determination of device- and/or procedure-relatedness include:

Not Related: Exposure to the device/procedure has not occurred (no temporal relationship), or the occurrence of the adverse event is not reasonably related in time, or there is a definite alternative etiology, or it is biologically implausible for the adverse event to be related to the use of the device.

Possibly Related: Exposure to the device/procedure has occurred; and it cannot be ruled out that the device/procedure is not responsible for the adverse event.

Definitely Related: Exposure to the device/procedure has occurred or the adverse event is related in time; and the device/procedure is definitely responsible for the adverse event.

9.4 Adverse Event / Device Deficiency Reporting

9.4.1 AE Monitoring

The investigator will monitor the occurrence of adverse events for each subject during the course of the study. Event description, date of onset, severity, duration, and relationship to device and/or procedure will be recorded on the appropriate eCRF by the investigator or designee.

For subjects implanted with the Tendyne device who exhibit signs or symptoms suggestive of valve dysfunction, a TTE must be performed. If evidence of valve dysfunction is detected via TTE, a CT (or TEE) must be performed.

For this clinical investigation, all AEs will be collected on each subject from the time of study registration through study completion. A summary of AE reporting requirements is further described in this section and summarized in **Table 4**.

9.4.2 SAE Reporting to Sponsor and IRB

SAEs may be reported by the subject, observed by the investigator, or documented in medical records and must be reported to the Sponsor on the Adverse Event eCRF. Additional information related to previously reported SAEs should be updated within the eCRF as soon as the information has been reviewed and verified by the investigator.

The investigator should report all SAEs to the Sponsor as soon as possible but no later than 3 calendar days from the day the study personnel became aware of the event or as per the investigational site's local requirements, if the requirement is more stringent than those outlined**.**

The investigator will further report the SAE to the local IRB according to the institution's IRB reporting requirements.

9.4.3 UADE Reporting to Sponsor and IRB

Tendyne Holdings, Inc., requires the investigator to report any UADE to the sponsor within 3 calendar days of the investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB per requirements.

The Sponsor is required to report the findings of the investigation of any UADE to the FDA and the IRB as soon as possible, but in no event later than 10 working days after knowledge of the event.

9.4.4 Device Deficiency

The investigator should report all device deficiencies related to the Tendyne device to the Sponsor as soon as possible but no later than three (3) calendar days from the day the study personnel becomes aware of the event or as per the investigative site's local requirements if the requirement is more stringent than those outlined. Device deficiencies should be reported to the IRB per the investigative site's local requirements.

The device, if not successfully implanted in the subject, should be returned to Tendyne Holdings, Inc.

9.4.5 Investigational Site AE Reporting Requirements to Sponsor

Investigators are responsible for preparation and submission to the Sponsor of all reportable AEs and DDs identified in the CIP. Adverse event reporting requirements are included in **Table 4**. All reports are subject to inspection and to the retention requirements described in **Section 13.4.1 Investigator Records**.

Table 4. Investigational Site AE Reporting Requirements to Sponsor

Event	Investigational Site	Reporting timelines
AE	All Sites	AEs (not including normal or expected post-operative sequelae) must be reported as soon as possible after study personnel becoming aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.
SAE	All Sites	SAEs must be reported no later than 3 calendar days from the day the study personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.
UADE	All Sites	UADEs must be reported no later than 3 calendar days from the day the study personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.
Device Deficiency	All Sites	DDs must be reported no later than 3 calendar days from the day the study personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

9.4.6 UADE Reporting to FDA by the Sponsor

The Sponsor will report UADEs to the FDA per IDE regulations (21 CRF 812.150(b)(1)).

9.5 Adjudication of AEs

All SAEs and device or procedure related AEs reported during the study will be reviewed and adjudicated by the CEC. Once adjudicated, final reporting of adverse events will be based upon

CEC adjudication. Refer to section **12.11.3 Clinical Events Committee** for the CEC's role and responsibility.

10 STATISTICAL METHODS

10.1 Sample Size Considerations

This is a feasibility study and no formal statistical hypotheses are to be tested for any of the study endpoints. Data collected from this study will provide preliminary device safety and effectiveness data for the use of the Tendyne Mitral Valve System in subjects with mitral regurgitation and mitral annular calcification. Descriptive statistics will be reported for the study data primarily. Inferential statistical analysis will be conducted in an exploratory manner. The sample size for this study is planned to be up to 30 at up to 10 investigational sites.

Statistical methods for the study are outlined below. Additional details will be provided in a Statistical Analysis Plan (SAP).

10.2 Data Analysis Plan

10.2.1 General Principles

All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.4, SAS Institute Inc. Cary, NC) or other widely accepted statistical or graphical software.

Descriptive statistics will be used to present the data and to summarize the results. Discrete variables will be presented using frequency distributions and cross tabulations. Continuous variables will be summarized by presenting the number of observations (N), mean, standard deviation, median, minimum, and maximum values.

In general, data for all study subjects combined will be presented. The primary analysis for all baseline characteristics and study outcomes will include all available data for all enrolled subjects. Individual data will be presented in subject listings.

Summaries of the following endpoints present the number and percentage of unique subjects with an event, unless specified otherwise: protocol deviations; subject status; study medications; adverse events. Thus, multiple occurrences of the same event are counted only once per subject, unless specified otherwise.

10.2.2 Subject Disposition

The number and percentage of subjects screened, screen failure, enrolled, treated, and completed will be summarized. Screen failure percentage is calculated from number of screened subjects and other percentages are calculated among number of enrolled subjects. A subject will be considered enrolled once they have signed the study patient informed consent form. Subjects who discontinue from the study will be summarized with reason and listed by their primary reason for discontinuation.

10.2.3 Study Conduct

Protocol deviations from the investigation plan will be summarized by deviation type as well as total. Protocol deviations by investigational site will also be provided.

10.2.4 Analysis Samples

The primary analysis sample will be based on the principle of intention-to-treat (ITT). All statistical analyses in this study will be "intent to treat" with enrolled subjects with attempted device implant included in the analysis. As-treated analysis will also be conducted, which includes subjects with study device remain implanted.

10.2.5 Analysis of Population Demographics, Baseline and Procedural Characteristics

Descriptive statistics will be summarized for baseline demographics, medical history, baseline disease characteristics, echocardiography core laboratory data, and procedural characteristics.

10.2.6 Analysis of Primary Safety Endpoint

For the composite primary safety endpoint, the proportion of subjects with device success and free from device- and/or procedure-related SAEs (per CEC adjudication) at 30 days, along with exact 95% confidence interval (CI), will be summarized. The summaries for each individual safety data point will also be provided.

10.2.7 Analysis of Clinical Endpoints

Definition of clinical endpoints are described in **Section 3.2**.

For composite endpoints, i.e., technical success, patient success, and device success, the number and percentage of subjects with success will be summarized. Descriptive statistics for components of each endpoint will also be provided.

For continuous variables (e.g., KCCQ scores and 6MWT distances), results will be summarized with the numbers of observations, means, standard deviations, minimums, maximums, and 95% confidence intervals. Change from baseline will be included using these same descriptive statistics.

For categorical variables such as mortality and NYHA classification, results will be summarized with subject counts and percentages/rates, and with 95% confidence intervals.

10.2.8 Subgroup Analysis

Sub-group analyses on performance, effectiveness, and safety endpoints are planned. These analyses are exploratory in nature and may include certain baseline demographics, disease characteristics, echocardiography parameters, and procedural characteristics selected by investigators and sponsor aimed at a comprehensive understanding of device performance and safety profile.

10.2.9 Handling of Missing Data

Primary analyses will consist of all available data evaluated under ITT principles, referred to in International Conference on Harmonization module E9 (Statistical Principles for Clinical Trials)

as the full analysis set. Consequently, data will only be absent from analyses of study outcomes in the event that they were not available for collection.

In general, missing values in any of the endpoints will not be inputted when summarizing these endpoints using descriptive statistics.

11 DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

The investigator/institution will permit and assure direct access to source data/documents (e.g., hospital/clinic/office charts, catheterization reports, laboratory results) in order for clinical investigation-related monitoring, audits, IRB review and regulatory inspections to be performed.

Subjects providing informed consent are agreeing to allow Sponsor and/or its designee access and copying rights to pertinent information in their medical records concerning their participation in this feasibility study.

The investigator will obtain, as part of the informed consent, permission for Sponsor monitors and designees, including auditors, or regulatory authorities to review, in confidence, any records identifying the subjects in this study. This information may be shared with regulatory agencies; however, per relevant confidentiality and privacy rules (HIPAA), the Sponsor and its designees will not otherwise release the subject's personal, private and protected health information.

12 QUALITY CONTROL AND QUALITY ASSURANCE

To ensure the study is conducted in accordance with the CIP and that both the Sponsor and investigational sites are in compliance, proper quality control and assurance procedures will be followed in this study. These controls include the establishment of training, monitoring, support of quality audits and study committees.

12.1 Selection of Clinical Sites and Investigators

The Sponsor will select investigational sites after review of a site assessment and the qualifications of the proposed investigators at the site. Each site will be required to have a Principal Investigator (either an interventional cardiologist or cardiothoracic surgeon) and a multidisciplinary team. The multidisciplinary team will consist of a minimum of the following:

- One (1) Interventional Cardiologist
- One (1) Cardiothoracic Surgeon
- One (1) Echocardiographer

Investigators must be qualified by education, training, and experience to assume responsibility for the proper conduct of human subject research. Investigators must use best practice guidelines to guide the management of subjects. Investigators must provide evidence of such qualifications through current CVs and other relevant documentation requested by the Sponsor, IRB, and regulatory agencies.

Investigators at the site are responsible for being familiar with the use of proposed investigational procedures, techniques and products, as described in current literature, product information, and other available sources. As part of their qualification to conduct the study, investigators are responsible for ensuring that investigational site resources are available and that the appropriate population of subjects can be identified/treated.

12.2 Clinical Investigation Plan Amendments

Approved CIP amendments will be provided to the investigators by the Sponsor prior to implementation. The Principal Investigator is responsible for notifying the IRB of the amendment (administrative changes) or obtaining IRB's approval of the amendment (changes in subject care or safety), according to the instructions provided by the Sponsor.

Acknowledgement/approval by the IRB of the CIP amendment must be documented in writing prior to implementation. Copies of this documentation must also be provided to the Sponsor.

12.3 Study Training

12.3.1 Site Training

Investigators and site clinical study personnel are required to attend Sponsor training sessions, which may be conducted at an investigator's meeting, a Site Initiation Visit (SIV) or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of investigators or site clinical study personnel will include, but is not limited to, the CIP requirements, investigational device usage, eCRF completion and study personnel responsibilities.

All investigators and site clinical study personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Investigator/study personnel must not perform any study-related activities that are not considered standard of care at the site prior to signing the training log.

12.3.2 Training of Sponsor's Designees or Vendors

All Sponsor partners and/or designated vendors (e.g., Echocardiography Core Laboratory) responsible for any function in the conduct of the clinical study will be trained to the CIP and other study documents (as appropriate).

12.3.3 Training of Sponsor's Monitors

Sponsor and/or designated monitors will be trained to the CIP, eCRFs and investigational device usage (as appropriate). Documentation of this training will be according to written procedures.

12.4 Monitoring

The Sponsor and/or designee will monitor the study over its duration according to the monitoring plan and relevant standard operating procedures.

12.4.1 Designated Monitors

Study monitors are individuals who are designated to oversee the progress of a study. These individuals are appropriately trained and qualified to monitor the progress of a clinical study. The study Sponsor may designate additional monitors at any time during the study. To request information on the person(s) responsible for monitoring activities, contact the Sponsor at the following address:

Abbott Global Clinical Operations
5050 Nathan Lane North
Plymouth, MN 55442 USA

12.4.2 Monitoring Visits

Scheduled visits to an investigational site may occur at the following times: prior to the start of the clinical study (pre-site qualification visit), at initiation of the study (at first implant or shortly thereafter), interim visits throughout the clinical study as required, and upon completion of the clinical study as outlined in the study monitoring plan.

12.5 Deviations from Clinical Investigation Plan

The investigator will not deviate from the CIP for any reason without prior written approval from Sponsor except in cases of medical emergencies, when the deviation is necessary to protect the rights, safety and well-being of the subject or eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing. All deviations must be reported to the Sponsor. For subject-specific deviations from the CIP, a deviation eCRF will be completed. The occurrence of CIP deviations will be monitored by the Sponsor for evaluation of investigator compliance to the CIP and regulatory requirements and dealt with according to written procedures. Investigators will inform their IRB of deviations in accordance with their specific reporting policies and procedures.

In the event of repeated non-compliance, the Sponsor, or designee, will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the investigator and/or delegate
- Telephoning the investigator and/or delegate
- Corresponding with the investigator and/or delegate

Repeated non-compliance with the signed agreement, the CIP or any other conditions of the study may result in further escalation in accordance with the Sponsor's written procedures including securing compliance or, at its sole discretion; Sponsor may terminate the investigator's participation in the study.

12.5.1 Deviations with Expedited Reporting Requirements

For the following types of protocol deviations (per 21 CRF 812.150), an investigator is required to notify the Sponsor and the IRB within five (5) business days of the deviation.

- Emergency deviation from the CIP (a deviation to protect the life or physical well-being of a subject in an emergency).
- Failure to obtain informed consent.

Notification to the Sponsor and/or the IRB should be documented and maintained in the clinical trial file at the site and at Tendyne Holdings, Inc.

12.5.2 Non-Critical Deviations

Protocol deviations which do not have the urgency associated with expedited notification or prior Tendyne/IRB approval (as discussed in the above paragraphs) will be reported upon discovery, such as during completion of eCRFs or during a monitoring visit.

12.6 Review of Study Imaging Assessments

MR severity, MR etiology, localization of MAC, left ventricular dimensions, along with other measures, will be assessed by Echocardiography and Cardiac CT Core Labs at baseline and during follow-up.

12.7 Safety and Effectiveness Monitoring

All AEs will be reviewed by Tendyne Holdings, Inc., (and/or designee). SAEs and all device or procedure related AEs will be adjudicated by an independent CEC.

12.8 Follow-up Compliance

The Sponsor will work with investigational sites to maintain high follow-up compliance. The following strategies may be used for increasing compliance:

- During site initiation and training, the Sponsor will emphasize the importance of subject follow-up to the site, and that the site should communicate this importance to each subject.
- Sites will be informed to promptly reschedule any missed subject visits, and to reinforce the necessity of a follow-up visit.
- If a scheduled visit is missed due to subject illness, transportation issues, or travel, the site will be advised to:
    - Reinforce the necessity of follow-up visits;
    - Identify alternate transportation sources, and involve the Sponsor if necessary
- Sites will be instructed to ask subjects who withdraw during the study to provide the reason for withdrawal and ask them if the investigator may contact them at the end of the study follow-up.
- Subject follow-up rates will be monitored closely so that problems may be identified and addressed as soon as possible.
- For subjects who are lost-to-follow-up, sites may be requested to examine the Social Security Death Index to determine subject status (only the status will be sent to Sponsor, not any subject identifying information).

12.9 Quality Assurance Audit

The Sponsor may conduct periodic Quality Assurance audits (on-site audits) at various investigational sites. A sponsor representative, or designee, may request access to all study records, including source documentation, for inspection and duplication during a Quality Assurance audit. The investigator and research coordinator must be available to respond to reasonable requests and queries made during the audit process.

12.10 Sponsor Support for Regulatory Body Inspection

In the event that an investigator is contacted by a Regulatory Agency regarding this feasibility study, the Investigator will notify the Sponsor immediately. The investigator and research coordinator must be available to respond to reasonable requests and inspection queries made during the inspection process. The investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current study (e.g., Form FDA 483, Inspectional

Observations, and warning letters). As necessary, the Sponsor may provide any assistance in preparing and/or responding to regulatory inspections.

12.11 Committees

12.11.1 Publications Committee

The Publication Committee will oversee and guide the ongoing scientific presentation and publication activities for the MAC feasibility study. The Publication Committee will determine policies and strategies regarding presentations and/or publications arising from study generated data. The committee will also review and approve all external requests for accessing study-related data and strategies for presentation and publication. The composition, guiding policies, and operating procedures governing the Publication Committee are described in detail in a separate Publication Committee Charter.

12.11.2 Data and Safety Monitoring Board (DSMB)

The DSMB is an independent multidisciplinary group that is restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. The composition of the DSMB, guiding policies, and operating procedures are described in detail in a separate DSMB Charter.

12.11.3 Clinical Events Committee (CEC)

The CEC is an independent adjudication body comprised of a multi-disciplinary team of qualified physicians who are not investigators in the study. The CEC will be responsible for adjudicating serious adverse events and device or procedure related adverse events reported in the study. The composition, guiding policies, and operating procedures are defined in a separate CEC Charter.

13 DATA HANDLING AND RECORD KEEPING

Clinical data will be collected pre-registration during the screening period to establish subject eligibility at baseline, during the pre- and post- procedural hospital stay, and during the follow-up period for all subjects.

All eCRF data collection will be performed through a secure web portal and all authorized personnel with access to the electronic data capture (EDC) system must use an electronic signature access method to enter, review or correct data. Electronic signature procedures shall comply with the CFR Title 21 Part 11 and the ICH Guidelines for Good Clinical Practice. Passwords and electronic signatures will be strictly confidential.

All eCRF data will be downloaded from the EDC system and reformatted for analysis into a data structure acceptable to Tendyne. The data will be subject to consistency and validation checks within the EDC system and to supplemental validation following download.

At the conclusion of the study, completed eCRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be archived for each investigational site and a backup copy archived with Tendyne.

For the study duration, the investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical trial progress records, laboratory reports, eCRFs, signed ICFs, device accountability records, correspondence with the IRB and study

monitor/Sponsor, AE reports, and information regarding subject discontinuation or completion of the study.

13.1 Data Management

The Sponsor's data management group (or designee) will perform all data management activities, including data review, database cleaning, and issuing and resolving data queries, and documentation of the systems and procedures to be used. The majority of these activities will occur at the following locations:

Tendyne Holdings, Inc.
177 County Road B East
St. Paul, MN 55117

13.2 Source Documentation

IDE regulations (21 CFR 812) and GCPs require that the investigator maintain information in the subject's medical records that corroborates data collected on the eCRFs. Throughout the clinical study duration, the sites' investigators (or designees as indicated on the delegation of authority log) will maintain complete and accurate documentation including but not limited to medical records, clinical study progress records, laboratory reports, eCRFs, signed ICFs, device accountability records, correspondence with the IRB and clinical study monitor or Sponsor, AE reports, and information regarding subject discontinuation or completion of the study. Any source documentation (procedure reports, imaging studies, lab reports, death certificates, etc.) that is sent to the Sponsor, reviewing committees, or the core lab, should have all subject identifiers removed and replaced with the subject number. In order to comply with GCP and regulatory requirements, the following information should be included in the subject record, at a minimum, and if applicable to the investigation:

- Medical history/physical condition of the subject before involvement in the study sufficient to verify CIP entry criteria.
- Dated and signed notes on the day of entry into the study referencing the Sponsor, CIP number, subject ID number and a statement that informed consent was obtained.
- Dated and signed notes from each subject visit (for specific results of procedures and exams).
- Adverse events reported and their resolution including supporting documents such as discharge summaries, imaging, ECGs, and lab results; including documentation of site awareness of SAEs and of investigator assessment of device/procedure relationship.
- Study required laboratory reports and 12-lead ECGs, signed and dated for review and annotated for clinical significance of out of range results.
- Notes regarding CIP required and/or prescription medications taken during the study (including start and stop dates).
- Subject's condition upon completion of or withdrawal from the study.
- Any other data required to substantiate data entered into the eCRF.

13.3 Electronic Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the CIP and eCRF completion. eCRF data will be collected for all subjects that are enrolled into the study.

13.4 Record Retention

The Sponsor will archive and retain all documents pertaining to the study as per the applicable regulatory record retention requirements.

The investigator will maintain all CRFs, essential study documents, and any source documentation that supports data collected on study subjects, in compliance with ICH/GCP guidelines and their local IRB requirements. Documents must be retained for at least two (2) years after the last approval of marketing application, or until at least two (2) years have elapsed since the formal discontinuation of the clinical investigation of the product. These documents will be retained for a longer period of time by agreement with the Sponsor or in compliance with other regulatory requirements.

The investigator will take measures to ensure essential documents are not accidentally damaged or destroyed. If for any reason the investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility. In such an event, the Sponsor must receive written notification of this custodial change. When these documents no longer need to be maintained, it is the Sponsor's responsibility to inform the investigator.

13.4.1 Investigator Records

Investigators will maintain the following complete, accurate, and current records relating to the investigator's participation in this study including, but not limited to:

- Study-related correspondence with another investigator, an IRB, the Sponsor, monitors, subjects, or regulatory agencies, including required reports that relate to this study
- Device Accountability log
- Delegation of Authority log
- Subject's case history records
- Signed informed consent form
- Signed HIPAA authorization (if separate from the consent form)
- Relevant subject complaints
- Protocol required CRFs and data sets
- Documentation of the dates and reasons for any study deviation
- Clinical investigation plan and amendments
- Study personnel training records
- Signed investigator agreement and clinical study reimbursement agreement
- Current curriculum vitae (current by address)
- Current medical license (current by date)

- Financial disclosure
- IRB approvals, renewals and correspondence

If records are stored elsewhere, a pointer will be placed in the investigational site file explaining where the records are located.

13.4.2 Sponsor Records

The Sponsor will maintain the following records:

- Study-related correspondence (including correspondence with regulatory authorities and IRBs) that pertains to the investigation, including IRB approval letters
- Records of device shipment and device disposition (e.g., shipping receipts, materials destruct records)
- Report of prior investigations summary
- Copy of signed investigator agreement, clinical study reimbursement agreement, financial disclosure information, medical license and curriculum vitae (CV) of investigators
- Training documentation of all research center staff personnel as well as Sponsor study personnel
- eCRFs submitted by investigator and center-specific samples of ICFs and protocols
- Progress reports
- Final clinical study report
- Records of adverse device effects (anticipated and unanticipated) and device deficiencies
- All other records required by FDA according to 21CFR812.140(b)(4), and any other regulatory/competent authority requirements.

Sponsor Reports

Sponsor is responsible for preparation and submission of the following reports as identified in **Table 5**.

Table 5. Description and Submission Requirements of Sponsor Reports

Report	Submit to	Description
UADE	FDA, IRB, PIs	Notification within 10 working days (21CFR 812.150(b)(1))
Withdrawal of IRB approval	FDA, IRB, PIs	Notification within 5 working days (21CFR 812.150(b)(2))
Withdrawal of FDA approval	IRB, PIs	Notification within 5 working days (21CFR 812.150(b)(3))
Current investigator list	FDA	Submitted at 6 month intervals, a current list of the names and addresses of all investigators participating in the investigation (21CFR 812.150(b)(4))
Progress reports	FDA, IRB	Progress reports will be submitted at least annually or as stipulated by the FDA (21CFR 812.150(b)(5))
Recall and device disposition	FDA, IRB	Notification within 30 working days and will include the reasons for any request that an investigator return, repair or otherwise dispose of any devices (21CFR 812.150(b)(6))
Final report	FDA, IRB, PIs	Sponsor will notify the FDA within 30 working days of the completion, termination of the investigation. A final report will be submitted to the FDA, investigators and IRBs within 6 months after completion or termination of this study. (21CFR 812.150(b)(7))
Failure to obtain informed consent form	FDA	Sponsor will submit to the FDA a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent form, within 5 working days of receipt of notice of such use. (21 CFR 812.150(b)(8))

14 ETHICAL CONSIDERATIONS

IRB approval for the CIP and ICF or other written information provided to the subject will be obtained by the Principal Investigator at each investigational site prior to participation in this feasibility study. The approval letter must be received prior to the start of the study and a copy must be provided to the Sponsor. No changes will be made to the CIP or ICF or other written information provided to the subject without appropriate approvals, including IRB, the Sponsor, and/or the regulatory agencies.

Until the study is completed, the investigator will update the IRB of the progress of this study, per IRB requirements. Written approval must be obtained from the IRB annually to continue the study,

or according to each institution's IRB requirements. Further, any amendments to the CIP as well as associated ICF changes will be submitted to the IRB and written approval obtained prior to implementation, according to each institution's IRB requirements.

No investigative procedures other than those defined in this CIP will be undertaken on enrolled subjects without the written agreement of the IRB and the Sponsor.

15 PUBLICATION POLICY

The data and results from this study are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the study. The investigators will not use study-related data without the written consent of the Sponsor for any other purpose than for study completion or for generation of publication material, as referenced in the clinical study agreement. The publication or presentation of results from a single investigational site are not allowed until publication or presentation of the multi-center results. The Sponsor acknowledges that the Publication Committee intends to publish a multi-center publication regarding the study results. The Sponsor must receive any proposed publication or presentation materials at least 60 days prior to the proposed date of the presentation or the initial submission of the proposed publication in order for the materials to be reviewed by the Sponsor in compliance with the Sponsor's publication policy set forth in the clinical study site agreement.

The Sponsor will register the feasibility study on www.clinicaltrials.gov, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. The Sponsor shall be responsible for any such registration and results posting as required by ClinicalTrials.gov. Investigational sites shall not take any action to register the study. A full report of the pre-specified outcomes, including any negative outcomes, will be made public through the ClinicalTrials.gov website according to the requirements of Section 801 of the FDA Amendments Act. If this clinical investigation is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through ClinicalTrials.gov website.

16 RISK ANALYSIS

Risk evaluation was conducted in accordance with EN ISO 14971:2012: Medical Devices - Application of Risk Management to Medical Devices.

16.1 Anticipated Clinical Benefits

Potential benefits of the use of the Tendyne System may include, but are not limited to, the following:

- Improved symptomatic status and quality of life
- Reduced mortality
- Avoidance of procedural risks such as: cardiopulmonary bypass (CPB); atrioventricular groove disruption; ventricular rupture; and injury to the left circumflex coronary artery

16.2 Risks Associated with Participation in the Clinical Study

As previously described, **Table 3** indicates all anticipated AEs/risks associated with the use of the Tendyne Mitral Valve System. The risk associated with study-required testing and assessments are summarized in **Table 6**. Although routine, these tests and assessments may be performed at greater frequency than standard of care practices.

Table 6. Study Procedure-Related Risks

Study Procedures	Risks
History, Clinical Status, QOL Surveys, 6-Minute Walk & Physical Exam	None, Minimal
Laboratory testing	Minimal. Usual risks associated with phlebotomy
ECG	None, Minimal
Echocardiography: TTE	None, Minimal
Echocardiography: TEE	A separate written informed consent process consistent with clinic policies and practices will occur outside of study
Hemodynamics	A separate written informed consent process consistent with clinic policies and practices will occur outside of study
Computerized tomography angiography (CTA)	A separate written informed consent process consistent with clinic policies and practices will occur outside of study
Angiography (LV Ventriculogram) / Hemodynamics	Written informed consent consistent with institutional policy

16.3 Possible Interactions with CIP-Required Concomitant Medications

Potential risks associated with warfarin may include, but are not limited to (refer to the product insert for a complete listing):

- Bruising
- Decrease in white blood cell count
- Diarrhea
- Fever
- Headache
- Inability to tolerate the medication
- Increased risk of internal bleeding
- Major bleeding which may result in death
- Nose bleeds
- Skin Rash
- Upset Stomach
- Vomiting

16.4 Steps Taken to Control or Mitigate the Risks

In-depth recommendations, special precautions and instructions regarding patient selection, device handling, device placement and system removal are included in the IFU.

The IFU also states that the devices can only be used by physicians who have received appropriate training on how to use the device. This statement is interpreted to mean physician users are expected to be aware of the known and foreseeable safety risks associated with the use of the device, including the surgical and/or non-surgical treatment of these conditions.

Risks associated with the use of the device during this clinical study are minimized through device design, investigator selection and training, pre-specified patient eligibility requirements, study monitoring to ensure adherence to the CIP and the use of a DSMB. Investigational sites will be notified of unexpected adverse device effects and other safety concerns that could negatively impact the safety of the subjects if such issues arise. Stopping rules will be discussed with the DSMB and applied for subject safety through enrollment. All SAEs and device deficiencies will be reported to the Sponsor and will be monitored internally for safety surveillance purposes.

16.5 Risk to Benefit Rationale

The Tendyne Mitral Valve System represents a novel, state-of-the-art technology for the treatment of Mitral Regurgitation. Residual risks are well tolerated when compared with other mitral regurgitation treatment options. The potential hazards associated with the design and use of the Tendyne Mitral Valve System for use in patients with Mitral Valve Regurgitation and Mitral Annulus Calcification do not outweigh the potential benefits to the subject.

APPENDIX I: ABBREVIATIONS AND ACRONYMS

Acronym	Definition	Acronym	Definition
6MWD/T	Six Minute Walk Distance/Test	IDE	Investigational Device Exemption
ACC	American College of Cardiology	IFU	Instructions for Use
AE	Adverse Event	INR	International Normalized Ratio
AHA	American Heart Association	IPG	Implantable Pulse Generator
CABG	Coronary Artery Bypass Grafting	IRB	Institutional Review Board
CCS	Canadian Cardiovascular Society	KCCQ	Kansas City Cardiomyopathy Questionnaire
CEC	Clinical Events Committee	LV	Left Ventricle
CFR	Code of Federal Regulations	LVEDD	Left Ventricular End Diastolic Dimension
CIP	Clinical Investigational Plan	LVEF	Left Ventricular Ejection Fraction
COPD	Chronic Obstructive Pulmonary Disease	LVOT	Left Ventricular Outflow Tract
CRO	Contract Research Organization	MI	Myocardial Infarction
CRT	Cardiac Resynchronization Therapy	MR	Mitral Regurgitation
CT	Computerized Tomography	MV	Mitral Valve
DD	Device Deficiency	MVARC	Mitral Valve Academic Research Consortium
DSMB	Data and Safety Monitoring Board	NYHA	New York Heart Association
ECG	Electrocardiogram	PAS	Pulmonary Artery Systolic pressure
EDC	Electronic Data Capture	PCI	Percutaneous Coronary Intervention
EROA	Effective Regurgitant Orifice Area	PROM	Predicted Risk of Mortality
ESC	European Society of Cardiology	QoL	Quality of Life
FDA	U.S. Food and Drug Administration	RVSP	Right Ventricular Systolic Pressure
GCP	Good Clinical Practices	SAE	Serious Adverse Event
HIPAA	Health Insurance Portability and Accountability Act	STS	Society of Cardiothoracic Surgeons
ICD	Implantable Cardioverter Defibrillator	TEE	Transesophageal Echocardiogram
ICF	Informed Consent Form	TTE	Transthoracic Echocardiogram
ICH	International Council for Harmonization	UADE	Unanticipated Adverse Device Effect

APPENDIX II: DEFINITIONS

The following definitions will be used in the MAC Feasibility Clinical Investigational Plan. All serious adverse events and device or procedure related events will be adjudicated by the independent Clinical Events Committee, along with relationship to the Tendyne device and/or procedure.

Canadian Cardiovascular Society Grading of Angina Pectoris (CCS Angina Classification)

CCS Angina Classification is defined by the Canadian Cardiovascular Society as [26]:

Grade	Definition
I	Ordinary physical activity does not cause angina, such as walking and climbing stairs. Angina with strenuous or rapid or prolonged exertion at work or recreation
II	Slight limitation of ordinary activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, or in cold, or in wind, or under emotional stress, or only during the few hours after awakening. Walking more than two blocks on the level and climbing more than one flight of ordinary stairs at a normal pace and in normal conditions.
III	Marked limitation of ordinary physical activity. Walking one or two blocks on the level and climbing on flight of stairs in normal conditions and at normal pace.
IV	Inability to carry on any physical activity without discomfort, anginal syndrome may be present at rest.

Causal Relationship (from ISO 5840-3)

Causal relationship is the relationship of the AE to the device, the implant procedure or the patient's condition. It should be established for both the Tendyne and Control device, based on the following categories:

Relatedness	Definition
Device-related	Any AE involving the function of the device, or the presence of the device in the body. Included in this category are events that are directly attributed to the device or the use of the device system.
Procedure-related	Any AE that results from the implant procedure. Events in this category are directly related to the general procedural sequelae.
Patient condition-related	Any AE that results from the worsening of a pre-existing condition or cannot be attributed to the device procedure.

Chronic Kidney Disease

The following definitions of Chronic Kidney Disease will be utilized in the study, as stated from National Institute for Health & Clinical Excellence [27]:

Stage	Definition
1	Slightly diminished function; kidney damage with normal or relatively high GFR (≥90 mL/min/1.73 m2). Kidney damage is defined as pathological abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.
2	Mild reduction in GFR (60–89 mL/min/1.73 m2) with kidney damage. Kidney damage is defined as pathological abnormalities or markers of damage, including abnormalities in blood or urine test or imaging studies.
3	Moderate reduction in GFR (30–59 mL/min/1.73 m2). British guidelines distinguish between stage 3A (GFR 45–59) and stage 3B (GFR 30–44) for purposes of screening and referral.
4	Severe reduction in GFR (15–29 mL/min/1.73 m2) Preparation for renal replacement therapy.
5	Established kidney failure (GFR <15 mL/min/1.73 m2), permanent renal replacement therapy, or end stage renal disease.

Coronary Artery Disease

Approximately two-thirds of patients with HF have underlying CAD (ischemic cardiomyopathy). Therefore, it is imperative that appropriate treatment for CAD be used in the MAC feasibility study, according to the ACC/AHA/HSFA Guidelines for Heart Failure. Specific recommendations listed in those guidelines are listed as follows:

- Use of nitrates and beta blockers for the treatment of angina,
- Coronary revascularization according to recommended guidelines in patients who have both HF and angina,
- Patients with coronary artery disease and HF should be treated in accordance with recommended guidelines for chronic stable angina,
- Use of antiplatelet agents for prevention of MI and death in patients with HF who have underlying coronary artery disease

In addition, revascularization (i.e., percutaneous coronary intervention, etc.) should occur prior to subject registration in the study, as applicable.

Hospitalization (All-cause)

Admission to inpatient unit or ward in the hospital for at least 24 hours, including emergency department stay. Excludes hospitalizations planned for pre-existing conditions, unless there is worsening in the baseline condition.

For the purpose of the CIP, overnight stays at nursing home facilities, physical rehab or extended care facilities, including hospice, do not meet the protocol definition of hospitalization. Hospitalizations will be adjudicated by the CEC per the following:

Hospitalization (Cardiovascular): Treatment in any inpatient unit or ward in the hospital for at least 24 hours, including emergency department stay for conditions such as heart failure (as defined below), coronary artery disease, acute myocardial infarction, stroke, hypertension, cardiac arrhythmias, cardiomegaly, pericardial effusion, atherosclerosis, peripheral vascular disease and mitral valve reintervention or reoperation.

Hospitalization (Heart Failure): Any inpatient or outpatient visit that requires IV (e.g., diuretics or inotropes) for the treatment of heart failure. This definition also includes any event that meets all of the following criteria:

- Subject has clinical signs and/or symptoms of heart failure, including new or worsening dyspnea, orthopnea, paroxysmal nocturnal dyspnea, increasing fatigue, worsening functional capacity or activity intolerance, or signs and/or symptoms of volume overload.
- Results in intravenous (e.g., diuretic or vasoactive therapy) or invasive (e.g., ultrafiltration, IABP, mechanical assistance) treatment for heart failure.

Hospitalization (Non-Cardiovascular): Hospitalizations that are not heart failure or other cardiovascular hospitalizations, as defined in this CIP, will be categorized as non-cardiovascular hospitalizations.

Index Procedure

The procedure in which the Tendyne or Control (repair with remodeling annuloplasty or total chordal-sparing replacement) device implant is first attempted.

Left Ventricular Dysfunction

Subjects enrolled in the MAC feasibility study should be treated with ICD and/or CRT, as per the following guidelines, prior to subject enrollment in the trial:

- An implantable cardioverter-defibrillator is recommended as secondary prevention to prolong survival in subjects with current or prior symptoms of HF and reduced LVEF who have a history of cardiac arrest, ventricular fibrillation, or hemodynamically destabilizing ventricular tachycardia.
- Implantable cardioverter-defibrillator therapy is recommended for primary prevention of sudden cardiac death to reduce total mortality in subjects with non-ischemic dilated cardiomyopathy or ischemic heart disease at least 40 days post-MI, a LVEF less than or equal to 35%, and NYHA Functional Class II or III symptoms while receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year
- Subjects with LVEF of less than or equal to 35%, sinus rhythm, left bundle-branch block (LBBB), a QRS duration of ≥ 150 ms, and NYHA Functional Class III or ambulatory class IV symptoms despite recommended optimal medical therapy, should receive cardiac resynchronization therapy, with or without an ICD, unless contraindicated

Local Site Heart Team

The Local Site Heart Team must consist of, at a minimum, the cardiothoracic surgeon, interventional cardiologist, and an echocardiographer. Additional members of the heart team may include: other imaging specialists (CT), heart failure specialists, cardiac anesthesiologists, intensivists, nurses, and social workers.

Mitral Regurgitation Severity

Defined in **Figure 1**, adapted from the 2017 ACC Expert Consensus Decision Pathway on the Management of MR [28]

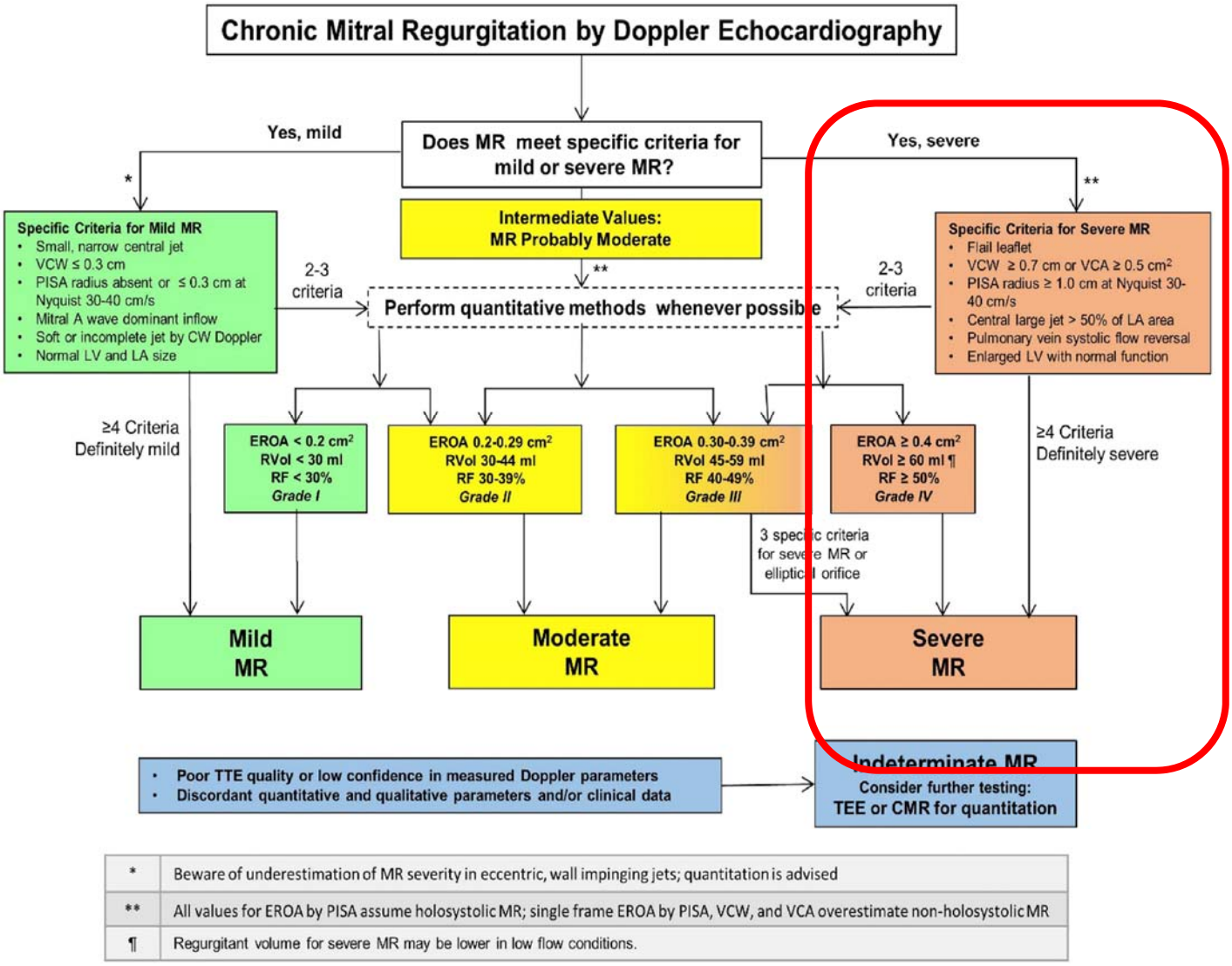

Figure 1. Mitral Regurgitation Severity

Subjects included in the MAC feasibility study

Modified Rankin Scale Score

The modified Rankin Scale (mRS) will be used to classify strokes as "disabling" or "non-disabling" and should be assessed at the following time intervals: ≤ 7 days following an event, at 30 days, and at 90 days.

Score	Definition
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead
Disabling stroke: an mRS score ≥2 with an increase in ≥1 mRS category from a subject's pre-stroke baseline at 90 days. **Non-disabling stroke:** an mRS score of < 2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline	

New York Heart Association Classification (NYHA Class):

Class	Definition
I	Patients with cardiac disease but without resulting limitations of physical activity.
II	Patients with cardiac disease resulting in slight limitation of physical activity. Patients are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
III	Patients with cardiac disease resulting in marked limitation of physical activity. Patients are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation dyspnea, or anginal pain.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Principal Investigator (from ISO 14155)

Qualified person responsible for conducting the clinical investigation at an investigation site. If a clinical investigation is conducted by a team of individuals at an investigation site, the principal investigator is responsible for leading the team.

Repositioning (from ISO 5840-3)

Change in implant position of a partially or fully deployed transcatheter heart valve substitute via a transcatheter technique, possibly requiring full or partial recapturing of the device.

Retrieval (from ISO 5840-3)

Removal of a partially or fully deployed transcatheter heart valve substitute via a transcatheter technique.

Stroke and TIA (from VARC II)

The following stroke and TIA diagnostic criteria will be used in this study, per VARC II [29]:

- Acute episode of a focal or global neurological deficit with at least one of the following: change in the level of consciousness, hemiplegia, hemiparesis, numbness, or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke.
- **Stroke:** Duration of a focal or global neurological deficit ≥24 hours; OR <24 hours if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death.
- **TIA:** Duration of a focal or global neurological deficit <24 hours, any variable neuroimaging does not demonstrate a new hemorrhage or infarct.
- No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist.
- Confirmation of the diagnosis by one of the following:
    - Neurologist or neurosurgical specialist
    - Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone.

Stroke Classification

The following stroke definitions will be used, per VARC II [29].

- **Ischemic:** An acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of the central nervous system tissue.
- **Hemorrhagic:** An acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage.

  Note: A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic.

Vulnerable Population (from ISO 14155)

Individuals with mental disability, persons in nursing homes, children, impoverished persons, persons in emergency situations, homeless persons, nomads, refugees, and those permanently incapable of giving informed consent. Vulnerable populations also may include members of a group with a hierarchical structure such as university students, subordinate hospital and laboratory personnel, employees of the Sponsor**,** members of the armed forces, and persons kept in detention.

APPENDIX III: STUDY ASSESSMENT AND FOLLOW-UP SCHEDULE

Exams, Tests and Data Collection	Screening / Baseline	Procedure	Pre-discharge	1 Month	3 Months	6 Months	1 and 2 years	Annual visits (3-5 years)
Visit Window		**Before and After Implant**	**72 hours prior to discharge**	**-3 days +14 days**	**±30 days**	**±30 days**	**±30 days**	**±45 days**
Informed Consent	X							
Inclusion/Exclusion Screening	X							
Medical history with Demographics	X							
Physical Exam including Vital Signs while sitting	X							
Cardiovascular Medications	X	X	X	X	X	X	X	X
STS PROM Risk Score	X							
CCS Angina class	X							
NYHA Classification	X			X	X	X	X	X
Six Minute Hall Walk Test	X			X	X	X	X	X
KCCQ	X			X	X	X	X	X
CLINICAL LABORATORY TESTS								
Pregnancy Test	X							
Creatinine	X		X	X	X	X	X	X
Plasma–free Hemoglobin	X			X	X	X	X	X
BNP or NT pro-BNP	X			X	X	X	X	X
International Normalized Ratio (INR)	X		X	X	X	X	X	X
Creatine Kinase-MB (CK-MB)	X		X	X	X	X	X	X
Troponin (Type I or T)	X		X	X	X	X	X	X
HEMODYNAMICS								
Cardiac Output		X						
PA Pressures		X						
RA Pressures		X						
LV Pressures		X						
EXAMS AND TESTS								
Coronary Angiogram (if clinically indicated)	X							
Cardiac CT#	X			X				
ECG (12-Lead)	X	X	X	X	X	X	X	X
TEE	X	X						
TTE^	X		X	X	X	X	X	X
Angiography: LV Gram (Optional)		X						
OTHER								
Device Deficiencies		X						
Adverse Events		X	X	X	X	X	X	X
Protocol Deviations	X	X	X	X	X	X	X	X

#Cardiac CT imaging (4D with contrast) is required for suspected thrombosis events in subjects implanted with the Tendyne device.
^TTE imaging must be conducted between 60 and 120 days after anticoagulation stoppage for subjects who receive the Tendyne device.
Note:
Baseline imaging for Cardiac CT must be acquired ≤ 120 days, and TEE / TTE echocardiograms must be acquired ≤ 60 days from intended subject registration. All other screening assessments must be completed 90 days prior to registration.
LV Gram is optional – only per investigator discretion.

APPENDIX IV: CONTACT INFORMATION

Any questions, including requests for a list of investigational sites, can be obtained upon request by contacting.

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177 County Road B East
St. Paul, MN 55117
United States
Phone: +1 651-289-5500

APPENDIX V: CLINICAL INVESTIGATION PLAN REVISIONS

This CIP may be revised as appropriate by the Sponsor. Rationale will be included with each version in the revision history table below. The version number and date of revision will be documented.

The acknowledgement of the revised CIP by the Coordinating Investigator (if applicable) and the Principal Investigators will be collected on the signature pages.

IRB and relevant Regulatory Authorities, if applicable, will be notified of revisions to the CIP. As necessary, approval will also be obtained prior to implementation of the CIP.

Revision History

Ver	Date	Details	Rationale
01P	28Mar2018	Not applicable	Initial release of CIP
02P	18Apr2018	Extended study follow-up period from 2 years to 5 years post procedure	Revision based on FDA feedback. Email dated 18Apr2018.
A	25Apr2018	• Versioning & date change to Rev. A dated 25Apr2018 • Correction to Sec. 6.1 – removed reference to EQ-5D and SF-12 QoL - not required for study	Administrative revision for Tendyne Quality System purposes

APPENDIX VI: BIBLIOGRAPHY

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