

TENDYNE

**Expanded Clinical Study
of
Tendyne Mitral Valve System**

Clinical Investigation Protocol

Protocol No. CS-03

Version H

20 February 2020

CONFIDENTIAL INFORMATION

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TENDYNE

PROTOCOL SIGNATURE PAGE

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I have read this protocol and agree to adhere to the requirements. I will provide copies of this protocol and all pertinent information to study personnel and my hospital Institutional Review Board (IRB)/ Ethics Committee (EC). I will discuss this material with them and ensure they are fully informed regarding the Tendyne Bioprosthetic Mitral Valve System and the conduct of the study according to this protocol, applicable laws and regulatory regulations, including hospital IRB/EC requirements.

Clinical Site Name

Site Investigator Signature

Date

Site Investigator Printed Name

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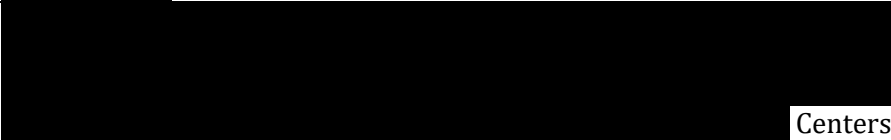
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Contact Information

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1 Study Summary

Protocol Title	Expanded Clinical Study of Tendyne Mitral Valve System
Investigational Device:	Tendyne Bioprosthetic Mitral Valve System
Purpose:	<p>The purpose of this expanded clinical study is to evaluate the performance and safety of the Tendyne Mitral Valve System in the treatment of severe mitral regurgitation in patients with functional disability greater than or equal to NYHA Class II, who are not suitable candidates for surgical replacement with otherwise available devices. The data gathered in this study will be used to support conformity requirements for CE Mark of the Tendyne Mitral Valve System, using an appropriately powered sample size to enable assessment of the study safety and performance endpoints of the Tendyne Mitral Valve System in the intended populations.</p> 
Design:	<p>Nonclinical assessments, pre-clinical data, and acute clinical study data have been used to evaluate the Tendyne Bioprosthetic Mitral Valve System design concept. This study is required to collect further data. This study is a single-arm, multicenter study designed in accordance with the MVARC 2015 guideline and standard ISO 5840-3:2013. The subjects will be individuals who have symptomatic mitral valve regurgitation and meet eligibility criteria.</p>
Population:	Subjects who are 18 years or older with a symptomatic mitral valve regurgitation may be invited to participate in this study.
Sample Size:	
Clinical Sites:	 Centers to be included in the study will meet study qualification requirements, have received necessary institutional review board/ethics committee and/or other approvals, be in countries in which the study has been approved as required by law, and be approved by the sponsor to participate. Geographies being considered for the study include Australia, Canada, Europe, and the United States.
Objective and Endpoints:	<p>Endpoints were selected to enable the sponsor, its safety committees, and regulatory agencies the ability to compare estimates obtained from this study to estimates from studies of other comparable procedures and devices. Objectives and endpoints were selected based on input from medical advisors experienced in related procedures and studies of other replacement valves and devices used to treat mitral regurgitation.</p>

Inclusion Criteria:	<p>Subjects must meet ALL of the following criteria:</p> <ol style="list-style-type: none"> 1. Severe mitral regurgitation of primary or secondary etiology according to MVARC (Mitral Valve Academic Research Consortium) 2015 defined as: <ul style="list-style-type: none"> • For Degenerative MR: EROA \geq 40 mm² or regurgitant volume \geq 60ml • For Secondary MR: EROA \geq 20 mm² or regurgitant volume \geq 30ml 2. New York Heart Association (NYHA) functional Class \geq II while on guideline directed medical therapy (GMDT), including device therapy (CRT) if indicated. 3. Heart team determines patient is not a suitable candidate for traditional surgical treatment according to valid guidelines. 4. Age 18 years or older.
Exclusion Criteria:	<p>Subjects will be excluded if any of the following criteria are met:</p> <ol style="list-style-type: none"> 1. Severe mitral annular calcification, severe mitral stenosis, valvular vegetation or mass. 2. Left Ventricle (LV) or Left Atrium (LA) thrombus. 3. Patient has a chest condition that prevents transapical access. 4. Left ventricular ejection fraction (LVEF) less than 30% by echocardiogram. 5. Left Ventricular End Diastolic Diameter (LVEDD) > 7.0 cm. 6. Prior surgical or interventional treatment of mitral or aortic valves (e.g. valve repair or replacement, MitraClip, edge to edge repair, aortic balloon valvuloplasty, etc.). 7. Any planned surgery or interventional procedure within the period of 30 days prior to 30 days following the implant procedure. This includes any planned concomitant cardiovascular procedure such as PCI, pulmonary vein ablation, left atrial appendage occlusion, septal defect repair, etc. 8. Cardiac resynchronization therapy device or implantable pulse generator implanted within three months of planned implant procedure. 9. Myocardial Infarction (MI) within 30 days of the planned implant procedure. 10. Symptomatic, unresolved multi-vessel coronary artery disease (CAD) or unprotected left main coronary artery disease requiring stenting or Coronary Artery Bypass Grafting (CABG). 11. Cerebrovascular accident (CVA) within six months of planned implant procedure. 12. Unresolved severe symptomatic carotid stenosis (> 70% by ultrasound). 13. Cardiogenic shock or hemodynamic instability requiring inotropes or mechanical support devices at the time of planned implant procedure. 14. Severe tricuspid regurgitation, tricuspid valve disease requiring surgery or severe right ventricular dysfunction. 15. Hypertrophic or restrictive cardiomyopathy, constrictive pericarditis or any other structural heart disease causing heart

	<p>failure other than dilated cardiomyopathy of either ischemic or non-ischemic etiology.</p> <ol style="list-style-type: none"> 16. Any of the following: leukopenia, acute anemia, thrombocytopenia, history of bleeding diathesis, or coagulopathy if cannot be adequately treated. 17. History of endocarditis within six months of planned implant procedure. 18. Active systemic infection requiring antibiotic therapy. 19. Known hypersensitivity or contraindication to procedural or post-procedural medications (e.g., contrast solution, anti-coagulation therapy) which cannot be adequately managed medically or hypersensitivity to nickel or titanium. 20. Patient is undergoing hemodialysis due to chronic renal failure. 21. Patient has pulmonary arterial hypertension (fixed PAS >70mmHg). 22. Patient has COPD and is on home oxygen. 23. Patient refuses blood transfusions. 24. Pregnant, lactating, or planning pregnancy within next 12 months. 25. Participating or planning participation in an investigational drug or another device study. 26. Patient or legal guardian unable or unwilling to give informed consent. 27. Patient unable or unwilling to comply with study required testing and follow-up visits. 28. Patients with non-cardiac co-morbidities that are likely to result in a life expectancy of less than one year.
Primary Safety Objective:	To evaluate one month procedural and device safety of the Tendyne Bioprosthetic Mitral Valve System.
Primary Safety Endpoints:	<p>Device success and freedom from the following device- or procedure-related serious adverse events (SAEs) at 30 days post implant, as classified by the Clinical Events Committee (CEC):</p> <ul style="list-style-type: none"> • Cardiovascular death • Reintervention caused by valve-related dysfunction • Disabling stroke • Myocardial infarction (MI) • Life-threatening bleeding • Major Vascular Complications • Renal failure requiring dialysis • Other device-related SAEs • Other procedure-related SAEs <p>Stroke and MI classifications will be per the Valve Academic Research Consortium – 2 (VARC-2). Life-threatening bleeding classifications will be per the Bleeding Academic Research Consortium (BARC) consensus (Type 2, 3, and 5).</p>

Secondary Safety Objective:	<p>To evaluate long-term safety of the Tendyne Bioprosthetic Mitral Valve System.</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
Secondary Safety Endpoints:	<p>Through two years post implant:</p> <ul style="list-style-type: none"> • Device success and, • No device or procedure related SAEs
Primary Performance Objective:	<p>To evaluate the performance of the Tendyne Mitral Valve System</p> <p>Endpoint definitions are derived from MVARC 2015 Guidelines.</p>
Technical Success Definition:	<p>Upon Exit from procedure room, alive with the following:</p> <ul style="list-style-type: none"> • Successful access, delivery and retrieval of the transcatheter valve delivery system, and • Deployment and correct positioning of the correctly sized valve, and • No need for additional emergency surgery or re-intervention related to the device or procedure.
Device Success Definition:	<p>At 30 day and all post-procedural time points, alive with the following:</p> <ul style="list-style-type: none"> • Disabling stroke free, with • Original intended device in place, and • No additional surgical or interventional procedures related to access or the device, and • Intended performance of the device: <ul style="list-style-type: none"> ○ No Device specific adverse events, such as migration, embolization, fracture, hemolysis, thrombosis or endocarditis, and ○ Maintenance of expected hemodynamic performance (e.g., central mitral regurgitation (MR) < 1+; mitral valve gradient < 6 mmHg or effective orifice area (EOA) > 1.5 cm²) and, ○ No para-device complications (left ventricular outflow tract (LVOT) obstruction: >20 mmHg increase in LVOT gradient vs. baseline; paravalvular leak (PVL) > 1+; effects on coronary circulation or other heart structures, e.g., erosion or need for permanent pacemaker implantation.
Primary Effectiveness: Individual Patient Success	<p>Individual patient success is defined as device success and all of the following at 1-year:</p> <ul style="list-style-type: none"> • No re-hospitalizations or re-interventions for heart failure • Change in NYHA functional class <ul style="list-style-type: none"> ○ Improvement is defined as NYHA grade \geq 1 compared to baseline

	<ul style="list-style-type: none"> • Change in distance walked, six-minute hall walk <ul style="list-style-type: none"> ○ Improvement is defined as ≥ 50 meters compared to baseline • Change in Kansas City Cardiomyopathy Questionnaire scores <ul style="list-style-type: none"> ○ Improvement is defined as ≥ 10 compared to baseline
Valve System Usability Objective:	Gather and evaluate information on the usability of the Tendyne Bioprosthetic Mitral Valve System.
Valve System Usability Data:	Data will be implanters' assessments of usability, especially as it relates to the ability to successfully deliver and deploy the Tendyne Mitral Valve in the desired anatomical location.
Additional Endpoints:	<ul style="list-style-type: none"> • Length of ICU stay • Length of hospital stay • 30-day mortality • 3-month mortality
Imaging Core Laboratories	<div style="background-color: black; width: 100%; height: 100%; min-height: 150px;"></div>

2 Introduction

2.1 Executive Summary

The purpose of this expanded clinical study is to evaluate the performance and safety of the Tendyne Mitral Valve System in the treatment of severe mitral regurgitation in patients with functional disability greater than or equal to NYHA Class II, who are not suitable candidates for surgical replacement with otherwise available devices. The data gathered in this study will be used to support conformity requirements for CE Mark of the Tendyne Mitral Valve System, using an appropriately powered sample size to enable assessment of the study safety and performance endpoints of the Tendyne Mitral Valve System in the intended populations.

This study will be continued after the CE Mark to collect long-term safety and performance data as part of the Tendyne Mitral Valve System post-market follow-up program. All patients shall continue to be followed through 5 years in the post-market setting.

2.2 Anatomy of the Mitral Valve

The mitral valve (MV) is located in the heart at the atrioventricular (AV) junction between the left atrium (LA) and the left ventricle (LV). The opening and closing of the MV is coordinated with the cardiac cycle to regulate the flow of blood from the lungs to the systemic circulation. A properly functioning MV is open during ventricular diastole to allow oxygenated blood to enter the LV from the LA, and closed during ventricular systole to prevent backflow into the LA.

The MV apparatus consists of the following: two leaflets, annulus, chordae tendinae, and papillary muscles (Figure 1). These four parts acting in concert with the walls of the LA and LV are required for the normal valvular function.

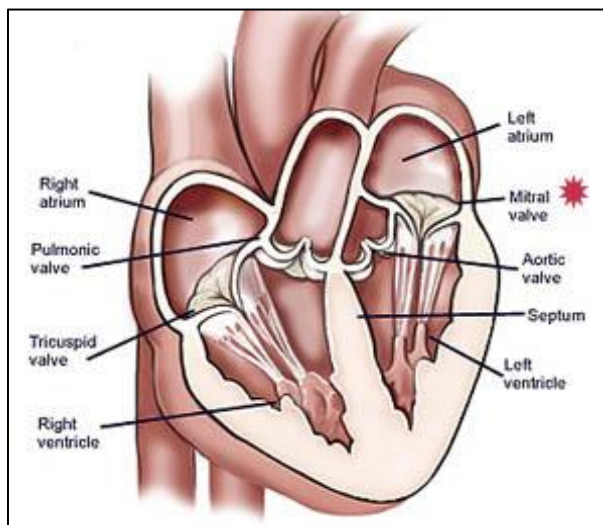


Figure 1. Human Heart Diagram

The MV is also referred to as the bicuspid valve, because it consists of two leaflets: anterior and posterior (Figure 2). The posterior leaflet extends around two-thirds of the AV junction.

The posterior leaflet has three indentations that form three scallops on the free edge that are labeled P1, P2 and P3. The three corresponding segments of the anterior leaflet are A1, A2 and A3. Complete coaptation and correct apposition of the leaflets is required for the prevention of regurgitation.

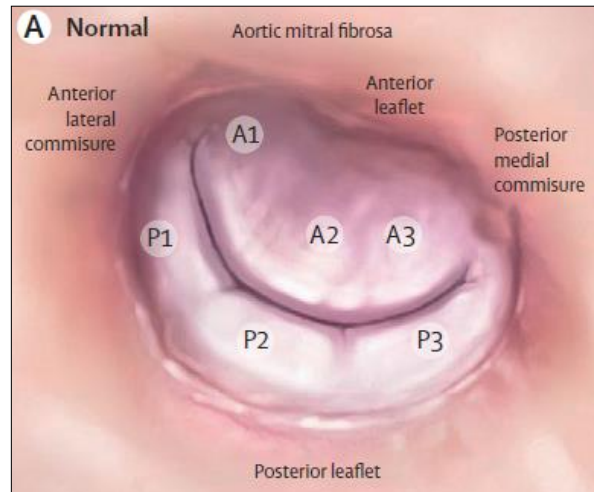


Figure 2. Normal Mitral Valve Leaflets Viewed from the Left Atrium¹

The MV annulus is in contact with the AV junction. The annulus is elliptical in shape, with the anteroposterior dimension/septal-lateral being shorter than the commissure-commissure/inter-commissural dimension. The anterior third of the annulus consists of fibrous connective tissue, which is shared with the aortic valve. The posterior two-thirds of the annulus consists of cardiac muscle. The annulus is pliable and changes shape throughout the cardiac cycle.

Papillary muscles (PMs) are fingerlike projections from the wall of the left ventricle. The chordae tendinae (CT) are inelastic fan-shaped cords that connect the PMs to the leaflets (Figure 3).

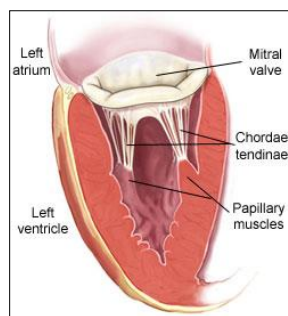


Figure 3. Long Axis View of Left Ventricle

Pathology that affects any part of the MV apparatus can lead to MV disease. Therefore, understanding the normal interaction of these parts provides the backdrop for understanding MV disease processes, the associated outcomes, and the currently utilized medical therapies.²

2.2.1 Mitral Valve Disease Prevalence and Etiology

Mitral valve disease can present in two general forms: (1) a narrowing of the valve, called mitral stenosis and (2) valvular insufficiency, which leads to mitral regurgitation.

2.2.2 Mitral Stenosis

Mitral stenosis (MS) is less prevalent than mitral regurgitation (MR). In MS, the narrowing of the mitral valve is the result of the post-inflammatory changes to the leaflets, which become thickened, nodular, and fused at the commissures. These leaflet changes can be accompanied by shortening of the CT and fibrosis of the PMs. These changes typically progress over time and secondary calcification of the valvular apparatus can occur. Fusion of the leaflets results in a funnel-shaped orifice. Restricted leaflet motion during both diastole and systole may result. This differs from secondary MR, in which the restricted leaflet motion normally only occurs during systole.³

The primary cause of MS is rheumatic fever. Although rheumatic fever is common in developing countries, it is comparably rare in developed countries due to the use of antibiotics for streptococcal infections. In a study of school-age children, there was a 12-fold higher prevalence of rheumatic fever in developing compared to developed countries.³ Thus, MS is also less prevalent in developed countries. In the Euro Heart Survey, which reviewed valvular heart disease across 25 European countries, only 27% of those patients who presented with isolated MV disease had MS. In 85% of the MS patients, the primary cause was rheumatic fever. Primary etiology accounted for most of the remaining MS cases,⁴ with the majority being older (>50 years of age). Similarly, Nkomo et al., in study of the general population in the US found that MS occurred in 0.1% of all people with a slight increase to 0.2% in persons ≥65 years of age.⁵

As noted, MR is the more prevalent form of isolated MV disease and will be the focus of the remainder of this overview.

2.2.3 Mitral Regurgitation

2.2.3.1 Prevalence

Two population-based studies in the US showed that mitral regurgitation (MR) is the most common heart valve disease.^{5,6} 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.⁶ 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 2030.⁵

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.^{7,8} 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.⁸ This suggests that patients with moderate or severe MR are not being properly referred for treatment, and important interventions are being delayed.

2.2.3.2 Etiology

There are two basic causes of MR: ischemic (e.g., subsequent to coronary artery disease) and nonischemic (all other causes).

The mechanisms are broadly classified as secondary (e.g., secondary to ischemia or LV remodeling) or primary (e.g., intrinsic valve lesions). The mechanisms can be further subdivided based on Carpentier's functional types, which describe leaflet motion in relation to the mitral annular plane:⁹

- Type I. Normal leaflet motion. MR is due to leaflet perforation or annular dilatation, which is usually the result of LV disease.
- Type II. Excessive leaflet motion above the annular plane (leaflet prolapsed) into the LA.
- Type III. Restricted leaflet motion.
 - Type IIIa. Restricted leaflet movement throughout the cardiac cycle (both systole and diastole).
 - Type IIIb. Restricted leaflet movement in systole alone.

The causes and mechanisms of MR are summarized, as follows, in Table 1.

Table 1: Causes and Mechanisms of Mitral Regurgitation¹

CAUSE	MECHANISM			
	Primary			Secondary
	Type I	Type II	Type IIIa	Type I/Type IIIb
Non-ischemic	<ul style="list-style-type: none"> • Endocarditis (perforation) • Degenerative (annular calcification) • Congenital (cleft leaflet) 	<ul style="list-style-type: none"> • Degenerative (billowing/flail leaflets) • Endocarditis (ruptured CT) • Traumatic (ruptured CT/PM) • Rheumatic (acute RF) 	<ul style="list-style-type: none"> • Rheumatic (chronic RF) • Iatrogenic (radiation/drug) • Inflammatory (anticardiolipin/eosinophilic endocardial disease/lupus/endomyocardial fibrosis) 	<ul style="list-style-type: none"> • Cardiomyopathy • Myocarditis • LV dysfunction (any cause)
Ischemic		<ul style="list-style-type: none"> • Ruptured PM 		<ul style="list-style-type: none"> • Functional ischemic

In developed countries, the most common etiologies for patients requiring surgical correction are primary (myxomatous), ischemic, rheumatic, and endocarditis.^{1,7,8} Primary MR represents approximately two-thirds of all surgical correction cases, with the most common form of primary MR being MV prolapse. Prolapse can be moderate, with leaflet edges remaining in the ventricle; or severe, with eversion of the leaflets, usually the posterior leaflet, into the LA. This severe eversion of the leaflets, also called flail leaflets, is usually the result of ruptured CT. A less common form of primary MR is calcification of the annulus.

Secondary MR accounts for approximately 20 to 25% of surgical correction cases. Secondary MR may result from annular enlargement secondary to LV dilatation or PM displacement due to LV remodeling.¹⁰ Because CT are non-extensible, PM displacement exerts traction on leaflets through the CT resulting in tethered and apically displaced leaflets. Changes in the annulus and the tethering of the leaflets, either alone or together, results in loss of coaptation that yields secondary MR.

2.3 Pathophysiology of Untreated Mitral Regurgitation

The pathophysiology of the disease is variable depending on the mechanism of MR. In significant primary 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 LA and increase in LA compliance. This increased LA compliance allows for near normal drainage from the pulmonary veins. This is the chronic, compensated phase of the disease during which patients may be asymptomatic and have 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. An additional complicating feature is that LA enlargement predisposes patients to AF and arterial thromboembolism. Left untreated, patients may develop pulmonary hypertension and right-sided heart failure.¹

There is a population of patients who can tolerate mild MR without an impact to clinical status or mortality. Approximately 50% of patients with primary MR have a normal life expectancy.¹¹ At the other end of the spectrum, 20% are at high risk for progression to heart failure or death without surgical correction. The predictors of this more severe course include moderate and severe MR and reduction in ejection fraction.¹¹

As noted above, secondary MR results from distortion of ventricular anatomy. In this population where ventricular dysfunction occurs prior to MR, diagnosis can be more difficult and the clinical course is often worse than in primary MR. The most common cause of

secondary MR is MI. In one cohort study of 773 patients underwent echocardiograms at 30 days post-MI. In this population, MR was present in 50% with 12% being categorized as moderate/severe.¹² Mitral regurgitation in this population increases atrial pressure, which leads to pulmonary hypertension and heart failure. Despite the fact that MR could be severe, the combination of increased atrial pressure and low ventricular driving force will paradoxically cause the calculation of RVol to be low.

Although there are no randomized controlled trials that have assessed the impact of secondary MR on heart chamber remodeling, clinical evidence strongly indicates that in patients with LV dysfunction, secondary MR worsens the prognosis.^{12,13,14,15,16} Grigioni et al. showed that patients with ischemic MR (IMR) had a significantly higher all-cause mortality and cardiac mortality incidence at 5 years when compared to a cohort of patients with ischemic heart disease and no MR.¹² Their work further showed that revascularization therapy alone did not eliminate the poor prognosis for patients with MR. A subgroup analysis of patients in the CADILLAC trial showed that MR was strongly associated with 30 day and 1 year mortality patients undergoing percutaneous coronary intervention procedures for acute MI.¹² More severe MR was associated with a higher mortality rates (1.4%, 3.7%, and 8.6% at 30 days; 2.9%, 8.5%, 20.8% at 1 year for no, mild, and moderate/severe MR, respectively). DeServi et al. reported similar results in a younger patient cohort experiencing a first MI.¹⁵ In this study, the 15-month mortality for patients with IMR was more than three times that of patients without IMR (9.8% versus 3.2%). Furthermore, patients with IMR were more likely to develop heart failure at 15 months (20% versus 3%).

Even though IMR is a strong predictor of poor outcomes following revascularization procedures, there are no guidelines for patient follow-up.¹⁶ Taken together, these data suggest that there is a substantial population of patients that could benefit from correction of IMR, which could lead to improved outcomes.

2.4 Treatment of Mitral Regurgitation

2.4.1 Treatment Guidelines and Guideline Adherence

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 valvular heart disease.^{17,18} In summary, the guidelines contain the following Class I recommendations.

Primary MR

- Symptomatic patients with severe primary MR and without severe LV dysfunction
- Asymptomatic patients with severe primary MR and LV dysfunction
- Repair is preferable to replacement when a successful and durable repair can be accomplished
- Patients with chronic severe primary MR undergoing cardiac surgery for other indications (ACC/AHA Guidelines only)

Secondary MR

- Patients with severe MR undergoing CABG and without severe LV dysfunction (ESC/EACTS only – there are no Class I recommendations for surgical intervention in the ACC/AHA Guidelines)

Despite the existence of well-defined guidelines and the abundant literature that indicates that the 10 year survival rate for medically managed patients ranges from 20 to 60%^{19,20,21,22,23}, several studies have shown that guideline adherence is poor, and many patients go without recommended treatment.^{24,25,26,27} An evaluation of surgical interventions in the Euro Heart Survey showed that only 193 of 396 (48.7%) of patients with severe symptomatic MR had a surgical valve procedure. Multivariate analysis identified five factors that led to the decision not to operate: LV dysfunction, non-ischemic etiology, patient age, comorbidities, and grade 3 versus more severe grades of MR. Specifically, these data showed that patients with LVEF between 30 and 60% accounted for 53% of the population that did not receive surgery, despite this level of LV dysfunction being a Class I recommendation in both the ACC/AHA and ESC/EACTS guidelines.²⁶ Similarly, Bach et al. evaluated 300 patients identified in the University of Michigan database with significant MR. Of these patients, 112 had primary MR, but mitral surgery was performed on only 59 (53%) of the patients. Of the patients who did not undergo surgical intervention, 39/53 (74%) met the guideline requirements for MV surgery.²⁴ Toledano et al. published on the results of a questionnaire mailed to all cardiologists in Canada to identify causes of non-compliance to the published guidelines. They found that only 57% of responding cardiologists correctly identified that an LVEF of 50 to 60% should trigger a referral for surgery. Further, only 16% would correctly refer an NYHA Class II patient with severe MR and an LVEF >60%.²⁷

To evaluate longitudinal outcomes of isolated MV repair in older patients, Badhwar et al. performed an analysis of linked data from the Society of Thoracic Surgeons (STS) adult cardiac surgery database and claims data from the Centers for Medicare & Medicaid Service (CMS) covering a period from 1991 through 2007. They identified over 14,000 isolated non-emergent MV repair operations, and one of the findings was that most elderly patients came to surgery late as they were more likely to have NYHA Class III or IV heart failure and AF, and nearly all had severe MR. Although the operative success rates were high and life expectancy for patients undergoing the MV repair procedure was restored to that of age-matched controls, the authors concluded that the practice of delayed referral, which is in conflict with the treatment guidelines, should be re-evaluated.²⁵

Methods for treatment of chronic functional and ischemic functional MR are less clear. The guidelines for management of valvular heart disease recommend consideration of MV repair or replacement with preservation of the subvalvular apparatus. However, no evidence was available for Class I or Class II regarding the best treatment approaches. 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^{28,29,30} and cardiac resynchronization therapy^{31,32} have been shown to reduce MR severity. As noted above,

patients with IMR have a worse prognosis than patients with MR from other causes. 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.¹⁶ 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.^{15,33,34} Some data suggest that MV repair or reduction of annular diameter with an annuloplasty ring concomitant with a CABG procedure may provide benefit.^{35,36,37,38} 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.

2.4.2 Treatment Methods for Mitral Regurgitation

Treatment methods for MR involve surgical or percutaneous interventions to repair or replace the mitral valve. Surgical repair and surgical valve replacement have been used for many years. Percutaneous methods are currently being developed and becoming increasingly more available.

2.4.2.1 Surgical Repair

Surgical repair for primary mitral valves can be traced to the technique developed by Carpentier, the “French correction”, which involved quadrangular resection of prolapsed leaflets, transposition of normal chords to other areas of the leaflet, as needed, and utilization of a ring annulus as part of a remodeling annuloplasty.⁹ The Carpentier method utilized a flat, rigid ring. In the years since this original publication, variations of annuloplasty rings have been developed to mimic the more anatomically correct “saddle-shaped” structure and flexibility of the mitral annulus. There are no conclusive data to suggest that these alternative ring forms enhance long-term clinical benefit.^{39,40,41,42} Using the Carpentier technique and associated variations, surgical repair and long-term outcomes were generally more favorable in patients with isolated posterior leaflet prolapse compared to anterior or bileaflet prolapse.⁴³ In a 12-year post-MV repair follow-up, freedom from reoperation was 96±2%, 88±4%, and 94±2% ($p=0.019$) for posterior, anterior and bileaflet prolapse, respectively. Freedom from >2+ MR at 12 years trended similarly, and anterior prolapse was an independent predictor of reoperation.

For the treatment of secondary MR, annuloplasty bands to restrict annulus diameter to facilitate leaflet coaptation have been employed.⁴⁴ Long term studies have shown that these bands become distorted over time, resulting in a recurrence of MR. Based on further analysis of the recurrent MR, it was determined that the anterior-posterior dimension must be reduced in order to maintain valve coaptation.⁴⁵

Two additional techniques have been developed that differ from the fundamentals of those first introduced by Carpentier: artificial chordae and edge-to-edge approximation.

The artificial chordae technique replaces diseased chordae without the chord transposition or resection that was introduced as part of the Carpentier method.⁴⁶ However Salvador et al.

published 15-year follow-up data on 608 patients who had MV repair with artificial chordae. These patients had an 84% survival rate, 92% freedom from reoperation, and 85% freedom from severe MR.⁴⁷ Because of the association with other techniques, isolated evaluations of artificial chordae in the literature are rare.

Edge-to-edge approximation also called the Alfieri technique.⁴⁸ Edge-to-edge approximation consists of suturing the anterior and posterior leaflets together to create a double orifice MV. This technique is recommended for use in combination with an annuloplasty, as results of an isolated edge-to-edge repair have been suboptimal. Edge-to-edge repair has, however, improved outcomes of patients with anterior leaflet prolapse. A single-center study compared 133 patients undergoing edge-to-edge repair of anterior leaflet prolapse and 605 patients undergoing quadrangular resection of the posterior leaflet with or without annuloplasty. Over the follow-up period (mean 4.5±3.1 years), freedom from reoperation in the anterior group was not inferior (96±2% in the anterior leaflet prolapse group versus 97±1% in the posterior leaflet prolapse group, $p=0.37$).⁴⁹

2.4.2.2 Surgical Replacement

There are conditions where the valve is not amenable to repair including prolapsed leaflets associated with extensive annular calcification, prolapse of one leaflet with hypoplasia of the opposite leaflet, extreme fibroelastic deficiency, and extensive postendocarditis tissue destruction.⁵⁰ In these cases, MV replacement is the most viable treatment option. There are two basic types of prosthetic valves: mechanical prostheses and bioprostheses. Mechanical prostheses require lifelong anticoagulation therapy but have longer durability, whereas bioprostheses do not require long-term anticoagulation but are subject to structural valve deterioration (SVD) over time. A 20-year follow-up of 1285 patients with MV bioprostheses determined the estimated freedom from SVD at 5, 10, and 15 years to be 98±1%, 69±2, and 32±4%, respectively.⁵¹ The choice of which type of valve prosthesis to use is largely related to patient life expectancy and risk of developing anticoagulant-related bleeding and thromboembolism.

The ESC/EACTS Class I recommendations for mechanical prostheses include patients that have no contraindications for long-term anticoagulation, who are at increased risk for accelerated SVD (<40 years of age or hyperparathyroidism), or are already on anticoagulation due to a mechanical valve in another location. The Class IIa recommendations include patients <65 years of age and/or those who have a reasonable life expectancy and for whom a reoperation would be contraindicated because of patient risk.

The ESC/EACTS Class I recommendations for bioprostheses include patients with a high risk of bleeding or those that are having a reoperation for mechanical valve thrombosis. The Class IIa recommendations include patients who are at low risk of future valve reoperation or are >70 years of age.⁵²

2.4.2.3 Comparison of Surgical Treatment Interventions

The Euro Heart Survey, which was conducted from April to July 2001, showed that the number of patients undergoing MV replacement versus repair were similar. Of 155 patients

who underwent surgery for MR, slightly more than half (83/155) had a valve replacement, with the majority being mechanical prostheses (67/83). O'Brien et al. showed similar trends using the Society of Thoracic Surgeons (STS) database for the period covering the years 2002 to 2006. Over 40,000 patients undergoing MV surgery were evenly divided between isolated MV replacement (21,229) and isolated MV repair (21,238).⁵³

Over time as knowledge and skills have increased, new techniques and devices have come into wider use to make surgical correction, rather than replacement, a viable option for increasingly greater numbers of patients. However, MV repair surgery tends to be more complex, requiring a surgical center that is experienced with repair techniques. There are a limited number of centers with the necessary expertise.

Despite important biases, the published guidelines for the management of valvular heart disease currently specify MV repair as the surgical intervention of choice.^{52,54} The recommendation is based largely on data that show a lower risk associated with MV repair over MV replacement. Evidence suggests that repair is effective and is associated with reduced morbidity and mortality compared to replacement.^{18,54} In the STS risk model for valvular surgery, patients with valve replacements were more than three times more likely to die within 30 days of the surgery (5.7% to 1.6%), and more than twice as likely to experience the one or more major morbidity or mortality events (26.7% to 12.7%).⁵³ It should be noted however that the patient group receiving prosthetic valves were older and had more complex valve pathology.^{53,55} Further, the valve replacement surgeries were often performed without sparing the valvular substructure, which has been shown to have a negative influence on outcomes.^{56,57,58,59} The apparent superiority of MV repair over replacement did not hold up to propensity matching analysis, which found no significant difference in mortality (at 5, 10, and 15 years) nor in freedom from reoperation (at 5 and 10 years) between repair and replacement.⁵⁵

Until recently, there has been a lack of randomized controlled data comparing repair and replacement. However, a recent report by Acker et al. of a randomized controlled trial that compared repair versus replacement in 251 patients with severe IMR showed that replacement had similar or better outcomes than repair.⁶⁰ Specifically, there was no significant difference in 12-month mortality (14.3% for repair versus 17.6% for replacement) or change in LVESV index from baseline (-6.6 mL/m² for repair versus -6.8 mL/m² for replacement). In fact the rate of recurrence of moderate or severe MR was significantly greater in the repair group (32.6% versus 2.3%, $p < 0.001$). The authors concluded that "replacement provided a more durable correction of mitral regurgitation."⁶⁰

Surgical interventions for MR are underutilized within the context of existing guidelines.^{24,25,26,27} An important goal in addressing the growing problem of MR is to raise awareness such that patients who would benefit from either MV repair or replacement are referred in a timely manner.

2.4.2.4 Percutaneous Mitral Valve Repair

Many MR patients, however, are not good surgical candidates. Age and comorbidities may make them unsuitable for anesthesia and open-heart surgery with cardiopulmonary bypass. With the aim of providing lower-risk therapies to improve MR related mortality and morbidity, treatments through percutaneous methods are being developed.

Percutaneous devices for MV repair have been evaluated in clinical trials and reported in peer-reviewed literature. One such device, MitraClip, is based on the edge-to-edge technique.^{61,62,63,64,65,66,67,68,69} Other companies have performed preliminary clinical evaluations of annuloplasty devices that are intended to reshape the mitral annulus and thereby reduce MR.^{70,71}

The MitraClip device has been evaluated in a pilot trial⁶¹, in a randomized controlled trial against MV repair surgery^{63,66} and in several registry studies.^{63,64,65,66,67,68,69} In the randomized controlled trial, the MitraClip patients fared worse on the 12-month primary endpoint of freedom from death, surgery for MV dysfunction, and MR grade 3+ or 4+ than did the patients undergoing MV repair surgery (55% to 73%; $p=0.007$).⁶² The MONARC and CARILLON annuloplasty devices were evaluated in multicenter, single-arm studies in 72 and 48 patients, respectively. Early clinical use has also been reported for the Cardioband device including a feasibility study on 29 patients with encouraging procedural success and patient clinical response. Whether any of these devices have a favorable risk-benefit profile is inconclusive, larger scale clinical studies and randomized controlled trials are required to further evaluate them.^{70,71,72}

2.4.2.5 Percutaneous Mitral Valve Replacement

Transcatheter aortic valve replacement (TAVR) has become a therapeutic option for high risk and extreme surgical risk patients with symptomatic calcific aortic stenosis⁷³ and is now being studied for intermediate risk, failed bioprosthetic valves, bicuspid aortic stenosis and aortic insufficiency. Several valves for TAVR are commercially available in Europe and The United States and more newly designed valves undergoing development.⁷²

The success of transcatheter valves for aortic stenosis have paved the way for transcatheter mitral valve replacements, but the mitral valve has been a much more elusive target. Transcatheter mitral valve replacement (TMVR) faces challenges arising from not only the heterogeneity of mitral valve pathology but also from its complete intracardiac positioning. The mitral annulus, leaflets and subvalvular apparatus offer significant obstacles to valve delivery.⁷⁴

These challenges have not deterred industry and physician inventors from pursuing TMVR devices. There is a parade of devices from both start-up and mature companies active in this field.⁷⁶ Several pre-clinical and clinical publications have emerged in recent years.

2.4.3 Preclinical Evaluation of Percutaneous Mitral Valve Replacement

Development and preclinical evaluation of candidate devices for MV replacement has focused in two general areas: devices that can be stably implanted within the native mitral valve

apparatus and devices that can be implanted within valves or rings that were surgically implanted in previous procedures (e.g., valve-in-valve).

The first literature reports of off-pump, percutaneous MV valves were in 2005 by Ma et al. and Boudjemline et al.^{75,76} Ma et al. utilized a “double-crown” stented valve. This valve was implanted at the mitral location through the transatrial route and centered on the mitral annulus that was previously marked with clips.

The Lutter group has performed the most extensive series of transapical mitral valve implantation in animal studies.^{73,77,78,79,80,81,82} Early device prototypes utilized self-expanding stent with a star-shaped atrial element that was designed to prevent migration into the left ventricle, and ventricular fixation system consisting of four individual neo-chordae attached to the ventricular rim of the stent. This group reported on four acute/short term studies on variations of the star-shaped prototype.^{76,77,78,79,80}

Gillespie et al. reported on the on-pump implant of a sutureless mitral valve device delivered via atrial access in ten sheep. In this acute study, the authors reported that the implanted valves displayed normal hemodynamic properties, no paravalvular leakage, and mild central regurgitation in three animals.⁸³

Several investigators have reported on preclinical evaluations of percutaneous valve-in-valve^{84,85,86} and valve-in-ring replacements.^{87,88,89,90} The impetus behind evaluating MV replacement into existing devices is to treat those patients that have had previous surgical implants at the mitral position, are having a recurrence of MR, and are at high risk of undergoing a repeat surgical procedure. The benefit of implanting into pre-existing valve or ring implants is that there is a structure by which to anchor the replacement valve. With the exception of Zou et al. who utilized a custom-made MV in four animals, the procedures utilized currently marketed aortic valves, Edwards Sapien and Medtronic Melody as the replacement devices.

In general, evaluations of MV replacement into native structures and existing implanted valves and rings have shown to be feasible and able to be performed off-pump. As the requirement for cardiopulmonary bypass is significant source of operative risk, this is a desirable procedural characteristic. Some early studies, utilized rapid ventricular pacing to assist with valve placement, which again would not be desirable for high-risk patients, but later studies were performed without the aid of pacing.

This series of studies indicates that beating heart procedures with transseptal, transatrial, and transapical access have all been shown to be feasible. Stented valves placed into the native valve structure have shown stability and functionality. Short deployment times, high success in deployment and good functional characteristics make these valves good candidates for pilot clinical evaluations.

The first published clinical use of a TMVR was the acute implantation of a Tendyne Mitral Valve. Two patients were treated under clinical protocol prior to receiving surgical mitral valve replacement.⁹¹ They reported safe implantation and reduction of severe MR with

immediate improvement in hemodynamics. In-hospital outcomes for the chronic implantation of the Tendyne Mitral Valve were subsequently reported in three patients. Implantation was safe resulting in elimination of severe MR in 2 of 3 patients (with trivial PV leak in the third) and all patients being discharged to their own home.⁹²

Neovasc has reported short-term clinical results of the Tiara valve in two patients. The experience demonstrated feasibility with safe implantation and excellent hemodynamic results and valve function through 2 months.⁹³

In addition to the percutaneous application of devices that are designed specifically for the MV, some surgical centers are now using percutaneous application of aortic replacement valves in the MV position. Most often these procedures are valve-in-valve implants for older patients with bioprosthetic valve dysfunction. These are poor candidates for reoperation and have limited life expectancy. Cheung and Al-Lawati reported encouraging data on 36 patients who underwent transcatheter mitral valve-in-valve implantation. Thirty-day mortality was 7.5%, and surviving patients had a decrease in MR severity from 3+ and 4+ to 1+ or 0.74. These data provide evidence that percutaneous MV replacement can be successfully utilized in high surgical risk patients.

2.5 Therapeutic Need

Although the guidelines for management of valvular heart disease suggest that surgical correction 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.

3 Device Description

3.1 Intended Use

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

The Tendyne Mitral Valve is implanted through the apex of the left ventricle via a left mini-thoracotomy while the heart remains beating. Compared to open-heart valve replacement surgery, access is less invasive and the risks of cardiopulmonary bypass are avoided. Thus, the Tendyne Mitral Valve System is designed to provide a mitral valve replacement alternative for patients who are not suitable candidates for surgical replacement/transcatheter valve repair.

Implantation of the Tendyne Mitral Valve does not involve concomitant surgical removal or revision of the failed native mitral valve. It is implanted within the native mitral valve, using minimally invasive techniques, such that the mitral apparatus is preserved. Preservation of the native structures has been shown to improve clinical outcomes in mitral valve replacement¹⁷, as they are essential for maintaining normal left ventricular shape, volume and function.

The Tendyne Mitral Valve can be repositioned and/or retrieved intraoperatively. These features are designed to allow optimization of the valve position following deployment and use of an alternative valve size if the initial valve does not have adequate performance.

3.2 Intended Clinical Performance

The Tendyne Mitral Valve is intended to reduce mitral regurgitation. Reduced mitral regurgitation may lead to favorable left ventricular remodeling, improved quality of life, fewer patient symptoms, and/or reduced hospitalizations for heart failure.

3.3 Identification

The Tendyne Bioprosthetic Mitral Valve System consists of the Tendyne Mitral Valve and an instrument set to facilitate placement of the valve.

The Tendyne Mitral Valve System is manufactured by Tendyne Holdings, Inc, a subsidiary of Abbott Vascular Inc. (also doing business as Abbott Medical).

[REDACTED]

The Tendyne Mitral Valve is available in several sizes to accommodate differing cardiac anatomies. Each valve size is described by major (AP, anterior-posterior) and minor (ICD, inter-commissural dimension) dimensions, see Section 3.4.1 for more information.

3.4 Design

3.4.1 Valve

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3.4.3 Instrument Set

The instrument set included in the Tendyne Mitral Valve System includes (1) an access system that can be configured multiple ways and (2) an apical pad tool.

The instrument sets are identical for the two valve models.

3.4.3.1 Access System

The access system is designed to facilitate Tendyne Mitral Valve implantation using standard transapical access methods. The system is designed to facilitate gradual, controlled deployment of the valve and proper seating within the mitral annulus. It is also designed to facilitate intraoperative repositioning, if necessary, to achieve optimal orientation within the annulus. The system allows intraoperative retrieval, if necessary, to pull the valve out. An alternate Tendyne Mitral Valve may then be implanted.

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4 Risk-Benefit Analysis

4.1 Risk Analysis

4.1.1 Risk Assessment

In conducting the risk analysis, the concepts of risk estimation, risk acceptability, risk control and overall risk evaluation were applied in accordance with ISO 14971. The intended use and implantation procedures were taken into consideration along with the materials and mechanical features of the Tendyne system. Based on an evaluation of residual risk acceptability, it was concluded that the overall residual risk did not exceed the criteria for acceptable risk.

4.1.2 Risk Mitigation

A major risk is potential damage to the left atrial and ventricular structures during implantation of the Tendyne Mitral Valve. Damage to the subvalvular apparatus is mitigated by the delivery system that is designed to cross the mitral valve with minimal risk of entanglement in the chordae tendinae. Damage to the atrium is mitigated by controlling valve deployment. The delivery instrument employs a fine ratcheting system, allowing the valve to exit the delivery sheath gradually. Damage to the atrium is further mitigated by employing a soft, flexible tip dilator and delivery sheath to introduce the device.

Transapical techniques have been used for many years. Transapical aortic valve implantation is done through a similar access, and left ventricular assist devices are traditionally attached at the apex. Nevertheless, puncture of the left ventricular apex and subsequent closure may cause bruising and scar tissue, with the potential for impaired cardiac function. The apex, however, contributes minimally to the overall ventricular contraction. Damage at the apex is mitigated by a relatively low-profile delivery system to make the puncture as small as possible.

The residual risks are disclosed in the labeling of the device (IFU) and are counterbalanced by the potential benefits of the therapy in the target patient population, as discussed in Section 4.2.

The mini-thoracotomy required for apical access is the same opening in which drainage tubes would be placed following mitral valve surgery. Therefore, the mini-thoracotomy does not add to the morbidity risks compared to surgical repair or replacement.

Not all risks may be known at this time. To see a list of anticipated adverse events, please see Section 0.

4.2 Potential Benefits

Patients who are contraindicated for mitral valve replacement surgery may benefit from receiving the Tendyne Mitral Valve because there are currently no other nonsurgical replacement options. Currently all prosthetic mitral valves for replacement within the native valve must be implanted surgically.

Unlike contemporary replacement mitral valves, the Tendyne Mitral Valve does not require open-heart surgery. The benefits here are twofold. First, less invasive access leads to lower operative risk. Second, the use of cardiopulmonary bypass carries several risks, including abnormal bleeding, acute respiratory distress syndrome, air embolism, atelectasis, blood clotting, capillary leak syndrome, hemolysis, pancreatitis, postperfusion syndrome, renal dysfunction and neurologic deficits in elderly, which can be substantial.

The Risk/Benefit analysis performed in accordance with ISO 14971 showed that the Tendyne Bioprosthetic Mitral Valve System has the same risks of the other mitral valve prosthetic devices currently used in clinical practice or in clinical studies. The benefit that the Tendyne Bioprosthetic Mitral Valve System can give to patients suffering of severe mitral regurgitation are important, considering that the system can give opportunities for therapy to elderly patients that are excluded by the surgical option. The clinical benefit of the device is balanced against the residual risk associated with the treatment.

4.3 Study Participation Associated Risks

The risks associated with study participation (Table 3) are those associated with standard clinical diagnostic and evaluative practices procedures:

Table 3: Study Participation Associated Risks

Study Procedures	Risks
History, Clinical Status, QOL Survey, 6-Minute Walk & Physical Exam	None, Minimal
Laboratory testing	Usual risks associated with phlebotomy
Concomitant Medication	Physician use and risk information in accordance with usual clinical practice and type of medication.
ECG	None, Minimal
Echocardiography TTE	None, Minimal
Echocardiography TEE	Written informed consent consistent with clinic policy
Angiography (LV Ventriculogram) / Hemodynamics	Written informed consent consistent with clinic policy
Computerized tomography angiography (CTA)	Written informed consent consistent with clinic policy

The obtainment of patient informed consent for study procedures determined to require prospective informed consent will be undertaken in accordance with the procedural informed consent procedures and documentation content defined by participating hospital policy. The procedures required per study protocol are consistent with standard of practice procedures given the indication for the associated intervention.

5 Study Purpose

The purpose of this expanded clinical study is to evaluate the performance and safety of the Tendyne Mitral Valve System in the treatment of severe mitral regurgitation in patients with functional disability greater than or equal to NYHA Class II, who are not suitable candidates for surgical replacement with otherwise available devices. The data gathered in this study will be used to support conformity requirements for CE Mark of the Tendyne system, using an appropriately powered sample size to enable assessment of the study safety and performance endpoints of the Tendyne System in the intended populations.

This study will be continued after the CE Mark to collect long-term safety and performance data as part of the Tendyne post-market follow-up program. All patients shall continue to be followed through 5 years in the post-market setting.

6 Study Design

Nonclinical assessments, pre-clinical data, and acute clinical study data have been used to evaluate the Tendyne Bioprosthetic Mitral Valve System design concept. This study is required to collect further data.

This study is a single-arm, multicenter study, designed in accordance with the MVARC 2015 guideline and standard ISO 5840-3:2013.^{94,95,96,97} The subjects will be individuals who have symptomatic mitral valve regurgitation and meet eligibility criteria.

6.1 Geographies and Centers

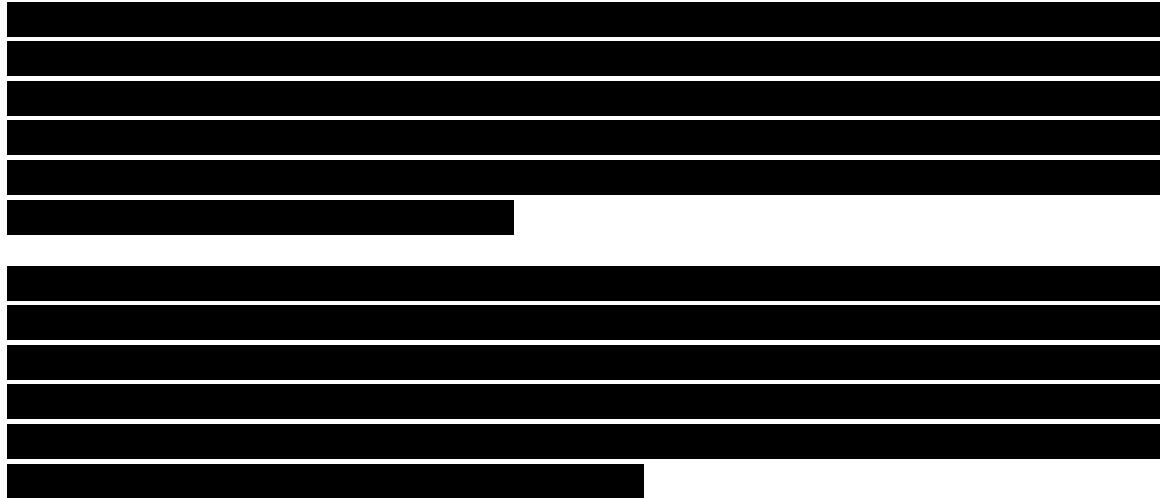
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[REDACTED]

[REDACTED] Centers to be included in the study will meet study qualification requirements, have received necessary institutional review board/ethics committee and/or other approvals, be in countries in which the study has been approved as required by law, and be approved by the sponsor to participate. Geographies being considered for the study include Australia, Canada, Europe, and the United States.

6.2 Duration

[REDACTED] The objective of this study is to enroll a maximum of 350 patients to allow evaluation of the primary endpoint as well as pre-planned subgroup analyses.



6.3 Sample Size

Up to 350 subjects will be enrolled in the study. Subjects shall be recruited by up to 40 clinical sites based upon availability of appropriate subjects. Enrollment shall be competitive and enrollment will be closed once a sufficient number of subjects have been included.

6.4 Eligibility Criteria

Candidates will have symptomatic mitral valve regurgitation and meet all eligibility criteria.

6.4.1 Inclusion Criteria

Subjects must meet ALL of the following criteria:

1. Severe mitral regurgitation of primary or secondary etiology according to MVARC (Mitral Valve Academic Research Consortium) 2015 defined as:
 - For Degenerative MR: EROA ≥ 40 mm² or regurgitant volume ≥ 60 ml
 - For Secondary MR: EROA ≥ 20 mm² or regurgitant volume ≥ 30 ml
2. New York Heart Association (NYHA) functional Class \geq II while on guideline directed medical therapy (GMDT), including device therapy (CRT) if indicated.
3. Heart team determines patient is not a suitable candidate for traditional surgical treatment according to valid guidelines.
4. Age 18 years or older.

6.4.2 Exclusion Criteria

Subjects will be excluded if any of the following criteria are met:

1. Severe mitral annular calcification, severe mitral stenosis, valvular vegetation or mass.
2. Left Ventricle (LV) or Left Atrium (LA) thrombus.

3. Patient has a chest condition that prevents transapical access.
4. Left ventricular ejection fraction (LVEF) less than 30% by echocardiogram.
5. Left Ventricular End Diastolic Diameter (LVEDD) > 7.0 cm.
6. Prior surgical or interventional treatment of mitral or aortic valves (e.g. valve repair or replacement, MitraClip, edge to edge repair, aortic balloon valvuloplasty, etc.).
7. Any planned surgery or interventional procedure within the period of 30 days prior to 30 days following the implant procedure. This includes any planned concomitant cardiovascular procedure such as PCI, pulmonary vein ablation, left atrial appendage occlusion, septal defect repair, etc.
8. Cardiac resynchronization therapy device or implantable pulse generator implanted within three months of planned implant procedure.
9. Myocardial Infarction (MI) within 30 days of the planned implant procedure.
10. Symptomatic, unresolved multi-vessel coronary artery disease (CAD) or unprotected left main coronary artery disease requiring stenting or Coronary Artery Bypass Grafting (CABG).
11. Cerebrovascular accident (CVA) within six months of planned implant procedure.
12. Unresolved severe symptomatic carotid stenosis (> 70% by ultrasound).
13. Cardiogenic shock or hemodynamic instability requiring inotropes or mechanical support devices at the time of planned implant procedure.
14. Severe tricuspid regurgitation, tricuspid valve disease requiring surgery or severe right ventricular dysfunction.
15. 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.
16. Any of the following: leukopenia, acute anemia, thrombocytopenia, history of bleeding diathesis, or coagulopathy if cannot be adequately treated.
17. History of endocarditis within six months of planned implant procedure.
18. Active systemic infection requiring antibiotic therapy.
19. Known hypersensitivity or contraindication to procedural or post-procedural medications (e.g., contrast solution, anti-coagulation therapy) which cannot be adequately managed medically or hypersensitivity to nickel or titanium.
20. Patient is undergoing hemodialysis due to chronic renal failure.
21. Patient has pulmonary arterial hypertension (fixed PAS >70mmHg).
22. Patient has COPD and is on home oxygen.
23. Patient refuses blood transfusions.
24. Pregnant, lactating, or planning pregnancy within next 12 months.
25. Participating or planning participation in an investigational drug or another device study.
26. Patient or legal guardian unable or unwilling to give informed consent.

27. Patient unable or unwilling to comply with study required testing and follow-up visits.
28. Patients with non-cardiac co-morbidities that are likely to result in a life expectancy of less than one year.

7 Objectives and Endpoints

Endpoints were selected to enable the sponsor, its safety committees, and regulatory agencies the ability to compare estimates obtained from this study to estimates from studies of other comparable procedures and devices. Objectives and endpoints were selected based on input from medical advisors experienced in related procedures and studies of other replacement valves and devices used to treat mitral regurgitation.

7.1 Performance

Provide initial insight into the performance of the Tendyne Mitral Valve System by measuring technical and device success.

7.1.1 Technical Success Definition (Exit from procedure room)

Alive with the following:

- Successful access, delivery and retrieval of the transcatheter valve delivery system, and
- Deployment and correct positioning of the correctly sized valve, and
- No need for additional emergency surgery or re-intervention related to the device or access procedure.

7.1.2 Device Success Definition (at 30 day and all post-procedural time points)

Alive with the following:

- Disabling stroke free, with
- Original intended device in place, and
- No additional surgical or interventional procedures related to access or the device, and
- Intended performance of the device:
 - No Device specific adverse events, such as migration, embolization, fracture, hemolysis, thrombosis or endocarditis, and
 - Maintenance of expected hemodynamic performance (e.g., central mitral regurgitation (MR) < 1+; mitral valve gradient < 6 mmHg or effective orifice area (EOA) > 1.5 cm²) and,
 - No para-device complications (left ventricular outflow tract (LVOT) obstruction: >20 mmHg increase in LVOT gradient vs. baseline; paravalvular leak (PVL) > 1+; effects on coronary circulation or other heart structures, e.g., erosion or need for permanent pacemaker implantation.

7.2 Primary Effectiveness: Individual Patient Success (1-year)

Individual Patient success is defined as device success and all of the following:

- No re-hospitalizations or re-interventions for heart failure
- Change in NYHA functional class
 - Improvement is defined as NYHA grade ≥ 1 compared to baseline
- Change in distance walked, six-minute hall walk
 - Improvement is defined as ≥ 50 meters compared to baseline
- Change in Kansas City Cardiomyopathy Questionnaire scores
 - Improvement is defined as ≥ 10 compared to baseline

7.3 Safety

Provide insight into the safety profile of the Tendyne Mitral Valve System and procedure.

7.3.1 Primary Safety Objective

To evaluate one month procedural and device safety of the Tendyne Bioprosthetic Mitral Valve System.

7.3.2 Primary Safety Endpoints

Device success and freedom from the following device- or procedure-related serious adverse events (SAEs) at 30 days post implant, as classified by the Clinical Events Committee:

- Cardiovascular death
- Reintervention caused by valve-related dysfunction
- Disabling Stroke
- Myocardial infarction (MI)
- Life-threatening bleeding (BARC Type 2, 3, and 5)
- Major Vascular Complications
- Renal failure requiring dialysis
- Other device-related SAEs
- Other procedure-related SAEs

Stroke and MI classifications will be per the VARC-2. Life-threatening bleeding classifications will be per the Bleeding Academic Research Consortium (BARC) consensus. Criteria are provided in Appendix A.

7.3.3 Secondary Safety Objective

To evaluate long-term safety of the Tendyne Bioprosthetic Mitral Valve System.

Follow-up for secondary endpoints will be continued for 2 years. Additional follow-up will be obtained for up to 5 years as recommended by most recent guidelines, to capture long-term

data on less common or unanticipated adverse events, on adverse events which are time-related (e.g., structural deterioration, adverse effects on native valve anatomy) and on long-term performance.

7.3.4 Secondary Safety Endpoints

Through two years post implant:

- Device success, and
- No device or procedure related SAEs

7.4 Valve System Usability

7.4.1 Valve System Usability Objective

Gather and evaluate information on the usability of the valve system.

7.4.2 Valve System Usability Data

Data will be implanters' assessments of usability, especially as it relates to the ability to successfully deliver and deploy the Tendyne Mitral Valve in the desired anatomical location.

7.5 Additional Endpoints

- Length of ICU stay
- Length of hospital stay
- 30 day mortality
- 3-month mortality

8 Analysis Plan and Sample Size Justification

[REDACTED]

[REDACTED]

[REDACTED]

8.1 Sample Size

[REDACTED]

8.2 Screen Failures and Point of Enrollment

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.

The point of enrollment is the time at which a subject signs and dates the informed consent form, in accordance with ISO 14155. [REDACTED]

[REDACTED]

8.3 Baseline Demographics, Clinical Background, and Protocol Administration

Descriptive statistics will be used to present the data and summarize the results. The study population will be summarized using descriptive statistics for baseline demographics, disease characteristics, echocardiography parameters, procedural characteristics, and follow-up data collected. Continuous variables will be summarized by reporting the number

of observations (N) mean, standard deviation, median, minimum and maximum values. Categorical variables will be summarized using frequency distributions and cross tabulations, incidence and event rate. Compliance with the protocol will be evaluated by summarizing the number of subjects enrolled, implanted, and completing study required follow-ups. Patients terminating the study early will be listed along with the reason for termination.

8.4 Handling Study Discontinuations

Study drop-outs will be listed along with the reason for termination per Section 8.1 of the protocol. Drop-outs will be censored from the analysis with no data imputation. Deviations from the protocol will also be summarized by deviation type as well as total. The primary statistical analysis will be based on subject counts. A subject with more than one deviation will be counted only once toward the rate based on the total number of subjects with protocol deviations.

8.5 Evaluation of Primary Endpoints

8.5.1 Primary Performance Objective

The primary performance objective is to estimate the proportion of subjects with MR grade ≤ 2 at 30 days post-implant.

Subjects included in the analysis: All subjects in whom the Tendyne Mitral Valve implant is completed.

Endpoint: Percentage of subjects with MR grade ≤ 2 at 30 days post-implant.

Data analysis: [REDACTED]

8.5.2 Primary Safety Objective

The primary safety objective is to evaluate one-month procedural and device safety of the Tendyne Bioprosthetic Mitral Valve System.

Subjects included in the analysis: All subjects in whom the Tendyne Mitral Valve System is introduced into the body.

Endpoint: Each of the individual primary safety endpoints will be evaluated (see list in 7.3.2 above). Additionally, composite endpoints may be estimated and evaluated for comparison to the literature.

Data analysis: [REDACTED]

8.5.3 Valve System Usability Objective

The valve system usability objective is to evaluate information on the usability of the Tendyne Bioprosthetic Mitral Valve System.

Data included in the analysis: All usability data gathered from implanters will be analyzed. Data will be implanters' assessments of usability, especially as it relates to the ability to successfully deliver, position, and deploy the Tendyne Mitral Valve in the desired anatomical location. Data will also include information on retrievability, if available.

Data Analysis: [REDACTED]

8.6 Evaluation of Secondary Endpoints

[REDACTED]

9 Regulations

This study will be conducted under good clinical practices, ISO 14155:2011(E) and ISO 5840-3:2013(E), and when not in contradiction to local standards, laws or requirements, also in alignment with the United States Food and Drug Administration Code of Federal Regulations Title 21 Parts 11, 50, 54, 56, 58, and 812.

The study shall be conducted consistent with the ethical principles of the Declaration of Helsinki.

Prospective review and approval of this study shall be undertaken consistent with the legal and regulatory requirements of those countries in which the program is to be undertaken.

The Study Protocol and associated essential documents, as well as any subsequent Amendments, shall require the prospective review and approval of the Competent Authority and responsible Ethics Committee consistent with applicable regulatory requirements.

The applicable laws and regulations and the communicated requirements of the Competent Authorities and Ethics Committee shall be respected during the conduct of the clinical study.

Clinical Study Insurance consistent with the laws and regulations in the countries of conduct shall be provided by the Study Sponsor.

10 Site Initiation Activities

10.1 Investigator and Site Selection

The sponsor will assess potential investigators to ensure that they are experienced and have the necessary expertise. Investigators must also have the ability to enroll an adequate number of subjects.

The sponsor will also assess the site to ensure that it is equipped with adequate facilities for the study. The sponsor will ensure that qualified personnel are available to conduct the study, including a designated research coordinator and a procedural heart team. At a minimum, the procedural heart team will be composed of an interventional cardiologist, a cardiac surgeon experienced in transapical procedures, a sonographer, and an experienced cardiac anesthesiologist.

Investigators must agree to comply with this protocol, all ethics committee requirements, and all applicable laws and regulations.

10.2 Initiation Requirements

Investigative sites may begin enrolling subjects after all initiation requirements are met and the sponsor has given notice of approval to start. Initiation requirements include: institutional review board/ethics committee approval of this protocol and the informed consent; training of all participating site personnel; a site initiation visit by the sponsor;

training by the echo core lab; and submission of all required documents to the sponsor. Required documentation includes: institutional review board/ethics committee approvals; curricula vitae (CVs); signed investigator agreements with conflict of interest/financial disclosure statements; documentation of site training; and any other documents requested by the sponsor.

10.3 Site Training

On-site training of investigators and site study personnel will be conducted by the sponsor as part of the initiation activities. Training sessions may be tailored to fit site personnel's roles in the study. The sponsor will ensure adequate training is provided on the following:

- Investigational device, principle of operation and system components
- Protocol
- IFU
- Data collection and eCRFs
- Investigator responsibilities
- Device accountability
- Implantation procedure
- Imaging and data acquisition
- Echo protocol
- CT protocol

11 Screening and Enrollment

11.1 Screening

Patients with symptomatic mitral regurgitation are to be evaluated to determine if they meet the eligibility criteria based on standard of care tests and procedures. All cases should be screened by a heart team.

11.2 Informed Consent

Once it is determined that a patient provisionally meets the eligibility criteria the investigator must: explain the nature, purpose, and consequences of study participation to the patient; answer any questions the patient may have; and provide the patient with the approved consent form to read. The oral informed consent process shall include: an overview of all aspects of the written patient information document with specific attention to the voluntary nature of participation; an overview of study obligations; risks associated with the study device implantation; study procedures; and alternative treatment modalities. In addition, the possibility to discontinue participation without impact upon on usual care shall be reviewed including requirements for routine clinical follow-up evaluations. The informed consent

form must be approved by the sponsor and the reviewing institutional review board/ethics committee. The investigator will inform the patient with new information, if applicable.

In the event a patient has limited or absent legal competence, the process for obtainment of informed consent defined by law involving the documented consent of the patient's legal representative shall be strictly observed and undertaken. Insofar as such a patient, independent of legal competence status, is able to understand the nature, purpose and consequences of study participation and to make his/her will known, such patient informed consent is mandatory, independent of any consent provided by his/her legal representative.

Minors, as well as pregnant or nursing women, or women intending to become pregnant in the ensuing 12 months are specifically excluded from participation.

In order to participate in the study, the patient and person performing the consent process must sign and date the informed consent form. Subjects may also be asked to consider signing a supplemental consent form pertaining to heart donation to the sponsor in the event of a transplant. Analysis of an in situ device would provide valuable histological information.

Insofar as additional institutional patient information documents for the following study procedures are implemented, such institutional standard documents shall be executed in conformance with institutional policy:

- Echocardiography
- Angiography
- Computerized Tomographic Angiography (CTA)

All applicable laws, regulations, and ethics committee requirements must be followed during the consent process.

11.3 Vulnerable Population

A vulnerable subject is defined as an individual whose willingness to volunteer in a clinical investigation could be unduly influenced by the expectation, whether justified or not, of benefits associated with participation or of retaliatory response from senior members of a hierarchy in case of refusal to participate.

EXAMPLES: Individuals with lack of or loss of autonomy due to immaturity or through mental disability, persons in nursing homes, children, impoverished persons, subjects in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, and those incapable of giving informed consent. Other vulnerable subjects include, for example, 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.

Individuals who fulfill these criteria shall not be approached for participation in the study.

11.4 Enrollment

The point of enrollment is the time at which a subject signs and dates the informed consent form, in accordance with ISO 14155.

Study subjects who are implanted with a permanent Tendyne Mitral Valve will be followed through two years and annually thereafter until study closure. Subjects who have any part of the Tendyne Mitral Valve System introduced into the body, but who do not end up with an implanted Tendyne Mitral Valve will be followed through one month or until any procedure or device related adverse event is resolved, whichever comes later. Subjects will then be exited from the study. Subjects who do not have any part of the Tendyne Mitral Valve System introduced into the body will be exited from the study immediately.

- LV and LA dimensions
- Effective regurgitant orifice area (EROA)
- Mitral valve gradient
- LVEF
- Cardiac output
- LVOT dimensions and gradient

12.3 Angiography

The subject's coronary artery disease status usually will be known in advance, via a routine diagnostic angiogram done as part of the work-up for cardiac surgery or transcatheter mitral valve repair if clinically indicated. Any stenting treatment should be administered prior to the implantation of the Tendyne Mitral Valve as outlined in the patient eligibility criteria in section 6.4 above. No simultaneous therapeutic procedures should be planned in conjunction with the Tendyne Mitral Valve implantation.

12.3.1 Preoperative Cardiac Computerized Tomography (CT)

Cardiac CT is performed as standard of care for transcatheter valve implantation; therefore, all subjects will have a Cardiac CT performed at baseline to evaluate cardiac dimensions relevant to valve sizing and aid in procedural planning. If a cardiac CT is obtained per non-research clinical practice at any follow-up, it should be provided to the study sponsor. Additionally, a follow-up cardiac CT should be performed at the 1 Month visit, if tolerable by the patient.

12.3.2 Intraoperative Angiography

Subjects will undergo left-heart catheterization with radiographic imaging as per standard-of-care. Imaging will include a left ventriculogram before and after the Tendyne Mitral Valve is placed, for radiographic assessment of 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 for subjects with stage 3, 4 or 5 chronic kidney disease.

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

12.4 Intraoperative Hemodynamic Measurements

Subjects will also 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 Tendyne Mitral Valve is placed via the right heart catheter. LV pressures should be measured via a pigtail catheter. LV pressures should be measured simultaneously and recorded digitally for post-processing analysis if possible.

12.5 History and Physical Examination

At baseline, a standard physical examination and complete medical history must be taken including co-morbidities and co-existing medical conditions; previous cardiovascular and peripheral vascular interventions; symptoms and diagnosis of mitral insufficiency.

12.6 Clinical Status

Clinical status including vital signs and NYHA functional classification must be evaluated at baseline and each scheduled follow-up visit. Vital signs include sitting pulse, sitting blood pressure and body temperature.

12.7 Kansas City Cardiomyopathy Questionnaire (KCCQ)

The KCCQ is a heart failure specific measure of health status and quality of life. It is a 12-item questionnaire that quantifies physical function, symptoms, social function, self-efficacy and quality of life for patients with heart failure. The KCCQ is self-administered and takes approximately 5 minutes to complete. It must be given to subjects at baseline and each scheduled follow-up visit.

12.8 Six-Minute Hall Walk

A six-minute hall walk test must be done at baseline and each scheduled follow-up visit. Subjects will be asked to walk as far as they can for six minutes, and the distance they cover is to be recorded. If a subject has a non-cardiovascular limitation such as an orthopedic restriction or hemiplegia, this must be noted. If a subject is non-ambulatory due to heart failure status, a score of 0 will be recorded.

12.9 Medications

All cardiovascular medications must be documented at baseline, and any changes in medications must be documented at each scheduled follow-up visit. Cardiovascular medications include anticoagulants, antiplatelet agents, ACE inhibitors, angiotensin II receptor blockers or inhibitors, beta blockers, calcium channel blockers, diuretics, digitalis preparations, and any medication that may increase the risk of bleeding.

12.10 Clinical Laboratory Tests

Blood laboratory analyses must be done at baseline and each scheduled follow-up visit. Assessments include: NT-proBNP, plasma free hemoglobin, serum creatinine, and International Normalized Ratio (INR). Creatinine kinase-MB (CK-MB) and/or Troponin (Type I or T) should also be collected according to standard of care at the clinical site. Additionally, serum creatinine, INR, CK-MB/Troponin must be assessed at pre-discharge.

12.11 Electrocardiogram

A 12-lead ECG must be recorded at baseline, intraoperatively both before and after implant and at pre-discharge.

12.12 Adverse Events

All adverse events (AEs) that occur to any subject during study participation must be documented on an AE case report form (CRF). Refer to Section 0 below for further reporting requirements.

12.13 Vigilance Officer

[Redacted]

[Redacted]

[Redacted]

13 Implant Procedure

13.1 Requirements

The implant should be performed by the procedural heart team (See Section 10.1). The cardiac surgeon should be the primary operator.

The following equipment is required for implantation:

- Standard cardiac catheterization lab equipment
- Fluoroscopy equipment appropriate for use in cardiac interventions
- Transesophageal echocardiographic equipment
- Angiographic equipment

For backup purposes, the following are needed:

- Circulatory support
- Temporary pacing equipment
- Defibrillator

13.2 Preparation

The Tendyne Mitral Valve implant procedure is to be performed without cardiopulmonary bypass, however, it must be available for backup support if needed.

Prepare the subject for the implant procedure as follows:

- Administer general anesthesia.
- Attach a 12-lead ECG (if not obtained immediately prior).
- Prepare the subject for a left mini-thoracotomy.
- Prepare the subject for TEE.
- Prepare the subject for right- and left-heart catheterization.

The subject must be on anticoagulant typical for transcatheter therapeutic interventions. Activated clotting time (ACT) is to be maintained at >250 seconds for the duration of the procedure.

13.3 Initial Data Acquisition

Tendyne will provide specific instruction on intraoperative imaging and data acquisition requirements as part of investigator training. A brief overview is provided here.

Using cardiac catheters, obtain the required measurements, including the following:

- Cardiac output using thermodilution method

- Intracardiac and vascular pressures

Perform the intraoperative TEE protocol to obtain views and measurements pertaining to the mitral valve and left ventricular function.

13.4 Implant Procedure

An overview of the recommended Tendyne Mitral Valve implant procedure is provided here. Refer to the Instructions for Use for additional detail.

13.4.1 Valve Placement

1. Ensure that all components are fully de-aired to avoid introducing air emboli into the heart, and continue to flush them with isotonic saline throughout the procedure.
2. Thoroughly rinse the valve with heparinized isotonic saline.
3. Compress and load the valve into the instrument, ensuring that the proud anterior segment is properly aligned with the corresponding marker on the instrument.
4. Determine the proper trajectory from the patient's left ventricular apex to the mitral valve. Puncture the apex and insert a standard .035" guidewire.
5. Ensure a path clear of entanglement in the chordae.
6. Advance the instrument over the guidewire to achieve access to the left ventricle. Further advance it across the mitral valve and into the left atrium.
7. Deploy the valve, while observing the deployment using echo and/or fluoroscopic imaging.
8. Pull the valve proximally into the mitral annulus ensuring that the proud anterior cuff is oriented toward the aortic-mitral continuity.
9. Using echo and/or fluoroscopic imaging, confirm that the valve is oriented correctly.
 - a) If the valve needs to be repositioned, use the instrument to partially recapture the valve, push it up into the left atrium, reorient, and pull it back into position.
 - b) If the valve is the wrong size or otherwise needs to be withdrawn, use the instrument to fully recapture the valve and pull it out through the apical access. If desired, an alternative valve can be deployed.
10. Once proper orientation has been confirmed, adjust tension using the apical pad tool to attain proper seating of the valve for mechanical stability and optimal paravalvular sealing.
11. Once stability is achieved and valve function is determined to be acceptable, remove the instrument and fasten the apical pad to the tether.

13.4.2 Valve Verification

1. Monitor the function of the implanted valve with periodic TEE.
2. Measure the cardiac output and cardiac index.
3. Measure transmitral pressure gradient (mean and peak).
4. Measure aortic and right arterial (RA) pressures.
5. Optionally perform a left ventriculogram.

6. Perform an ECG.
7. Trim the tether proximal to the apical pad.
8. Close the surgical incision in the usual manner.

13.5 Post-Operative Care

In the immediate post-operative period, the subject's blood pressure is to be closely monitored and maintained below 135 mmHg systolic if possible.

Subjects are required to be on anticoagulation therapy, warfarin with a target INR range of 2.5 to 3.5, for a minimum of three months. Antiplatelet therapy may also be administered during this timeframe. Thereafter, subjects should be on aspirin alone or in combination with anticoagulation therapy.

14 Follow-up Visits

14.1 Pre-Discharge

Pre-discharge data collection is to be done within 24 hours prior to discharge (or, in the event of prolonged hospitalization, within 10 days after the implant procedure). Pre-discharge requirements include clinical status, medications, an ECG, and documentation of any peri-operative AEs. It is recommended that serum creatinine be assessed at approximately 48 hours post implant.

An Implant card will be delivered to the patient when required by National regulation per specific Tendyne instructions for implant card distribution and completion, as applicable.

14.2 Scheduled Follow-up Visits

Follow-up data must be documented using the appropriate eCRFs and image data must be submitted in electronic format.

Follow-up visits must occur at the following time points following implantation:

- Pre-discharge Within 24 hours prior to discharge or up to 10 days post-procedure, whichever occurs first
- One month 28 - 40 days
- Three months 90 ± 14 days
- Six months 180 ± 30 days
- One year 365 ± 45 days
- Two years 730 ± 60 days
- Annually thereafter until 5 years.

Subjects who have any part of the Tendyne Mitral Valve System introduced into the body but who do not end up with an implanted Tendyne Mitral Valve only need to be followed through one month or until resolution of any procedure or device related adverse event and then exited from the study. Subjects who are not exposed to the Tendyne Mitral Valve System will be exited from the study immediately. Documentation for subjects exited from the study must be completed using the appropriate CRF.

14.3 Study Exit

After the 2-year study visit, subjects should be followed annually until study completion and closure. Consistent with ongoing, interim communication with each patient's community care physician/cardiologist, upon study completion, each patient will be returned to the full care of such patient-identified physicians. The clinical study team shall remain available to each patient's community care physician in the event of any specific follow-up evaluations and consultations.

14.4 Unscheduled Follow-Up Visits

If a subject presents for an unscheduled visit due to an AE that is serious (SAE) and/or device- or procedure-related, the following are required: clinical status; medication changes; and documentation of the AE using the appropriate eCRFs.

14.5 Lost to Follow-Up

If a subject fails to comply with follow-up schedule, the site must make repeated attempts (at least three) to contact the patient. If a patient cannot be contacted anymore, the investigator should contact a third person (normally the patient's general practitioner) to get information about the patients' health. The permission and the contact details are stated in the Informed Consent form of the subject. Each attempt and the method used (e.g., telephone) must be documented in the patient's records. A subject who is lost to further follow-up must be reported to the sponsor using the appropriate eCRF.

14.6 Withdrawals

A subject may voluntarily withdraw from the study at any time. A subject may also be withdrawn from the study at the discretion of the investigator. In the event of withdrawal from the study, the investigator must ensure that the reason for the withdrawal is documented. If the subject had an AE, the subject must be followed until it is resolved, if possible, or until the investigator determines that the condition is stable. Withdrawn subjects will not be replaced.

All withdrawals must be reported to the sponsor using the appropriate eCRF.

15 Reinterventions and Explants

In the event that a subsequent procedure related to the Tendyne Mitral Valve is required at any time during a subject's study participation, the physician should obtain image data and otherwise attempt to characterize the valve *in situ*, to the extent feasible.

If an open-chest procedure is performed, then photographs should be taken. Photographs should be taken of the valve and/or native tissues before and after any modification or explant is done. The sponsor is particularly interested in understanding host response to the implanted valve (tissue ingrowth) and other device-host interfaces such as potential damage to native tissues including native leaflets, subvalvular structures and myocardium.

If a valve is explanted, the valve should immediately be placed in 10% neutral buffered formalin and returned to the sponsor for analysis. The valve must be handled carefully and as little as possible to prevent damage and preserve its integrity. The sponsor must be contacted for shipping and packaging materials and to arrange for transport.

All relevant data pertaining to the reintervention or explant must be documented on the appropriate eCRF. The physician should dictate an operative report and submit it to the sponsor along with any image data and photographs.

16 Heart Transplants or Subject Death

In the event of subject death or heart transplant, histological and engineering analyses of the *in situ* valve would provide valuable information. Therefore, a supplemental consent form may be used to authorize explant and donation of the heart to the sponsor. The sponsor must be contacted for shipping and packaging materials and to arrange for transport.

17 Data Management

17.1 Subject Identification

Each subject will be assigned a unique identification code (ID) for the purpose of identity protection. Any subject names that may inadvertently appear on study documents submitted to the sponsor will be redacted upon receipt.

17.2 Central Database

All study documentation will be collected and compiled in a central database. Appropriate quality control measures will be established to ensure accurate and complete transfer of information from the study documentation to the central database.

17.3 Electronic Case Report Forms (eCRF)

Electronic case report forms are designed to capture study data. The investigator is responsible for completing all appropriate sections of the eCRFs and submitting them to the sponsor in a timely manner. The investigator is also responsible for responding to queries (e.g., data clarification forms) from the sponsor to clarify any pending questions about the data.

17.4 Protocol Deviations

The investigator must document any deviation to this protocol using the appropriate eCRF. Study monitoring will include review for protocol deviations. Under emergency circumstances, deviations from the Study Protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to the sponsor and the EC as soon as possible.

An investigator must notify the sponsor and the reviewing institutional review board/ethics committee as soon as possible of any deviation from this protocol that was done to protect the life or physical well-being of a subject.

17.5 Centre Noncompliance

Protocol deviations will be closely monitored. If unacceptable deviations, repeated deviations, or other compliance problems are noted, the sponsor reserves the right to suspend study enrollment at that site until a sufficient system is in place to reduce further deviations and ensure compliance.

17.6 Data Processing and Management

Data will be reviewed manually and electronically for accuracy and completeness. Standard checks such as range checks will be incorporated into the central database. Data clarification Forms (DCF) will be issued to resolve data discrepancies. Study monitoring will be conducted to ensure that the site is submitting complete and accurate data, and to verify source data.

17.7 Confidentiality and Protection of Study Files

All information and data concerning subjects and their participation in this study will be considered confidential. Only authorized personnel will have access to confidential files. Passwords will be issued for sponsor personnel to ensure confidentiality and protection of electronic data. Hard copy data will be stored in a locked file. No data will show subject names.

When required by law, consistent with the specifications of Annex VII of Council Directive 93/42/EEC, patient identification information, patient consent, individual patient clinical course documentation, as well as documentation of regulatory compliance with clinical study legal requirements shall be retained by the investigational site for a minimum period of 15 years (implantable medical devices). Original clinical data documentation provided for study analysis, as well as such documentation of regulatory conformance with legal requirements shall be retained by the study sponsor for a period of 15 years. The secure retention of site copies of clinical data documentation provided for study analysis may be delegated for appropriate third party storage in collaboration between sponsor and investigational site.

17.8 Monitoring

The sponsor will be responsible for monitoring at each site to ensure adequate protection of the rights and safety of study subject, and to verify the quality and integrity of the data collected and submitted. The sponsor will identify and train qualified personnel to conduct monitoring visits. Monitoring will consist of review of subject records, source documents, and other required documentation, including institutional review board/ethics committee approvals and correspondence.

Monitors will conduct site visits to ensure accuracy of data, timeliness of data submission, adequate patient enrollment, compliance with applicable laws and regulations, compliance with this protocol, compliance with the signed investigator agreement, and compliance with institutional review board/ethics committee conditions and guidelines. Any noncompliance with these items that is not adequately addressed by the investigator is cause for the sponsor to put the investigator on probation or withdraw the investigator or site from the study.

The site staff must be available to meet with the monitor or other sponsor representative during monitoring visits. The investigator must allow monitoring by the sponsor and its authorized representatives and any other local governmental body to review the study subjects' medical records, including any test or laboratory data.

Frequency of monitoring will be based on enrollment, study duration, site compliance, and any suspected inconsistency in data that requires investigation.

18 Adverse Event Reporting

An adverse event (AE) is defined as any untoward medical occurrence in a study subject, which does not necessarily have to have a causal relationship with study treatment. An AE can be an unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease, temporary or permanent, whether or not related to the prosthetic valve implantation or procedure. Refer to 22 for further AE definitions.

Reportable AEs are any that occur from the time a subject becomes enrolled through the subject's exit from the study. Any AE that occurs to any subject during the study must be documented on an AE electronic case report form. Information collected includes: date of onset of first observation; description of the event; seriousness; causal relationship to the device; causal relationship to the procedure; treatment required; and outcome or status of the event.

Serious Adverse Events (SAE) require reporting without delay to the Competent Authorities. In such cases, the investigator will inform the Sponsor immediately, but not later than 3 calendar days after learning of the event and shall provide the required documentation to the Sponsor for assessment and regulatory reporting without delay.

Pre-existing conditions must be documented so that related AEs can be correctly reported. An event that is a continuation of an unresolved AE must be reported as ongoing, not as a new AE. Worsening of a pre-existing condition must be reported. Complications and hospitalizations must also be reported.

The sponsor and principal investigators must comply with all reporting requirements of the ethics committees and applicable laws and regulations.

18.1 Adverse Event (AE) Review and Classification

All AEs will be reviewed and classified by a Clinical Events Committee (CEC). In addition, a Data and Safety Monitoring Board (DSMB) may review AE data as it relates to their role. Refer to Sections 19.5 and 19.6 for more information.

18.2 Anticipated AEs

Anticipated AEs are those that may be reasonably expected to occur in association with a surgical or transcatheter valve procedure. Anticipated AEs include, but are not limited to, those listed here; those reported in the risk analysis report; those reported in the IFU; and those reported in the literature associated with valve procedures:

- Adverse foreign body response
- Adverse reaction to anesthesia
- Allergic reaction
- Anemia
- Annular dissection
- Aortic insufficiency
- Atrial or ventricular injury
- Bioprosthetic valve dysfunction
- Bleeding complications
- Blood loss which may require transfusion
- Cardiac arrest
- Cardiac perforation
- Conduction defect with or without need for pacemaker
- Cardiac arrhythmia, Atrial or Ventricular
- Damage to cardiac tissue and/or structures
- Death
- Decreased LV function and/or cardiac output
- Device embolism
- Device erosion, migration or malposition
- Device thrombosis
- Embolism (device, air, blood clot, tissue, etc.)
- Endocarditis
- Esophageal irritation, stricture or perforation
- Foreign Body Response
- Fever
- Heart Failure, new or worsening
- Hematoma
- Hemolysis
- Hypotension
- Infection / Sepsis
- Liver failure
- Mitral valve injury
- Mitral valve prolapse / stenosis
- Myocardial infarction
- Obstruction
- Pain
- Pleural effusion
- Pulmonary embolism
- Pulmonary hypertension
- Paravalvular leak
- Pericardial effusion / tamponade
- Renal insufficiency or failure
- Respiratory difficulty, insufficiency or failure
- Stroke or transient ischemic attack
- Tear or damage to device
- Vascular and access-related complications
- Worsening of mitral regurgitation

18.3 Relationship of AEs to the Device or Procedure

The investigator must specify whether an AE has a causal relationship to either the device or the implant procedure.

The Clinical Events Committee will have final classifications. In addition to categorizing the causal relationship, the probability will also be specified as definitely, possibly, or not related to the device or procedure by the Clinical Events Committee.

Refer to 22 for AE definitions.

18.4 Seriousness of AEs

The investigator must categorize each AE as either serious (SAE) or non-serious, according to the definition in 22. Final classifications will be made by the CEC.

18.5 Device Deficiencies

All failures and malfunctions of the investigational device must be documented and communicated to the sponsor as soon as possible, preferably within 24 hours of knowledge of the event. If a failed or malfunctioning Tendyne Mitral Valve is explanted, it should be returned to the sponsor as biohazardous material without re-sterilization and reuse. Procedures for returning explanted devices are detailed in Section 15. All other device deficiencies should be reported to the sponsor on the appropriate eCRF as technical observations.

19 Responsibilities

This study will be performed in conformance with this protocol and all applicable laws and regulations.

19.1 Investigator Responsibilities

The investigator is responsible for ensuring the study is conducted according to all signed agreements, this protocol, the reviewing ethics committee, and all applicable laws and regulations. Investigator responsibilities include, but are not limited to, the following:

- Assume responsibility for proper conduct of the clinical study.
- Disclose potential conflicts of interest, including financial, that may interfere with the conduct of the study or interpretation of results, and promptly update this information if any relevant changes occur during the course of the study.
- Submit this protocol and the sponsor-approved informed consent form (ICF) to the reviewing ethics committee, and obtain written approval before beginning study participation.
- Fulfill any conditions of approval imposed by the institutional review board/ethics committee, such as regular reporting.
- Provide the sponsor with copies of approvals and reports.
- Comply with the informed consent procedures, using the approved ICF.
- Ensure that the investigational device is used solely by authorized users for purposes of conducting the study in accordance with this protocol and the IFU.
- Maintain accurate, complete, and current records relating to the conduct of the study.
- Report study data and any protocol deviations to the sponsor promptly.
- Report adverse events, device deficiencies and device malfunctions to the sponsor (and to the institutional review board/ethics committee as required) promptly.
- Make available, at the sponsor's request, all study-related data (including source documentation) and study-related documentation (including institutional review board/ethics committee approvals and correspondence) for monitoring or auditing purposes.


19.2 Sponsor Responsibilities

Tendyne is the sponsor of this study. Sponsor responsibilities include, but are not limited to, the following:

- Select and qualify investigative sites and principal investigators.
- Provide training to investigators and investigative site staff.
- Ensure approval/permission from regulatory body as required by geography.
- Select qualified monitors and ensure that adequate monitoring of clinical data occurs at the investigative sites.
- Retain ownership of all data generated in this study, and control the use of the data for appropriate purposes only.
- Collaborate with investigators on publishing study results.


19.3 Echocardiography Core Laboratory

The sponsor will contract with an echocardiography core lab to manage and evaluate the echocardiogram studies. Interpretation of echocardiograms will be done by experienced personnel with appropriate expertise. The echocardiography core lab will provide independent analysis of echocardiogram images and will maintain a database in accordance with their established standard operating procedures. The data will then be transferred to and reported by the sponsor.



19.4 Computed Tomography Core Laboratory

The sponsor will contract with a computed tomography core lab to manage and evaluate the tomographic studies. Interpretation of tomographic images will be done by experienced personnel with appropriate expertise. The computed tomography core lab will provide independent analysis of computed tomography images and will maintain a database in accordance with their established standard operating procedures. The data will then be transferred to and reported by the sponsor.



It is a responsibility of the Core Laboratories to evaluate whether a subject is suitable for treatment with the Tendyne Mitral Valve and select the most suitable valve model and size

based on the imaging evaluation of the individual's mitral valve by multiple modalities including echocardiography and computed tomography. The anatomy of the mitral valve is complex and highly variable between subjects. For this reason, it is not possible to determine generic criteria applicable to all subjects, and an in-depth evaluation must be performed in every single candidate by the Echo and CT Core Labs using dedicated software programs. Mitral valve modeling is performed with the aid of special software: Circle cardiovascular imaging software, www.circlecvi.com as recently published by the core lab;⁹⁸ and Mimics (biomedical.materialise.com/mimics) for medical image segmentation and engineering on anatomy. The anatomical suitability is documented in each subject, see example in the IB (Appendix 2, Pre-procedural plan example).

19.5 Clinical Events Committee (CEC)

An independent Clinical Events Committee (CEC) will be established. The CEC will consist of clinicians who are not investigators in the study and who do not have any significant investment in the sponsor or its competition. At least three clinicians will serve on the CEC.

The CEC will be responsible for reviewing and classifying all serious adverse events, device-related adverse events, and deaths. Refer to 22 for AE definitions.

The CEC will meet periodically throughout the study. CEC operations will be determined early in the study and formalized in a CEC charter.

19.6 Data and Safety Monitoring Board (DSMB)

An independent Data and Safety Monitoring Board (DSMB) will be established. Members will not have any significant investment in the sponsor or its competition. The DSMB will consist of one statistician and at least two physicians.

The role of the DSMB will be to monitor the overall conduct of the study, the rights, safety, and welfare of the study participants, and to evaluate interim data to determine if there are any specific safety concerns. The DSMB will be responsible for communicating any safety or scientific concerns or perceived problems with the study to the sponsor as soon as possible. At the conclusion of each DSMB meeting, a recommendation will be made to the sponsor on whether to continue, suspend, modify, or stop the study.

The DSMB will meet periodically throughout the study. DSMB operations will be determined early in the study and formalized in a DSMB charter. DSMB activities and members may overlap with the CEC as appropriate.

19.7 Publications Committee

The sponsor may form a publications committee to make decisions regarding authorship and content of publications. The publications committee's mission would be to construct a plan for topics and journals to target. Any investigator intending to publish should inform the sponsor and attempt to collaborate.

20 Device Accountability

The investigator or delegate must maintain a log to document the status/location of each investigational device provided by the sponsor for use in the study. The log will include the following as applicable: date of receipt, lot number, subject ID, disposition, reason, quantity and date of return to sponsor. Devices allocated to a site must be stored in a secured area until used. All explanted devices must be returned to the sponsor.

Procedures for returning explanted devices are provided in Section 15. At study closeout, the sponsor will collect all unused devices.

21 Study Closure

21.1 Suspension or Early Termination

The entire study or any individual site may be suspended or terminated prematurely by the sponsor based on recommendation from the DSMB or if otherwise deemed necessary. In the event of suspension or early termination, the sponsor will promptly inform principal investigators and ensure that institutional review boards/ethics committees are notified of the stoppage and the reason for it in line with Medical Device Directive 93/42/EEC Article 15.7 and national regulations. Subjects must continue to be followed per the protocol unless there is other direction from the sponsor.

21.2 Routine Closeout

At the end of the study, routine closeout activities will be conducted to ensure site records are complete, study data are complete and accurate, remaining study materials and investigational devices are returned to the sponsor, arrangements are made for record retention, and institutional review boards/ethics committees are notified.

22 Appendix A

Normative References

- ISO 14155 ISO 14155:2011(E). Clinical investigation of medical devices for human subjects — Good clinical practice.
- ISO 5840-3 ISO 5840-3:2013(E). Cardiovascular implants — Cardiac valve prostheses — Part 3: Heart valve substitutes implanted by transcatheter techniques.
-

Adverse Device Effect (from ISO 14155)

Adverse event related to the use of an investigational medical device.

Adverse Event

Events that fall under the definition of Adverse Event from either ISO 14155 or ISO 5840-3: (from ISO 14155) 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.

Note 1 This definition includes events related to the investigational medical device or the comparator.

Note 2 This definition includes events related to the procedures involved.

Note 3 For users or other persons, this definition is restricted to events related to investigational medical devices.

(from ISO 5840-3) Untoward medical occurrence in a study subject, which does not necessarily have to have a causal relationship with study treatment.

Bleeding (from BARC)

Six types are hierarchically defined from type 0 in which there is no bleeding to type 5 with fatal bleeding. Type 1 is in which the patient does not seek treatment. Type 2 is in which intervention or admission to hospital occurs. Type 3a is overt bleeding plus hemoglobin drop of 3 to less than 5 g/dl or transfusion. Type 3b is overt bleeding plus hemoglobin drop of at least 5 g/dl, cardiac tamponade, bleeding requiring surgical intervention or intravenous vasoactive agents. Type 3c is intracranial hemorrhage or intraocular bleeding compromising vision. Type 4 is coronary artery bypass grafting-related bleeding and type 5 is fatal bleeding.

Body Surface Area (from ISO 5840-3)

Total surface area (m²) of the human body. NOTE: This can be calculated (Mosteller's formula) as the square root of product of the weight in kg times the height in cm divided by 3600.

Cardiac Index (from ISO 5840-3)

Cardiac output divided by the body surface area in units L/min/m².

Cardiovascular Death (from VARC II)

Any of the following criteria:

- Death due to proximate cardiac cause (e.g., myocardial infarction, cardiac tamponade, worsening heart failure)
- Death caused by non-coronary vascular conditions such as neurological events, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular disease
- All procedure-related deaths, including those related to a complication of the procedure or treatment for a complication of the procedure
- All valve-related deaths including structural or non-structural valve dysfunction or other valve-related adverse events
- Sudden or unwitnessed death
- Death of unknown cause

Non-cardiovascular death is any death in which the primary cause of death is clearly related to another condition (e.g., trauma, cancer, suicide).

Causal Relationship (from ISO 5840-3)

Causal relationship is the relationship of the AE to the study device, the implant procedure or the patient's condition. It should be established in line with the following categories:

- **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.
- **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.
- **Unknown:** Any AE that cannot be assigned to any of the above three conditions.

Chronic Kidney Disease, Stages (from National Institute for Health & Clinical Excellence. Clinical Guideline 73: Chronic Kidney Disease, London 2008)

- **Stage 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.
- **Stage 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.
- **Stage 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.
- **Stage 4:** Severe reduction in GFR (15–29 mL/min/1.73 m²) Preparation for renal replacement therapy.

- **Stage 5:** Established kidney failure (GFR <15 mL/min/1.73 m²), permanent renal replacement therapy, or end stage renal disease.

Cycle (from ISO 5840-3)

One complete sequence in the action of a heart valve substitute under pulsatile flow conditions.

Contract Research Organization (from ISO 14155)

Person or organization contracted by the sponsor to perform one or more of the sponsor's clinical investigation-related duties and functions.

Data Monitoring Committee/Data and Safety Monitoring Board (from ISO 14155)

Independent committee that may be established by the sponsor to assess, at intervals, the progress of the clinical investigation, the safety data or the critical performance endpoints and to recommend the sponsor whether to continue, suspend, modify, or stop the clinical investigation.

Device Deficiency (from ISO 14155)

Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors, and inadequate labeling.

Device Embolization (from ISO 5840-3)

Dislodgment from the intended and documented original position to an unintended and non-therapeutic location.

Device Failure (from ISO 14155 and ISO 5840-3)

Inability of a device to perform its intended function sufficient to cause a hazard.

Device Migration (from ISO 5840-3)

Detectable movement or displacement of the device from its original position within the implant site, without embolization.

Ethics Committee (from ISO 14155)

Independent body whose responsibility it is to review clinical investigations in order to protect the rights, safety, and well-being of human subjects participating in a clinical investigation. NOTE: "Ethics Committee" is synonymous with "research ethics committee", "independent ethics committee" or "institutional review board". The regulatory requirements pertaining to ethics committees or similar institutions vary by country or region.

Follow-up (from ISO 5840-3)

Continued assessment of patients who have received the heart valve substitute.

Heart Valve Substitute (from ISO 5840-3)

Device used to replace the function of a natural valve of the heart.

Implant Site (from ISO 5840-3)

Intended site of transcatheter heart valve substitute deployment.

Informed Consent Process (from ISO 14155)

Process by which an individual is provided information and is asked to voluntarily participate in a clinical investigation. NOTE: Informed consent is documented by means of a written, signed and dated informed consent form.

Intended Use (from ISO 5840-3)

Use of a product, process or service in accordance with the specifications, instructions and information provided by the manufacturer.

Investigation Site/Investigational Site (from ISO 14155)

Institution or site where the clinical investigation is carried out. NOTE: "Investigation site" is synonymous with "investigation centre".

Investigational Device/Investigational Medical Device (from ISO 14155)

Medical device being assessed for safety or performance in a clinical investigation.

Investigator (from ISO 14155)

Individual member of the investigation site team designated and supervised the principal investigator at an investigation site to perform critical clinical-investigation-related procedures or to make important clinical-investigation-related decisions. NOTE: An individual member of the investigation site team can also be called "sub-investigator" or "co-investigator".

Legally Authorized Representative (from ISO 14155)

Individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical investigation.

Malfunction (from ISO 14155)

Failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or clinical study protocol.

Myocardial Infarction, Peri-procedural (from VARC II)

Peri-procedural is ≤ 72 hours after the index procedure.

- New ischemic symptoms (e.g., chest pain or shortness of breath), or new ischemic signs (e.g., ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q-waves in at least two

contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality) AND

- Elevated cardiac biomarkers (preferable CK-MB) within 72 hours after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15 x as the upper reference limit for troponin or 5 x for CK-MB. If cardiac biomarkers are increased at baseline (> 99th percentile), a further increase in at least 50% post-procedure is required AND the peak value must exceed the previously stated limit.

Myocardial Infarction, Spontaneous (from VARC II)

Spontaneous is prior to or >72 hours after the index procedure.

Any one of the following criteria:

- Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with the evidence of myocardial ischemia with at least one of the following:
 - Symptoms of ischemia
 - ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block (LBBB))
 - New pathological Q-waves in at least two contiguous leads
 - Imaging evidence of a new loss of viable myocardium or new wall motion abnormality
 - Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumable new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
 - Pathological findings of an acute myocardial infarction.

Non-Structural Valve Dysfunction (from ISO 5840-3)

Abnormality extrinsic to the transcatheter heart valve substitute that results in valve dysfunction (stenosis, regurgitation, or both).

Principal Investigator (from ISO 14155)

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

Protocol Deviation

Instance of failure to follow, intentionally or unintentionally, the requirements of the clinical study protocol.

Regurgitant Fraction (from ISO 5840-3)

Regurgitant volume expressed as a percentage of the forward flow volume.

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.

Serious Adverse Device Effect (SADE) (from ISO 14155)

Adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Serious Adverse Event (from ISO 14155)

Adverse event that

- a) Led to death,
- b) Led to serious deterioration in the health of the subject, that either resulted in
 - 1) A life-threatening illness or injury, or
 - 2) A permanent impairment of a body structure or a body function, or
 - 3) In-patient or prolonged hospitalization, or
 - 4) Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) Led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the study protocol, without serious deterioration in health, is not considered a serious adverse event.

Severity (from ISO 5840-3)

Measure of the possible consequences of a hazard.

Source Data (from ISO 14155)

All information in original records, certified copies of original records of clinical findings, observations, or other activities in a clinical investigation, necessary for the reconstruction and evaluation of the clinical investigation.

Source Document (from ISO 14155)

Printed, optical, or electronic document containing source data.

Stroke and TIA (from VARC II)

Diagnostic criteria:

- 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.
- **Disabling Stroke:** A modified Rankin Scale (mRS) score of 2 or more at 90 days and an increase in at least one mRS category from an individual's pre-stroke baseline.
- **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.

Stroke Classification

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

- **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.

Structural Valve Dysfunction (from ISO 5840-3)

Structural abnormality intrinsic to the transcatheter heart valve substitute that results in valve dysfunction (stenosis and/or transvalvular and/or paravalvular regurgitation)

Subject (from ISO 14155)

Individual who participates in a clinical investigation.

Usability (from ISO 5840-3)

Characteristic of the user interface that established effectiveness, efficiency, ease of user learning and user satisfaction.

Unanticipated Serious Adverse Device Effect (USADE) (from ISO 14155)

Serious adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Use Error (ISO 14155)

Act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

23 Appendix B, Statistical Methodologies

23.1 Scope of Analysis

This addendum integrates the analysis plan described in protocol Section 8. The analysis presented in this Addendum, will be applied to data from all patients enrolled in the study and suitable to be implanted with the Tendyne 1.0 valve and Tendyne LP valve in Europe and worldwide.

23.2 Purpose

The data gathered in this study will be used to support conformity requirements for CE Mark of the Tendyne Mitral Valve using an appropriately powered sample size as described in Section 1 to enable assessment of the 30-day safety and performance endpoints of the Tendyne Mitral Valve System in the intended populations.

This study will be continued after the CE Mark to include a maximum of 350 patients enrolled at a maximum of 40 clinical sites with the purpose to collect broader safety and performance data as part of the Tendyne post-market follow-up program. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

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.

23.3 Hypotheses (H0, HA) for 30-day mortality

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

23.4 Calculation of Sample Size for Mortality

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

23.5 Criteria for Termination

[REDACTED]

Additionally, the independent Data Safety Monitoring Board (DSMB) will be monitoring the conduct of the trial. The protocol Section 21.1 states that the entire study or any individual site may be suspended or terminated prematurely by the sponsor based on recommendation from the DSMB or if otherwise deemed necessary. Possible reasons for early study termination include the discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study. For details, refer to protocol Section 19.6.

The role of the DSMB is described in the protocol Section 19.6. The DSMB is responsible for the study review and to recommend any modification or study termination for any perceived safety concern based on clinical judgement, including but not limited to: a higher than anticipated rate for any component of the primary safety endpoint; device failures resulting in adverse events; or unexpected SAEs. Possible reasons for early study termination include the discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.

At the conclusion of each DSMB meeting, a recommendation will be made to the sponsor on whether to continue, suspend, modify or stop the study.

23.6 Analysis Populations

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24 Appendix C

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