Abbott	Clinical Investigation Plan Cover Page

NCT Number: NCT03433274
SUMMIT
Trial to Evaluate the Safety and Effectiveness of Using the Tendyne Transcatheter Mitral Valve System for the Treatment of Symptomatic Mitral Regurgitation (SUMMIT)
Study Document No: ABT-CIP-10241
Version E
Date: 05-MAY-2022

Sponsor

Abbott Medical
177 County Road B East
St. Paul, MN 55117
United States of America

Abbott

[redacted]

SUMMIT

Clinical Trial to Evaluate the **S**afety and Effectiveness of **U**sing the Tendyne Transcatheter **M**itral Valve System for the Treatment of Symptomatic **Mit**ral Regurgitation

IDE Number	G140240
Version Number	Version E
Date	5 May 2022
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
Trial Type	Prospective, controlled, multicenter clinical investigation of the Tendyne™ Transcatheter Mitral Valve System for the treatment of eligible subjects with symptomatic, severe mitral regurgitation.
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Tendyne™ Transcatheter Mitral Valve System

CLINICAL INVESTIGATION PLAN
SITE PRINCIPAL INVESTIGATOR (PI) SIGNATURE PAGE

Clinical Trial to Evaluate the **S**afety and Effectiveness of **U**sing the Tendyne Transcatheter **M**itral Valve System for the Treatment of Symptomatic **Mit**ral Regurgitation (SUMMIT)

Clinical Investigation Plan No. [redacted]

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

Investigational Site Name

Site PI Signature Date

Site PI Printed Name

[redacted]

SUMMIT
TENDYNE TRIAL

Tendyne™ Transcatheter Mitral Valve System

CLINICAL INVESTIGATION PLAN
STUDY PRINCIPAL INVESTIGATOR (PI) SIGNATURE PAGE

Clinical Trial to Evaluate the **S**afety and Effectiveness of **U**sing the Tendyne Transcatheter **M**itral Valve System for the Treatment of Symptomatic **Mit**ral Regurgitation (SUMMIT)

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Investigational Site Name

Study PI Signature Date

Study PI Printed Name

[redacted]

Table of Contents

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TABLE OF FIGURES

TABLE OF TABLES

COMPLIANCE STATEMENT

This trial will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812 and OUS ISO 14155:2020) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations will always be followed. The conduct of the trial will be approved by the appropriate IRB/EC of the respective investigational site and by the applicable regulatory/competent authorities (e.g. FDA, PMDA, Health Canada, etc.).

[redacted]

CLINICAL INVESTIGATION PLAN SUMMARY

Trial Name and Number	SUMMIT [redacted]
Title	Clinical Trial to Evaluate the **S**afety and Effectiveness of **U**sing the Tendyne Transcatheter **Mi**tral Valve System for the Treatment of Symptomatic **Mit**ral Regurgitation
Objectives	To evaluate the safety and effectiveness of the Tendyne™ Transcatheter Mitral Valve System for the treatment of patients with symptomatic, moderate-to-severe or severe mitral regurgitation or for patients with symptomatic mitral valve disease due to severe mitral annular calcification.
Investigational Device	Tendyne Transcatheter Mitral Valve System
Clinical Trial / Investigation Design	Prospective, controlled, multicenter clinical investigation of the Tendyne Transcatheter Mitral Valve System (Tendyne) for the treatment of eligible subjects with symptomatic, moderate-to-severe or severe MR (≥ Grade III per American Society of Echocardiography criteria), or severe mitral annular calcification (MAC) for whom the site heart team deems transcatheter treatment is more appropriate than conventional mitral valve surgery. SUMMIT is a pre-market, interventional, pivotal investigation of the Tendyne Transcatheter Mitral Valve System. Subjects will be assigned to a cohort of the study at the discretion of the local site heart team. Subjects must satisfy the trial inclusion/exclusion criteria and be approved by the Subject Eligibility Committee (SEC), prior to treatment in the trial. **Randomized Cohort:** Subjects suitable for transcatheter mitral valve replacement (TMVR) with Tendyne and indicated for transcatheter edge-to-edge repair (TEER) with the MitraClip™ will be randomized in a 1:1 ratio to receive either Tendyne (Treatment) or MitraClip (Control). Subjects with primary MR must be at prohibitive surgical risk, while subjects with secondary MR must be symptomatic despite maximally-tolerated guideline-directed medical therapy in accordance with the MitraClip Indications for Use. Randomization will be stratified by investigational site. **Non-repairable Cohort**: Subjects with valve anatomies appropriate for Tendyne TMVR but not suitable for TEER will be eligible to enroll in the Non-repairable cohort, in which all subjects will receive treatment with the Tendyne system.

[redacted]

	Severe MAC Cohort: Subjects who have severe MAC resulting in symptomatic mitral valve disease (MR ≥ Grade III, or severe mitral stenosis (MS), or both moderate MR and moderate MS in the assessment of the Echocardiographic Core Laboratory) rendering the subject unsuitable for mitral valve surgery will be eligible to enroll in the MAC cohort, in which all subjects will receive treatment with the Tendyne system. **Severe MAC Continued Access Plan (CAP) Cohort**: After completion of enrollment in the Severe MAC cohort [redacted] who have severe MAC rendering the subject unsuitable for mitral valve surgery may be eligible to enroll in the Severe MAC CAP Cohort, in which all subjects will receive treatment with the Tendyne system.
Planned Sample Size / Investigational Sites	[redacted] up to 80 sites in United States, Canada, Europe, and Japan. [redacted]
Randomized Cohort - Primary Composite Endpoint (Non-Inferiority)	
Primary Composite Endpoint	Freedom from all-cause mortality and heart failure hospitalization at 12 months post index procedure
Randomized Cohort – Secondary Endpoints	
Secondary Endpoints	• *Effectiveness*: Freedom from MR > mild at 30 days post index procedure among survivors • *Safety*: Freedom from all-cause mortality and mitral valve reintervention at 12 months post index procedure

[redacted]

	• Improvement in Quality of Life (QoL), as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) by at least 10 points at 12 months from baseline compared between treatment and control • Proportion of New York Heart Association (NYHA) Functional Classification I or II at 12 months compared between treatment and control • Improvement in distance walked on the 6 Minute Walk Test (6MWT distance or 6MWD) by at least 50 meters at 12 months from baseline compared between treatment and control
Non-repairable Cohort - Primary Composite Endpoint (Performance goal)	
Primary Composite Endpoint	Freedom from all-cause mortality and heart failure hospitalization at 12 months post index procedure
Non- repairable Cohort – Secondary Endpoints	
Secondary Endpoints	• Change in Quality of Life (QoL), as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 6 months and 12 months • Improvement of New York Heart Association (NYHA) Functional Classification I or II at 12 months • Change in distance walked on the 6 Minute Walk Test (6MWT distance or 6MWD) at 6 months and 12 months
Severe MAC Cohort - Primary Endpoint (Performance goal)	
Primary Endpoint	Freedom from all-cause mortality and heart failure hospitalization at 12 months post index procedure
Severe MAC Cohort - Secondary Endpoints (Performance goals)	
Secondary Endpoints	• Freedom from MR > mild in severity at 30 days post index procedure among survivors • Change in Quality of Life (QoL), as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 6 months and 12 months • Improvement of New York Heart Association (NYHA) Functional Classification I or II at 12 months • Change in distance walked on the 6 Minute Walk Test (6MWT distance or 6MWD) at 6 months and 12 months
Severe MAC CAP Cohort - Primary Endpoint (Descriptive)	

[redacted]

Primary Endpoint	Freedom from all-cause mortality and heart failure hospitalization at 12 months post index procedure
Secondary Endpoints	• Freedom from MR > mild in severity at 30 days post index procedure among survivors • Change in Quality of Life (QoL), as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 6 months and 12 months • Improvement of New York Heart Association (NYHA) Functional Classification I or II at 12 months • Change in distance walked on the 6 Minute Walk Test (6MWT distance or 6MWD) at 6 months and 12 months
Descriptive Endpoints – All cohorts	
Clinical Endpoints	• All-cause mortality, CV hospitalizations, all stroke or MV reintervention or reoperation, at 2 years post index procedure and then yearly through 5 years • Change from baseline in distance walked on the 6MWT at each follow-up visit • Change from baseline in QoL, as measured by the KCCQ at each follow-up visit • Change from baseline in health outcomes, as measured by the EQ-5D questionnaire, at each follow-up visit • Change from baseline in health outcomes, as measured by the 12-item Short Form Health Survey (SF-12), at each follow-up visit • NYHA Functional Classification at each follow-up visit • Number of days alive and out of hospital from the time of the index procedure to 12 months, and then yearly through 5 years • Length of index hospitalization for procedure • Annualized rate of heart failure hospitalization • Change from baseline in BNP or NT pro-BNP levels, at all follow-up visits • All-cause mortality at 30 days, 1 year, and then yearly through 5 years
MVARC Endpoints	The following Mitral Valve Academic Research Consortium (MVARC) measures of success will be captured: • Technical Success (measured at exit from procedure room) • Device Success (measured at 30 days and at all later post-procedural intervals) • Procedural Success (measured at 30 days)

[redacted]

	• Patient Success (measured at 12 months)
Echocardiographic Endpoints	The following echocardiographic endpoints, as adjudicated by the Echocardiography Core Laboratory, will be reported at baseline, discharge, 1 month, 6 months, 12 months, and then annually through 5 years. For continuous variables, change from baseline to each follow-up will also be reported: • MR severity grade • Effective Regurgitant Orifice Area (EROA) • Regurgitant Volume • Regurgitant Fraction • Left Ventricle End Diastolic Volume (LVEDV) • Left Ventricular End Systolic Volume (LVESV) • Left Ventricular End Diastolic Dimension (LVEDD) • Left Ventricular End Systolic Dimension (LVESD) • Left Ventricular Ejection Fraction (LVEF) • Right Ventricular Systolic Pressure (RVSP) • Mitral Valve Area • Mean Mitral Valve Gradient • Mean Left Ventricular Outflow Tract Gradient • Cardiac Output • Forward Stroke Volume
Subject Follow-up	Subjects will be evaluated at the following trial intervals: **Visit 1** – Screening / Baseline **Visit 2** – Procedure **Visit 3** – Pre-discharge **Visit 4** – Follow up 30 days post procedure **Visit 5** – Follow-up 90 days post procedure **Visit 6** – Follow-up 182 days post procedure **Visit 7** – Follow-up 365 days post procedure **Visit 8** – Follow-up 731 days post procedure **Visit 9** – Follow-up 1096 days post procedure **Visit 10** – Follow-up 1461 days post procedure **Visit 11** – Follow-up 1826 days post procedure / End of Trial

[redacted]

Planned Duration of Trial	[redacted]
Eligibility Criteria	
Inclusion Criteria	1. Symptomatic, moderate-to-severe or severe mitral regurgitation (MR ≥ Grade III per American Society of Echocardiography criteria), or severe mitral annular calcification (MAC), where a transcatheter therapy is deemed more appropriate than conventional mitral valve surgery by the local site heart team. **Note:** MR and MS severity must be determined by assessment of a qualifying transesophageal echocardiogram (TEE) and transthoracic echocardiogram (TTE), obtained within 120 days prior to subject consent, and must be confirmed by the Echocardiography Core Laboratory. **Note:** Patients with severe MAC must have symptomatic mitral valve disease associated with MR ≥ Grade III, or severe mitral stenosis (MS), or both moderate MR and moderate MS as assessed by the Echocardiography Core Laboratory. 2. NYHA Functional Classification ≥ II (if Class IV, patient must be ambulatory). 3. The local site heart team determines that the subject has been adequately treated per applicable standards for coronary artery disease (e.g., revascularization), left ventricular dysfunction (e.g., cardiac resynchronization therapy) and heart failure (e.g., GDMT). The SEC must concur that the subject has been adequately treated. 4. The local site heart team and the SEC concur on the intended study cohort for the subject. **Randomized cohort:** Eligibility for this cohort is limited to subjects where the local site heart team deems the mitral valve anatomy is suitable for TEER and are within approved MitraClip indications, which must be confirmed by experienced MitraClip operators from the SEC. Subjects with primary MR must be at prohibitive surgical risk, while subjects with secondary MR must be symptomatic despite maximally-tolerated guideline-directed medical therapy and meet the MitraClip Indications for Use. **Non-repairable cohort:** Eligibility for this cohort is limited to subjects where the local site heart team deems the mitral valve anatomy is not suitable for TEER with MitraClip or does not meet MitraClip indications, which must be confirmed by experienced MitraClip operators from the SEC.

[redacted]

	Severe MAC cohort: Eligibility for this cohort is limited to subjects where the local site heart team deems the degree of MAC renders the subject unsuitable for mitral valve surgery. **Severe MAC CAP cohort:** Eligibility for this cohort is identical to the pivotal SUMMIT Severe MAC cohort. 5. Age 18 years or older at time of consent. 6. Subject has been informed of the nature of the trial and agrees to its provisions, including the possibility of randomization to the Control group, complying with trial required testing, medications, and follow-up visits, and has provided written informed consent.
Exclusion Criteria	1. Mitral valvular vegetation or mass. 2. Left Ventricle (LV) or Left Atrium (LA) thrombus. 3. Chest condition that prevents transapical access. 4. Left Ventricular Ejection Fraction (LVEF) less than 25% assessed by the site based on a TTE obtained within 120 days prior to subject consent. **Note:** LVEF will be principally based on TTE and must be confirmed by the Echocardiography Core Laboratory. 5. Left Ventricular End Diastolic Diameter (LVEDD) > 7.0 cm assessed by the site based on a TTE obtained within 120 days prior to subject consent. **Note:** A qualifying LVEDD must be confirmed by the Echocardiography Core Laboratory. 6. Prior surgical or interventional treatment of mitral valve involving implantation of prosthetic material (e.g. valve repair or replacement, or MitraClip). 7. Mitral pathoanatomy and Left Ventricular Outflow Tract (LVOT) anatomy deemed not suitable for Tendyne transcatheter mitral valve implantation. 8. Aortic valve disease requiring surgery or transcatheter intervention. 9. Tricuspid valve disease requiring surgery or transcatheter intervention. 10. Severe tricuspid regurgitation or severe right ventricular dysfunction. 11. Any surgical or interventional procedure within the period of 60 days prior to or planned procedure 60 days following subject registration. 12. Implant or revision of Cardiac Resynchronization Therapy (CRT) device within 90 days prior to intended subject registration.

[redacted]

	13. Myocardial Infarction (MI) within 30 days prior to intended subject registration. 14. Symptomatic, unresolved multi-vessel or unprotected left main coronary artery disease (e.g., active ischemia) requiring stenting or Coronary Artery Bypass Grafting (CABG). 15. Cerebrovascular accident (CVA) within 6 months prior to intended subject registration. 16. Unresolved severe symptomatic carotid stenosis (> 70% by ultrasound). 17. Cardiogenic shock or hemodynamic instability requiring inotropes or mechanical support devices at the time of planned implant procedure. 18. Hypertrophic or restrictive cardiomyopathy, or constrictive pericarditis. 19. Any of the following: leukopenia, acute anemia, thrombocytopenia, history of bleeding diathesis, or coagulopathy if cannot be adequately treated. 20. History of endocarditis within 6 months of planned implant procedure. 21. Active systemic infection requiring antibiotic therapy. 22. Known hypersensitivity or contraindication to procedural or post-procedural medications (e.g., contrast solution, anti-coagulation and antiplatelet therapy) that cannot be adequately managed medically. 23. Subjects in whom TEE is contraindicated or high risk. 24. Known hypersensitivity to nickel or titanium. 25. Subject is undergoing hemodialysis due to chronic renal failure. 26. Subject has pulmonary arterial hypertension (fixed PAS >70mmHg). **Note:** If PAS > 70mmHg, site must provide documentation PAS is not fixed in order to be eligible. 27. Subject has Chronic Obstructive Pulmonary Disease (COPD) requiring continuous home oxygen therapy or chronic outpatient oral steroid use. 28. Subjects with non-cardiac comorbidities that are likely to result in a life expectancy of less than 12 months. 29. Modified Rankin Scale ≥ 4 disability. 30. Status 1 heart transplant or prior orthotopic heart transplantation. 31. Pregnant, lactating, or planning pregnancy during the clinical investigation follow-up period. **Note:** Female subjects of childbearing age should be instructed to use safe contraception (e.g. intrauterine devices, hormonal

[redacted]

	contraceptives: contraceptive pills, implants, transdermal patches hormonal vaginal devices, injections with prolonged release). 32. Currently participating in an investigational drug or another device trial that has not reached its primary endpoint. **Note:** Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials. 33. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.

[redacted]

1 INTRODUCTION

SUMMIT is a pre-market, interventional, pivotal investigation of the Tendyne Transcatheter Mitral Valve System. The objective of SUMMIT (Clinical Trial to Evaluate the **S**afety and Effectiveness of **U**sing the Tendyne Transcatheter **M**itral Valve System for the Treatment of Symptomatic **Mit**ral Regurgitation) is to evaluate the safety and effectiveness of the Tendyne Transcatheter Mitral Valve System in eligible subjects with symptomatic, moderate-to-severe or severe mitral regurgitation (MR ≥ Grade III per American Society of Echocardiography criteria), or severe mitral annular calcification, where the site heart team deems a transcatheter approach is more appropriate than conventional mitral valve surgery.

The SUMMIT Severe MAC Continued Access Plan (CAP) is an expansion of the SUMMIT pivotal study designed to collect additional safety and clinical effectiveness data on the Tendyne Transcatheter Mitral Valve System in patients with severe MAC following completion of enrollment of subjects in the primary analysis population of the severe MAC cohort. The Severe MAC CAP cohort will allow additional patients to enroll in SUMMIT after completion of enrollment in the pivotal cohort. Conduct of the Severe MAC CAP cohort will follow the same protocol outlined for the pivotal IDE trial.

As the Sponsor, Abbott Medical ("Abbott") has the overall responsibility for the conduct of the trial, including assurance that the trial will be performed according to this Clinical Investigation Plan (CIP) and U.S. Food and Drug Administration (FDA) and any other applicable country's regulations. The Sponsor will have direct and indirect responsibilities for day-to-day trial management and may delegate responsibilities for some trial management activities to a Contract Research Organization (CRO).

This clinical investigation will be conducted in accordance with this CIP. All investigators involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

This CIP describes the requirements for the SUMMIT trial.

2 BACKGROUND INFORMATION

2.1 Background and Rationale

2.1.1 Clinical Need

Symptomatic, moderate-to severe and severe MR are associated with high morbidity and mortality [1]–[5]. This is particularly true of MR that results from myocardial dysfunction and adverse left ventricular (LV) remodeling (secondary or functional MR) [2]–[4], as opposed to MR arising from mitral leaflet pathology (primary or degenerative MR)[5]. Mitral annular calcification (MAC) is a degenerative process that can result in either mitral stenosis or MR, or a combination of both disorders.

Although medical therapies, such as beta-blockers and inhibitors of the renin-angiotensin-aldosterone pathways have been associated with reverse LV remodeling [6], and in some cases, a reduction in the severity of MR [7], the outlook for patients whose MR persists in spite of optimal medical therapy remains poor [2]. For these patients, surgical valve repair or replacement is an

[redacted]

option described in the current recommendations to guide management decisions [8]–[10]. Transcatheter mitral valve repair systems have also been evaluated for the treatment of MR. The most widely-used transcatheter mitral valve repair system is the MitraClip, which is based on the edge-to-edge repair technique [11]–[19]. However, to date, no transcatheter mitral valve implantation system is approved by the FDA for use, demonstrating a clinical need for additional transcatheter therapeutic options, in particular to treat patients with anatomies not suitable for transcatheter repair.

2.1.2 Current Guidelines

The American College of Cardiology/American Heart Association (ACC/AHA) have published guidelines for the management of valvular heart disease in 2017 [9], updated in 2020 [10]. Recommendations for intervention in secondary MR are in Class IIa or IIb, are included in **Table 1**. Note that management of patients with severe MAC is not addressed in the current guidelines. These patients do not have treatment options currently available except for continuation of medical care.

Table 1. ACC/AHA 2017 Recommendations for Secondary MR Intervention

COR	LOE	Recommendations	Comment/Rationale
IIa	**C**	**Mitral valve surgery is reasonable for patients with chronic severe secondary MR (stages C and D) who are undergoing CABG or AVR.**	2014 recommendation remains current.
IIa	**B-R**	**It is reasonable to choose chordal-sparing MVR over downsized annuloplasty repair if operation is considered for severely symptomatic patients (NYHA class III to IV) with chronic severe ischemic MR (stage D) and persistent symptoms despite GDMT for HF** [3], [4], [28]–[31], [20]–[27]	**NEW:** An RCT has shown that mitral valve repair is associated with a higher rate of recurrence of moderate or severe MR than that associated with mitral valve replacement (MVR) in patients with severe, symptomatic, ischemic MR, without a difference in mortality rate at 2 years' follow-up.
IIb	**B**	**Mitral valve repair or replacement may be considered for severely symptomatic patients (NYHA class III to IV) with chronic severe secondary MR (stage D) who have persistent symptoms despite optimal GDMT for HF** [3], [4], [30]–[32], [20]–[23], [26]–[29]**.**	2014 recommendation remains current.
IIb	**B-R**	**In patients with chronic, moderate, ischemic MR (stage B) undergoing CABG, the usefulness of mitral valve repair is uncertain [32,33]. MODIFIED: LOE updated from C to B-R.**	The 2014 recommendation supported mitral valve repair in this group of patients. An RCT showed no clinical benefit of mitral repair in this population of patients, with increased risk of postoperative complications.

The ACC/AHA recommendations are based on the following studies:

In a randomized control trial (RCT) of surgical mitral valve repair versus MVR in 251 patients with severe ischemic MR (IMR), mortality rate at 2 years was 19.0% in the repair group and 23.2%

[redacted]

in the replacement group (p=0.39) [25]. There was no difference between repair and MVR in LV remodeling. The rate of recurrence of moderate or severe MR over 2 years was higher in the repair group than in the replacement group (58.8% versus 3.8%, p<0.001), leading to a higher incidence of heart failure (HF) and repeat hospitalizations in the repair group. The high mortality rate at 2 years in both groups emphasizes the poor prognosis of secondary MR.

The lack of apparent benefit of surgical valve repair over valve replacement in secondary MR versus primary MR highlights that primary and secondary MR are two different disease etiologies [4], [30]–[32], [20]–[27].

The most recent guidelines concluded that the best mitral valve intervention for chronic secondary MR (beyond guideline directed medical therapy and cardiac resynchronization therapy) is unclear due to the limited evidence in the published literature. Consequently, there are no Class I recommendations for surgical mitral valve intervention (repair or replacement), and only a single IIa recommendation if surgical intervention is performed concomitant to other surgical interventions.

If left untreated, however, secondary MR will likely progress due to the associated progressive LV systolic dysfunction and adverse remodeling. Despite this, approximately half the patients with indications for correction of MR are not treated surgically due to advanced age, comorbidities, surgical contraindications, or a perception of low likelihood of benefit [33]. For these patients, less invasive transcatheter therapies have been evaluated as an adjunct to optimal medical therapy [34]. These therapies include strategies directed at leaflet repair [35], [36], annular reduction[37], or valve replacement[38].

As an alternative to conventional mitral valve surgery, two RCTs recently evaluated transcatheter mitral valve repair with the MitraClip system in conjunction with GDMT vs. GDMT alone in patients with secondary MR [39], [40]. The COAPT trial found a significant reduction in the annualized rate of all hospitalizations for heart failure within 24 months in the MitraClip + GDMT group vs. GDMT alone (35.8% per patient-year vs. 67.9% per patient-year) [39]. Additionally, 2-year mortality was also significantly reduced in the MitraClip + GDMT group compared to GDMT control (29.1% vs. 46.1%), demonstrating that treating moderate-to-severe or severe secondary MR improves outcomes in patients with advanced heart failure. Unlike COAPT, the MITRA-FR trial failed to demonstrate any benefit over GDMT [40]. Differences in outcomes between these trials are likely due to differences in the patients enrolled, i.e., COAPT enrolled patients with more severe MR that was disproportionate to the degree of LV dilatation compared to MITRA-FR [41]. These two complementary trials indicate that patients with moderate-to-severe or severe secondary MR benefit from valvular intervention and associated reduction in MR severity. Based on the results of these trials, the FDA recently approved an expanded indication for the MitraClip system to include secondary MR. Subsequently, TEER was recently added as a Class IIa recommendation in the ACC/AHA guidelines for patients who have chronic severe secondary MR, persistent symptoms (NYHA class II, III or IV) while on GDMT, appropriate valvular anatomy, LVEF between 20% and 50%, LVESD ≤ 70 mm, and pulmonary artery systolic pressure ≤ 70 mmHg [10].

Mitral stenosis (MS) is the most frequent valvular disorder caused by rheumatic fever [42]. While the prevalence of MS has overall decreased, rheumatic MS still accounts for approximately 10% of left-sided valve diseases in Europe, with a higher frequency observed in developing

[redacted]

countries[43], [44]. Interventional procedures are performed in over half of patients diagnosed with MS [43]. Recommendations for intervention in MS are in Class I, IIa or IIb, are included in **Table 2.**

Table 2: ACC/AHA 2020 Recommendations for Mitral Stenosis Intervention

COR	LOE	Recommendations
I	**A**	**In symptomatic patients (NYHA class II, III, or IV) with severe rheumatic MS (mitral valve area ≤1.5 cm2, Stage D) and favorable valve morphology with less than moderate (2+) MR* in the absence of LA thrombus, percutaneous mitral balloon commissurotomy (PMBC) is recommended if it can be performed at a Comprehensive Valve Center**
I	**B-NR**	**In severely symptomatic patients (NYHA class III or IV) with severe rheumatic MS (mitral valve area ≤1.5 cm^2, Stage D) who 1) are not candidates for PMBC, 2) have failed a previous PMBC, 3) require other cardiac procedures, or 4) do not have access to PMBC, mitral valve surgery (repair, commissurotomy, or valve replacement) is indicated.**
IIa	**B-NR**	**In asymptomatic patients with severe rheumatic MS (mitral valve area ≤1.5 cm^2, Stage C) and favorable valve morphology with less than 2+ MR in the absence of LA thrombus who have elevated pulmonary pressures (pulmonary artery systolic pressure >50 mm Hg), PMBC is reasonable if it can be performed at a Comprehensive Valve Center.**
IIb	**C-LD**	**In asymptomatic patients with severe rheumatic MS (mitral valve area ≤1.5 cm^2, Stage C) and favorable valve morphology with less than 2+/ MR* in the absence of LA thrombus who have new onset of AF, PMBC may be considered if it can be performed at a Comprehensive Valve Center.**
IIb	**C-LD**	**In symptomatic patients (NYHA class II, III, or IV) with rheumatic MS and an mitral valve area >1.5 cm^2, if there is evidence of hemodynamically significant rheumatic MS on the basis of a pulmonary artery wedge pressure >25 mm Hg or a mean mitral valve gradient >15 mm Hg during exercise, PMBC may be considered if it can be performed at a Comprehensive Valve Center.**
IIb	**B-NR**	**In severely symptomatic patients (NYHA class III or IV) with severe rheumatic MS (mitral valve area ≤1.5 cm^2, Stage D) who have a suboptimal valve anatomy and who are not candidates for surgery or are at high risk for surgery, PMBC may be considered if it can be performed at a Comprehensive Valve Center.**

Of patients receiving treatment for MS, over half of patients in developed nations undergo surgical valve replacement, which was attributed to more advanced valve deformities that could not be addressed with commissurotomy [43]. In such patients with significant valve deformation, if they

are unable to undergo surgery, a transcatheter mitral valve replacement (TMVR) may be the only option to effectively treat their valve disease.

2.1.3 Barriers to Guideline Adherence

Despite the existence of well-defined guidelines and the abundant literature that indicates the 10 year survival rate for medically managed patients ranges from 20 to 60% [45]–[49], several studies have shown that guideline adherence is poor, and many patients go without recommended surgical treatment [33], [50]–[52].

An evaluation of surgical interventions in the Euro Heart Survey showed that only 193 of 396 (48.7%) patients with symptomatic, severe MR had a surgical valve procedure [33]. 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 European Society of Cardiology (ESC) / European Association for Cardio-Thoracic Surgery (EACTS) guidelines [33]. Of the patients who do undergo surgery, an analysis of the STS Adult Cardiac Surgery Database found that secondary MR accounts for only 4.3% of isolated mitral valve surgeries [53].

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 [52]. 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 appropriately refer an NYHA Class II patient with severe MR and an LVEF >60%. Together, these studies demonstrate that mitral valve surgery is often not performed in the majority of patients with severe MR, motivating alternative treatment options.

2.1.4 Treatment of Mitral Annular Calcification

Patients with MAC are a unique subgroup of patients due to their marked increased surgical risk. In these patients, there is a high risk of atrioventricular groove disruption, a complication that is nearly universally fatal [54], [55]. Other potential complications that can occur with open surgical treatment of MAC include ventricular rupture and injury to the left circumflex coronary artery. The presence of MAC is associated with increased intraoperative conversion from valve repair to replacement [56]. In addition, MAC is typically accompanied by severe morbidities that significantly increase surgical risk, such as coronary atherosclerosis, vascular disease, and renal failure. Operative mortality for patients with severe MAC at a single center was 9.3%, compared to 1.5% for other mitral procedures over the same time period [57]. Thus, mitral valve surgery for treatment of MAC is reserved only for select patients.

In order to avoid or minimize the risk of surgical complications with treatment of MAC, several technical refinements to the surgical procedure have been developed. Mitral valve replacement without debridement of the mitral annulus has been utilized, though paravalvular regurgitation may occur due to the non-uniform sewing borders. In other instances, an edge-to-edge repair has been employed; the main limitation with this approach is worsening of pre-existing mitral stenosis that is common in these patients. Success with surgical dissection and reconstruction of the calcified annulus with suturing, a pericardial patch, or an atrial flap, followed by mitral repair or replacement also has been reported [58]–[60].

[redacted]

Transcatheter techniques for treatment of MAC using balloon-expandable aortic prostheses have been developed to obviate the need for open surgical correction and minimize the procedural risk. These off-label techniques have utilized direct atrial access, transseptal puncture, and transapical approaches for implanting transcatheter valves designed for treatment of calcific aortic stenosis. In the largest registry of transcatheter implantation of valve prostheses for the treatment of MAC (n=116), initial technical success was achieved in 89 patients (76.7%) [61]. While this registry demonstrates the feasibility of employing balloon-expandable aortic prostheses in patients with MAC, there were significant procedure-related complications including valve embolization in 4.3% of patients, left ventricular outflow tract obstruction with hemodynamic compromise in 11.2%, conversion to open heart surgery in 3.4%, and valve embolization in 4.3%. MR was reduced to trace or none in 51 patients (62.2%), highlighting the challenge of effective MR elimination in anatomies with significant MAC. The 30-day mortality observed was 25%, with a 1-year mortality of 53.7%. While these results represent an important advance in transcatheter therapies for patients not suitable for surgery, the rate of procedural complications and subsequent mortality observed in follow-up highlight the challenges of treating patients with severe MAC, motivating the study of novel transcatheter therapeutic options that may provide more effective MR reduction or an improved safety profile.

2.1.5 Transcatheter Edge-to-Edge Mitral Valve Repair (TEER)

Transcatheter mitral valve repair techniques have been developed with the aim of providing lower-risk therapies to improve MR-related mortality and morbidity, and to expand treatment options for patients who are not good surgical candidates. The leading system for transcatheter mitral valve repair is the MitraClip, which performs edge-to-edge repair. The MitraClip device has been evaluated in multiple feasibility studies in various patient cohorts [13], [16], [18], [62], in RCTs against MV repair surgery [12], [15] and guideline-directed medical therapy (GDMT) [39], [40], and in several registry studies [36], [63]–[65]. Compared to conventional mitral valve surgery, MitraClip treatment was less effective at reducing mitral regurgitation; however, MitraClip treatment was associated with fewer major adverse events at 30 days, and demonstrated sustained improvements in quality of life and heart failure symptoms [12]. Registry data has also demonstrated that while transcatheter repair can be safely performed in patients at prohibitive surgical risk and result in significant MR reduction, rates of death and heart failure hospitalization following treatment with MitraClip remain higher in patients with secondary MR than primary MR [36].

The outcomes from the Cardiovascular Outcomes Assessment of the Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial were recently published, which compared MitraClip + GDMT to GDMT alone in patients with moderate-to-severe or severe secondary MR [40]. The outcomes showed that MitraClip repair resulted in a significantly greater number of patients with sustained reduction of MR to Grade $\leq$ 2+ ($p < 0.004$), significantly improved quality of life (KCCQ; $p < 0.001$) and functional capacity (NYHA Class I/II; $p < 0.001$) at 12-months compared to GDMT treatment alone. At 24 months of follow-up, the MitraClip group also had a lower rate of hospitalization for heart failure ($p < 0.001$), and lower mortality ($p < 0.001$) versus GDMT treatment alone. These outcomes strongly suggest that there is a significant clinical benefit from transcatheter intervention in patients with severe secondary MR who may not be candidates for surgery.

[redacted]

Although the MitraClip system has demonstrated good procedural safety and clinical benefit from MR reduction, there is a population of patients with cardiac anatomies that are not suitable for the MitraClip procedure. A recent publication from the Heart Valve Collaboratory identified specific criteria that render patients as unsuitable TEER [66]. For these patient populations who are not candidates for open heart surgery and not suitable for transcatheter repair, including those with severe MAC, a transcatheter mitral valve replacement system may be the only option for treating their mitral valve disease.

2.1.6 Transcatheter Mitral Valve Replacement

Transcatheter mitral valve replacement (TMVR) has recently emerged as an exciting new frontier in the field of cardiac structural interventions. Although transcatheter aortic valve replacement (TAVR) is a well-established treatment option for patients with symptomatic severe calcific aortic stenosis, the experience with transcatheter mitral valve implantation remains at an earlier stage.

There have been important challenges in the development of this technology, including the complexity of the mitral valve anatomy involving a saddle-shaped elliptical annulus, the subvalvular apparatus, the interaction with the left ventricular outflow tract (LVOT) and the aortic valve, as well as the large size of TMVR devices and catheters for implantation [67].

Furthermore, the patients being considered for TMVR are usually high risk with multiple comorbidities, including frailty, pulmonary hypertension, or severe left ventricular systolic dysfunction, each of which negatively impact the overall clinical outcome. Despite these technical, anatomic, and clinical limitations, there has been significant progress in recent years.

2.1.7 Clinical Experience with the Tendyne Transcatheter Mitral Valve System

The Expanded Clinical Study of the Tendyne Transcatheter Mitral Valve System (NCT02321514), prospectively evaluated the use of the Tendyne Transcatheter Mitral Valve System, deployed using a transapical approach without cardiopulmonary bypass, in patients with severe native valve MR. The results of the first 30 patients through 30-day follow-up as well as the results of the first 100 patients through 1-year follow-up have been published in the Journal of the American College of Cardiology [68], [69].

The first 100 patients were enrolled between November 2014 and November 2017 at 24 sites (3 in Australia, 8 in Europe, and 13 in the United States) [69]. The MR etiology for these patients was secondary or mixed in 89 subjects, and primary in 11. The Tendyne Transcatheter Mitral Valve System had a high implantation success rate (97%) and a low procedural adverse event rate, with no operative deaths, strokes, or conversions to open heart surgery.

[redacted]

TTE at one-month follow-up showed no more than trace residual MR in 98.8% of patients, and 98.4% of patients having trace or less MR at one year, demonstrating sustained MR elimination. The majority (88.5%) of surviving patients reported mild or no symptoms at one-year follow-up (NYHA Class I or II). Improved quality of life was also observed, where 73.4% of surviving patients had >10-point improvement in their Kansas City Cardiomyopathy Questionnaire score.

[redacted]

The Tendyne Transcatheter Mitral Valve System has also been successfully implanted in nine patients with severe MAC under compassionate use [70]. Device implantation with complete relief of MR occurred in all patients, and there were no instances of device embolization, significant mitral stenosis, or need for cardiopulmonary bypass or hemodynamic support. Technical success was achieved in eight of the nine patients. [redacted] The positive experience in these patients motivated Abbott to develop a formal Feasibility Study of up to 30 patients that is ongoing in the US. Eleven patients were treated in this study, which is now closed for enrollment. To date, there has been one death within 30 days of the procedure in the combined compassionate use and MAC feasibility study experience (1/20, 5%). Though the current experience in patients with severe MAC is limited, these early outcomes compare extremely favorably to those reported with off-label use of balloon-expandable aortic prostheses in MAC, where 30-day mortality was 25% [61].

[redacted] The SUMMIT trial will continue to help define the role of TMVR in the array of management options for patients with symptomatic, moderate-to-severe or severe MR or severe MAC.

2.1.8 Rationale for Conducting this Clinical Trial / Investigation

The SUMMIT trial is designed to compare the Tendyne Transcatheter Mitral Valve System to the current standard of care for patients with mitral regurgitation. The objective of this trial is to investigate whether this technology holds promise for the large number of patients suffering from the debilitating symptoms of moderate-to-severe or severe mitral regurgitation and compare the outcomes to TEER with the MitraClip system. In addition, for patients who are not appropriate for mitral valve surgery and whose valve anatomy is not suitable for transcatheter repair or do not meet the MitraClip indications, including patients with severe MAC, the trial will offer the opportunity of treatment with the Tendyne system when patients are symptomatic in spite of pharmacologic management.

Based on the results of the Expanded Clinical Study of the Tendyne Transcatheter Mitral Valve System, the majority of patients enrolled in the randomized cohort are expected to have secondary MR. Therefore, MitraClip is the appropriate comparative treatment for this trial due to the significant reduction in mortality and HF hospitalization demonstrated by COAPT compared to GDMT alone, as well as the lack of strong guideline recommendations for mitral valve surgery [9] and the low rate of surgical corrections performed [33], [50]–[52] for patients with secondary MR.

The MitraClip system has demonstrated an excellent procedural safety profile [36], even in high-risk surgical patients [19], [71]. However, certain patients indicated for MitraClip have cardiac

[redacted]

anatomies that are less likely to experience effective MR reduction with MitraClip. Recurrent MR >1+ at 12-month follow-up was observed in 31% of subjects studied in COAPT and in 38% of patients in the TVT registry [36], [39]. In comparison, <2% of patients treated with Tendyne had more than trace MR at 1 year of follow-up, demonstrating the consistent MR reduction achieved with transcatheter replacement compared to repair [69]. This study will examine if more effective MR elimination achieved via transcatheter replacement is associated with improved clinical outcomes despite the increased invasiveness of the procedure. The higher likelihood of detrimental, residual MR following MitraClip treatment supports clinical equipoise between Tendyne and MitraClip treatment, balancing the greater likelihood of MR elimination with the Tendyne system that is achieved by a more invasive transapical procedure.

Additionally, the SUMMIT study will collect detailed clinical and anatomic data on patients in both the Randomized and Non-repairable cohorts. These data will be used to identify criteria predictive of outcomes for repair and replacement. Furthermore, these data will describe clinical and anatomic features used by the local site heart team to determine eligibility for either study cohort as part of the therapy selection process.

Patients who are not appropriate for MV surgery and whose valve anatomy is deemed not suitable for transcatheter repair by the local site heart team have limited treatment options. Patients with severe MAC are included in this category, as severe MAC often precludes both surgical treatment and MitraClip implantation. For these patients, medical management is the only therapeutic option. These patients will undergo the Tendyne procedure in the Non-repairable and Severe MAC cohorts.

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

- Reduction in hospitalization rate due to complete elimination of MR
- Improved symptomatic status and quality of life
- Reduced mortality
- Reduced rates of recurrent MR
- Mitral valve replacement with avoidance of risks associated with cardiopulmonary bypass (CPB)

Early data obtained from the Expanded Clinical Study of the Tendyne Transcatheter Mitral Valve System demonstrated that patients experience (post-procedure) reductions in MR severity and heart failure symptoms, along with improvements in quality of life and functional capacity, with relatively low mortality and rehospitalization rates (**Section 2.1.7**). These clinical benefits were also observed in patients with severe MAC. In consideration of the potential benefits and the risk profile of the Tendyne device, this clinical trial is scientifically and clinically justified.

2.1.9 Severe MAC CAP Rationale

The rationale for the Severe MAC CAP is to allow current study implanters to maintain their technical proficiency in Tendyne device implantation in the Severe MAC population, and to continue to collect safety and effectiveness data in this patient population. Data from the Severe MAC CAP cohort may be used to support the Pre-Market Approval (PMA) application for the Tendyne Transcatheter Mitral Valve system in patients with severe MAC.

[redacted]

2.2 Summary of Investigational Device

2.2.1 Name of the Investigational Device

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

2.2.2 Intended Indication for Use

The Tendyne Transcatheter Mitral Valve System is indicated for patients with symptomatic, moderate-to-severe or severe MR (MR ≥ Grade III per American Society of Echocardiography criteria), severe mitral stenosis, or both moderate MR and moderate MS, for whom a transcatheter therapy is deemed more appropriate than conventional mitral valve surgery by the local site heart team, whose valve and ventricular anatomies are suitable for Tendyne transcatheter mitral valve implantation and whose symptoms persist despite maximally-tolerated GDMT.

2.2.3 Description of the Investigational Device (Tendyne Transcatheter Mitral Valve System)

The Tendyne Transcatheter Mitral Valve System consists of the Tendyne Transcatheter Mitral Valve with Apical Pad and a Tendyne Transcatheter Mitral Valve Delivery System that facilitates placement of the valve. The Tendyne Transcatheter Mitral Valve is a bioprosthesis intended for transapical implantation within the native mitral valve. The valve includes two parts; a porcine pericardial bioprosthetic valve and an Apical Pad (connected by a braided tether). The valve has three porcine pericardial tissue leaflets sewn onto a circular, self-expanding frame made of nitinol. The inner frame is sewn inside a self-expanding nitinol outer frame. The outer frame helps orient the prosthesis inside the native mitral valve. There is a radiopaque marker at A1 that can be visualized under fluoroscopy to confirm orientation of the valve. The outer frame cuff is raised along the anterior aspect and is referred to as the A2 region. The valve is designed for radial orientation such that the anterior aspect of the cuff rests upon the aortomitral continuity. This orientation aligns the cuff with the anterior portion of the native mitral valve.

The frame is covered with a PET (polyethylene terephthalate) fabric cuff that provides the sealing surface within the native annulus. The self-expanding prosthesis is connected to a braided fiber tether made of polyethylene, intended to stabilize the valve by passing through the left ventricular myocardium near the apex, where it is fastened to an Apical Pad on the epicardium.

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

The Tendyne valve is available in several sizes to accommodate differing cardiac anatomies. The valve size should be selected to provide proper fit for paravalvular sealing, device stability and LVOT area. Standard imaging techniques should be used to assess the native mitral valve dimensions and left ventricular dimensions for valve sizing.

The Tendyne Transcatheter Mitral Valve Delivery System consists of a Tendyne Loading System, Tendyne Delivery System, and Tendyne Pad Positioning System. The Tendyne Retrieval System is also available to retrieve the valve intraoperatively, in the event the valve implant is suboptimal.

[redacted]

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

2.2.4 Procedures Involved in the Use of the Device

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

2.2.5 Training Required for the Use of the Device

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

2.2.6 Investigational Device Accountability

The Sponsor is responsible for the availability and distribution of all investigational products. Product will only be distributed to trial sites when the Sponsor has provided written documentation of investigational site readiness. The Sponsor will ship and/or hand-carry devices (the Tendyne device) to the Principal Investigator or his/her designee at each site, after sites receive documentation of site activation and shipping authorization is complete. The Tendyne device must be stored according to the labeling and Instructions for Use in a secure location to prevent unauthorized access or use.

The investigator, or designee, will maintain adequate records of the receipt and disposition of the investigational device, including reference/serial/lot numbers (as appropriate), date of use, subject number and implanting physician(s). A Device Accountability Log supplied by the Sponsor will be used. The Sponsor requires clinical sites to store all investigational products according to the labeling and Instructions for Use in a secure area to prevent unauthorized access or use. Storage locations for the devices at investigational sites must be locked with access restricted to only the investigators and authorized personnel. All unused investigational devices must be returned to the Sponsor when trial registration is complete (completed device accountability reports will be generated for the site) or as otherwise deemed necessary (e.g., expired devices).

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

2.2.7 Description of the Control Group Device Used in the Randomized Cohort

Subjects randomized to the Control group in the randomized cohort will receive TEER with the commercially-approved MitraClip system. Prior to randomization, the anatomic suitability for using MitraClip will be initially proposed by the local site heart team with the final determination made by the SEC in order to ensure concordance with the recently published criteria by the Heart Valve Collaboratory [66].

[redacted]

3 TRIAL OBJECTIVES / ENDPOINTS

The objective of the SUMMIT trial is to evaluate the safety and effectiveness of the Tendyne Transcatheter Mitral Valve System for the treatment of symptomatic, moderate-to-severe or severe mitral regurgitation, severe mitral stenosis, with or without severe MAC in subjects who are treated per standard of care and meet trial eligibility criteria.

The Randomized, Non-Repairable and Severe-MAC cohorts each have one primary composite endpoint. The primary endpoint is the same across all 3 cohorts. The trial has several secondary safety, effectiveness and descriptive endpoints.

3.1 Primary Endpoints

3.1.1 Primary Composite Endpoint - Randomized Cohort

The primary composite endpoint is: freedom from all-cause mortality and heart failure hospitalization at 12 months post index procedure. The composite endpoint will evaluate whether the Tendyne device is non-inferior to TEER with MitraClip.

3.1.2 Primary Composite Endpoint - Non-repairable Cohort

The primary composite endpoint is: freedom from all-cause mortality and heart failure hospitalization at 12 months post index procedure. The composite endpoint will be evaluated based on a performance goal.

3.1.3 Primary Endpoint – Severe MAC Cohort

The primary composite endpoint is: freedom from all-cause mortality and heart failure hospitalization at 12 months post index procedure. The composite endpoint will be evaluated based on a performance goal.

3.1.4 Primary Endpoint – Severe MAC CAP Cohort

The primary composite endpoint is: freedom from all-cause mortality and heart failure hospitalization at 12 months post index procedure. The endpoint will be descriptively summarized and compared to the results in the Severe MAC Cohort primary analysis population.

3.2 Secondary Endpoints - Randomized Cohort

The following secondary endpoints will be evaluated:

- *Effectiveness*: Freedom from MR > mild in severity at 30 days post index procedure among survivors (superiority)
- *Safety*: Freedom from all-cause mortality and MV reintervention at 12 months (non-inferiority)
- Improvement in Quality of Life (QoL), as measured by the Kansas City Cardiomyopathy Questionnaire (KCCQ) by at least 10 points at 12 months from baseline
- Proportion of New York Heart Association (NYHA) Functional Classification I or II at 12 months

[redacted]

- Improvement in distance walked on the 6 Minute Walk Test (6MWT distance or 6MWD) by at least 50 meters at 12 months from baseline

Additionally, if non-inferiority is demonstrated, superiority of Treatment over Control for the primary composite endpoint will also be tested.

3.3 Secondary Endpoints – Non-repairable Cohort

The following secondary endpoints will be evaluated:

- Change in QoL as measured by the KCCQ from baseline to 6 months and 12 months
- Improvement of NYHA Functional Classification I and II at 12 months
- Change in distance walked on the 6MWT from baseline to 6 months and 12 months

3.4 Secondary Endpoints – Severe MAC Cohort

The following secondary endpoints will be evaluated:

- Freedom from MR > mild in severity at 30 days post index procedure among survivors (performance goal)
- Change in QoL as measured by the KCCQ from baseline to 6 months and 12 months
- Change in proportion of NYHA Functional Classification I and II at 12 months
- Change in distance walked on the 6MWT from baseline to 6 months and 12 months

3.5 Secondary Endpoints – Severe MAC CAP Cohort

The following secondary endpoints will be evaluated descriptively:

- Freedom from MR > mild in severity at 30 days post index procedure among survivors
- Change in QoL as measured by the KCCQ from baseline to 6 months and 12 months
- Change in proportion of NYHA Functional Classification I and II at 12 months
- Change in distance walked on the 6MWT from baseline to 6 months and 12 months

3.6 Descriptive Endpoints – Randomized, Non-repairable, Severe MAC and Severe MAC CAP Cohorts

3.6.1 Clinical Endpoints

The following clinical endpoints will be reported:

- All-cause mortality, CV hospitalizations, all stroke or MV reintervention or reoperation, at 2 years post index procedure and then yearly through 5 years
- Distance walked on the 6MWT at baseline, 30 days, 6 months, 12 months and then yearly through 5 years (change from baseline to follow-up).
- KCCQ QoL scores at baseline, 30 days, 6 months, 12 months and then yearly through 5 years (change from baseline to follow-up).

[redacted]

- EQ-5D index scores at baseline, 30 days, 6 months, 12 months and then yearly through 5 years (change from baseline to follow-up).
- SF-12 QoL scores at baseline, 30 days, 6 months, 12 months and then yearly through 5 years (change from baseline to follow-up).
- NYHA Functional Classification at baseline, 30 days, 6 months, 12 months and then yearly through 5 years.
- Number of days alive and out of hospital from the time of index procedure to 12 months, and then yearly through 5 years.
- Annualized rate of heart failure hospitalization
- Change from baseline in BNP or NT pro-BNP levels, at all follow-up visits.
- All-cause mortality at 30 days, 1 year, and then yearly through 5 years

3.6.2 MVARC Endpoints

The following MVARC endpoints will be captured for the Tendyne device and Control group in the Randomized, Non-repairable and Severe MAC cohorts (see **Appendix II: Definitions**) [72]:

- Technical Success
- Device Success
- Procedural Success
- Patient Success

3.6.3 Echocardiographic Endpoints

The following echocardiographic data will be reported, as adjudicated by the Echocardiography Core Laboratory, at baseline, discharge, 1 month, 6 months, 12 months, and then yearly through 5 years. For continuous variables, change from baseline to each follow-up will also be reported:

- MR severity grade
- Effective Regurgitant Orifice Area
- Regurgitant Volume
- Regurgitant Fraction
- Left Ventricle End Diastolic Volume
- Left Ventricular End Systolic Volume
- Left Ventricular End Diastolic Dimension
- Left Ventricular End Systolic Dimension
- Left Ventricular Ejection Fraction
- Right Ventricular Systolic Pressure
- Mitral Valve Area
- Mean Mitral Valve Gradient

[redacted]

- Mean Left Ventricular Outflow Tract Gradient
- Cardiac Output
- Forward Stroke Volume

3.6.4 Health Economic Data (U.S. Investigational Sites)

During the course of the trial, the Sponsor (or third-party designee) will collect health economic data from investigational sites located in the United States. This includes gathering information regarding hospitalizations for initial treatment and throughout the follow-up period. The data collected may include billing information (provided as a UB-04 form or equivalent and itemized hospital bills, where applicable) for items such as hospital care, physician services, laboratory tests and diagnostic procedures.

These data will be used as part of a dedicated health economic study in order to evaluate the cost-effectiveness of alternative therapies for mitral valve disease and potentially to support coverage and reimbursement policy. All information collected for the purposes of the heath economic evaluation will be stored in a HIPAA-compliant secure database and will be appropriately de-identified for analytic purposes.

4 TRIAL DESIGN, SCOPE AND DURATION

4.1 Trial Design

SUMMIT is a pre-market, interventional, pivotal investigation of the Tendyne Transcatheter Mitral Valve System. This trial is a prospective, controlled, multicenter clinical investigation of the Tendyne Transcatheter Mitral Valve System for the treatment of symptomatic, moderate-to-severe or severe mitral regurgitation or severe MAC, for whom the site heart team deems transcatheter treatment is more appropriate than conventional mitral valve surgery. The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risk Analysis section of this clinical investigation plan for details. **Figure 1** provides an overview of the SUMMIT trial design.

[redacted]

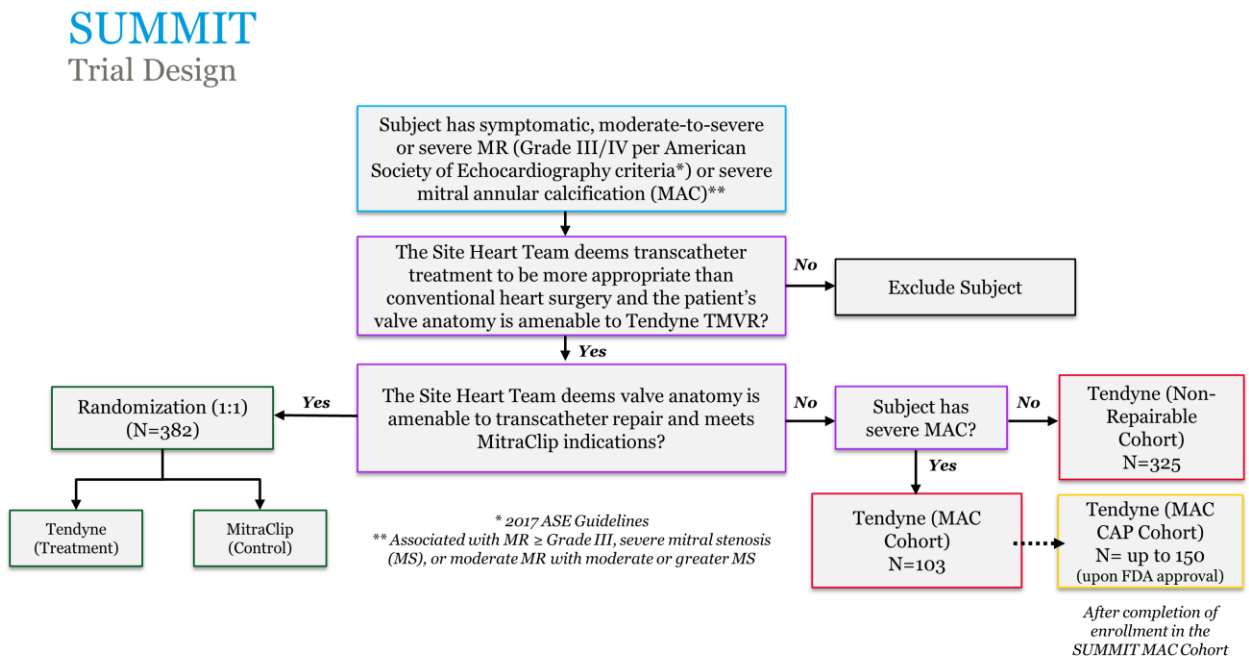


Figure 1. SUMMIT Trial Design

Participating sites may initially propose the study cohorts in accordance with the trial content. The final determination of the study cohorts will be made by the SEC. Subjects must satisfy the trial inclusion/exclusion criteria and be approved by the SEC, prior to inclusion in the trial.

Randomized cohort: Subjects suitable for TMVR with Tendyne and indicated for TEER with the MitraClip will be randomized in a 1:1 ratio to receive either Tendyne (Treatment) or MitraClip (Control). Subjects with primary MR must be at prohibitive surgical risk, while subjects with secondary MR must be symptomatic despite maximally-tolerated guideline-directed medical therapy in accordance with the MitraClip Indications for Use. Randomization will be stratified by investigational site. See **Appendix X** for the FDA-approved MitraClip indication for use.

Non-repairable cohort: Subjects with valve anatomies appropriate for Tendyne TMVR but not suitable for TEER will be eligible to enroll in the Non-repairable cohort, in which all subjects will receive treatment with the Tendyne system.

Severe MAC cohort: Subjects who have severe MAC rendering the subject unsuitable for mitral valve surgery will be eligible to enroll in the Severe MAC cohort, in which all subjects will receive treatment with the Tendyne system.

Severe MAC CAP cohort: After completion of enrollment in the Severe MAC Cohort, up to an additional 150 subjects (upon FDA approval) with severe MAC rendering the subject unsuitable for mitral valve surgery may enroll in the Severe MAC CAP cohort, in which all subjects will receive treatment with the Tendyne system.

A recent publication from the Heart Valve Collaboratory (HVC, which includes the FDA, academic leaders, and industry representatives) has identified specific criteria that render potential

[redacted]

subjects as unsuitable for MitraClip™ [66]. Only subjects satisfying these criteria are eligible for enrollment into the non-randomized (Non-Repairable and Severe MAC) cohorts. The SUMMIT SEC will ensure that MitraClip suitability is evaluated in concordance with the guidance published by the HVC. The HVC criteria for MitraClip non-suitability described by Lim et al. is outlined in **Appendix VIII**.

4.2 Number of Subjects to be Registered

This trial will enroll male and female subjects who satisfy the inclusion and exclusion criteria and provide written informed consent. Investigational sites will attempt to recruit consecutive subjects who must meet all eligibility criteria. Subjects are considered registered for the SUMMIT trial upon Tendyne procedure attempt (subjects in the Non-repairable and Severe MAC cohorts) or upon randomization (subjects in the Randomized cohort).

This trial will register approximately 382 subjects within the Randomized cohort, approximately 325 subjects within the Non-repairable cohort, and approximately 103 subjects in the Severe MAC cohorts, at up to 80 investigational sites in the U.S., Canada, Europe and Japan. No site may enroll more than [redacted] of the total number of subjects in any cohort.

Up to an additional [redacted] roll-in subjects may be treated by operators without recent or prior experience with the Tendyne device to gain hands-on experience before registering subjects in the trial cohorts (see **Section 6.1.1 Roll-in Subjects** for further details). Once the site completes the roll-in phase, all subsequent subjects must be registered in either the Randomized, Non-repairable or Severe MAC cohorts. Roll-in subjects will not count toward the subject caps in the Randomized (382 subjects), Non-repairable (325 subjects) or MAC (103 subjects) cohorts. Additionally, subjects enrolled in the Non-randomized cohort prior to publication of the criteria by Lim et al. will be re-evaluated by the SEC to determine if they satisfy the revised criteria for the Non-repairable cohort [66]. Any subject who does not satisfy the revised criteria by Lim et al. will be excluded from the Non-repairable cohort for analysis. Subjects who are excluded in this regard from the primary analysis population will be followed-up as per the protocol through 60 months and reported separately. [redacted]

4.3 Expected Duration of the Clinical Investigation

The total duration of the trial is estimated as [redacted]. This includes a [redacted] subject recruitment period, with subject follow-up continuing for an additional 60 months.

Subjects will have required follow-up evaluations at pre-discharge, 30 days, 3 months, 6 months, 12 months, and annually thereafter through 60 months (see **Table 3** for visit windows). When all registered subjects have been followed for 60 months, or have exited the trial, the trial will be closed.

4.4 Number of Subjects and Expected Duration of the Severe MAC CAP Cohort

Enrollment in the Severe MAC CAP cohort will be initiated following completion of enrollment of the Severe MAC Cohort. The Severe MAC CAP cohort is anticipated to have [redacted] enrollment duration, which is based on a 12-month follow-up requirement for the primary analysis of the Severe MAC cohort followed by a [redacted] duration for PMA submission and review.

[redacted]

Subjects will have required follow-up evaluations at pre-discharge, 30 days, 3 months, 6 months, 12 months, and annually thereafter through 60 months (see **Table 3** for visit windows). When all registered subjects have been followed for 60 months, or have exited the trial, the Severe MAC CAP will be closed.

4.5 Enrollment of Traditionally Underrepresented Demographic Subgroups

Historically, specific demographic subgroups such as women and racial or ethnic minorities have been under-represented in or excluded from many clinical trials. This has led to a lack of information on these subgroups for many medical treatments. Therefore, it is important to ensure there is an adequate representation of such demographic subgroups and to assess if there is a difference in treatment response between these subgroups.

The Sponsor intends to implement FDA's guidance on the evaluation of sex-specific data in medical device clinical studies [73], to ensure adequate representation of women and other traditionally under-represented demographic subgroups in the SUMMIT trial.

As noted in the guidance, some barriers to participation of women and ethnic minorities in clinical investigations have traditionally been:

- Lack of understanding about main obstacles to participation of such subgroups in clinical research
- Inclusion/exclusion criteria potentially not needed to define the clinical investigation population may unintentionally exclude specific subgroups
- Under diagnosis of disease etiologies and pathophysiology leading to under referral of demographic subgroups
- Avoidance of specific subgroups by investigators and Sponsors due to the perception that it takes more time and resources to recruit them
- Fear of fetal consequences (for female participants)
- Family responsibilities limiting women's ability to commit time for follow-up requirements

The Sponsor will take steps, including the following, to ensure adequate representation of women and racial or ethnic minorities in this clinical investigation:

- The Sponsor will approach sites without bias or consideration for specific demographic subgroups
- The Sponsor will have informed consent materials in alternative languages at the request of the site

4.5.1 Prevalence of Valvular Heart Disease, Diagnosis and Treatment Patterns

Population-based studies demonstrate no difference in the prevalence of valvular heart disease in men and women and that the population is diverse (40% black, 59% white, and 1% other) [74], [75]. These studies also report that in the community setting, women are diagnosed with valvular heart disease less often than men.

[redacted]

In another study, which looks at data from the STS database between the years 2000 and 2007, women and men had a nearly equal representation for having mitral valve surgery. However, women underwent mitral valve replacement at a higher rate than men (65% women; 35% men) and mitral valve repair at a lower rate than men (44% women; 56% men) [76]. An additional study of the TVT registry data between October 2013 and September 2015 identified 2,952 patients treated with the MitraClip system, of which 55.8% were male, demonstrating similar rates of transcatheter mitral interventions between genders [36].

4.5.2 Representation of Underrepresented Demographic Subgroups

The traditional barriers to enrollment of women (such as fear of fetal consequences, family responsibilities that may limit the ability for time commitment to trial follow-up) are not expected to occur in this trial. Furthermore, valvular heart disease is also prevalent in traditionally underrepresented non-white subgroups.

In the Tendyne CE Mark Study, which was a global study that enrolled throughout Europe, the U.S. and Australia, women represent 31% (31/100) and non-whites represent 5% (5/100) of treated subjects. As the SUMMIT trial will primarily enroll subjects in the U.S., which has a diverse population, a high proportion of non-white subjects are expected to enroll. Furthermore, the Sponsor will take the following actions in this trial:

- Provide training to investigational site personnel to ensure adequate representation of these demographic subgroups.
- Regularly review enrollment/registration demographics to investigate whether there is under-representation of these subgroups.
- Regularly review withdrawal rates for under-represented subgroups and compare these rates to the overall trial population.
- Select sites that have experience performing mitral valve surgery and transcatheter mitral valve repair without consideration for racial or ethnic minorities.
- Provide informed consent materials in alternative languages and will work with sites and IRBs/ECs on recruitment materials.
- As appropriate and necessary, re-train sites on the importance of recruiting and retaining subjects in the trial.

4.5.3 Subgroup Analysis for Underrepresented Demographic Subgroups

The Statistical Analysis Plan (SAP) pre-specifies analyses to assess heterogeneity of safety and effectiveness endpoints across demographic subgroups.

5 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Screening and Informed Consent

This clinical investigation will enroll male and female subjects with symptomatic, moderate-to-severe or severe mitral regurgitation (MR; MR ≥ Grade III per American Society of Echocardiography criteria), or severe mitral annular calcification. Subjects must meet all eligibility criteria and provide written informed consent prior to conducting any investigation-specific procedures not considered standard of care. A patient who does not satisfy all general eligibility

[redacted]

criteria prior to informed consent is considered a recruitment failure and should not be enrolled in the clinical investigation.

The Investigator or his/her authorized designee (if applicable) will conduct the Informed Consent process, as required by applicable regulations and the center's IRB/EC. This process will include a verbal discussion with the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. Subjects must be informed about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty or loss of benefits to which the subject is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the subject and will respect subject's legal rights. Financial incentives will not be given to the subject. Subjects may be compensated for time and travel directly related to the participation in the clinical investigation. The subject shall be provided with the Informed Consent form written in a language that is understandable to the subject and has been approved by the center's IRB/EC. The subject shall have adequate time to review, ask questions, and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the subject understands the information provided. If the subject agrees to participate, the Informed Consent form must be signed and dated by the subject and thereafter by the person obtaining the consent prior to any clinical investigation-specific procedures. The signed original will be filed in the subject's hospital or research charts, and a copy will be provided to the subject. The dated signatures can be electronic. The site will follow local hospital and local EC/IRB provisions for documenting electronic ICF signature

Failure to obtain informed consent from a subject prior to clinical investigation enrollment should be reported to Sponsor within 5 working days and to the reviewing center's IRB/EC according to the IRB's/ EC's reporting requirements.

If, during the clinical investigation, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee (if applicable) will provide this information to the subject. If relevant, the subject will be asked to confirm their continuing informed consent in writing.

All subjects must be screened by the site's investigator and clinical research staff, who have been trained to the CIP and delegated to screen subjects, to determine if the potential subject is eligible for trial registration. Subjects will be assigned a unique subject identifier through the electronic data capture (EDC) system. All consented subjects considered for the trial must be reported to the Sponsor on a frequent basis during the trial registration period. The result of the subject screening process should be documented within the baseline screening eCRF to include: whether the subject met eligibility criteria (and if not, which eligibility criteria were not met) and whether the subject was subsequently registered (and if not, the reason for not registering).

Patients are enrolled (i.e., become "subjects") after they sign the Informed Consent Form (ICF). During the informed consent process, the investigator or designee, who has been trained on the CIP, will explain the nature and scope of the trial, potential risks and benefits of participation, and answer questions from potential subjects. All subjects must sign and date the IRB/EC approved

[redacted]

ICF prior to any clinical trial-specific procedures. Subjects who are not subsequently registered will be withdrawn from the clinical investigation.

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

For sites in the United States, an authorization for use and disclosure of the subject's protected health information, in accordance with the Health Insurance Portability and Accountability Act (HIPAA), must be obtained from the subject.

For live cases at congresses, subjects need to sign a specific Live Case ICF, approved by the IRB/EC and by the Sponsor, as well as by the applicable regulatory/competent authorities (e.g., U.S. FDA, Health Canada). The investigator must request the Sponsor approval prior to performing a Live Case.

5.1.1 Special Circumstances for Informed Consent

Incapacitated individuals, defined as persons who are mentally ill, mentally handicapped, or individuals without legal authority, are excluded from the study population. Individuals under the age of 18 or age of legal consent are excluded from the study population. Pregnant or breastfeeding women are excluded from the study population.

Individuals unable to read or write may be enrolled in this clinical investigation. Informed consent will be obtained through a supervised oral process. An independent witness will be present throughout the Informed Consent process. The written Informed Consent form and any other information will be read aloud and explained to the prospective subject or his/her legally acceptable representative and either will sign and personally date the Informed Consent form. The witness will also sign and personally date the Informed Consent form attesting that the information was accurately explained and that informed consent was freely given.

5.1.2 Enrollment of Medicare Beneficiaries (U.S. Subjects Only)

This clinical investigation will enroll appropriate Medicare beneficiaries that qualify based on the inclusion and exclusion criteria set forth in the trial. The investigational device exemption (IDE) clinical trial adheres to all standards of Medicare coverage requirements set forth by CMS's IDE and clinical trial coverage policies. The Risk Analysis section of this CIP (see **Section 17)** describes how all enrolled subjects, including Medicare beneficiaries, may be affected by the device under investigation.

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

5.2 Eligibility Criteria

5.2.1 General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records at the site and interview with a potential subject. Clinical and laboratory tests used to assess eligibility shall be per site standard.

[redacted]

If a specific test required to determine subject's eligibility is not included in a site's standard tests, the test must be performed after written informed consent has been obtained from the subject.

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

If subjects are registered into the clinical investigation and are later found to have met exclusion criteria or not all inclusion criteria, these subjects will continue follow-up in the clinical investigation and will be included in the analysis population.

Note: Roll-in subjects must also meet the eligibility criteria listed below.

5.2.2 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to participate in the trial:

1. Symptomatic, moderate-to-severe or severe mitral regurgitation (MR ≥ Grade III per American Society of Echocardiography criteria), or severe mitral annular calcification (MAC), where a transcatheter therapy is deemed more appropriate than open surgery by the local site heart team.

   Note: MR and MS severity must be determined by assessment of a qualifying transesophageal echocardiogram (TEE) and transthoracic echocardiogram (TTE), obtained within 120 days prior to subject consent, and must be confirmed by the Echocardiography Core Laboratory.

   Note: Patients with severe MAC must have symptomatic mitral valve disease associated with MR≥ Grade III, or severe mitral stenosis (MS), or both moderate MR and moderate MS as assessed by the Echocardiography Core Laboratory.

2. NYHA Functional Classification ≥ II (if Class IV, patient must be ambulatory).

3. The local site heart team determines that the subject has been adequately treated per applicable standards for coronary artery disease (e.g., revascularization), left ventricular dysfunction (e.g., cardiac resynchronization therapy) and heart failure (e.g., GDMT). The SEC must concur that the subject has been adequately treated.

4. The local site heart team and the SEC concur on the intended study cohort for the subject.

   Randomized cohort: Eligibility for this cohort is limited to subjects where the local site heart team deems the mitral valve anatomy is suitable for TEER and are within approved MitraClip indications, which must be confirmed by experienced MitraClip operators within the SEC. Subjects with primary MR must be at prohibitive surgical risk, while subjects with secondary MR must be symptomatic despite maximally-tolerated guideline-directed medical therapy and meet the MitraClip Indications for Use.

   Non-repairable cohort: Eligibility for this cohort is limited to subjects where the local site heart team deems the mitral valve anatomy is not suitable for TEER with MitraClip or does not meet MitraClip indications, which must be confirmed by experienced MitraClip operators from the SEC.

[redacted]

Severe MAC cohort: Eligibility for this cohort is limited to subjects where the local site heart team deems the degree of MAC renders the subject unsuitable for mitral valve surgery.

Severe MAC CAP cohort: Eligibility for this cohort is identical to the original Severe MAC cohort.

5. Age 18 years or older at time of consent.
6. Subject has been informed of the nature of the trial and agrees to its provisions, including the possibility of randomization to the Control group, complying with trial required testing, medications, and follow-up visits, and has provided written informed consent.

5.2.3 Exclusion Criteria

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

1. Mitral valvular vegetation or mass.
2. Left Ventricle or Left Atrium thrombus.
3. Chest condition that prevents transapical access.
4. LVEF less than 25% assessed by the site based on a TTE obtained within 120 days prior to subject consent.

   Note: LVEF will be principally based on TTE and confirmed by the Echocardiography Core Laboratory.
5. LVEDD > 7.0 cm assessed by the site based on a TTE obtained within 120 days prior to subject consent.

   Note: A qualifying LVEDD must be confirmed by the Echocardiography Core Laboratory.
6. Prior surgical or interventional treatment of mitral valve involving implantation of prosthetic material (e.g. valve repair or replacement, or MitraClip).
7. Mitral pathoanatomy and LVOT anatomy deemed not suitable for Tendyne transcatheter mitral valve implantation.
8. Aortic valve disease requiring surgery or transcatheter intervention.
9. Tricuspid valve disease requiring surgery or transcatheter intervention.
10. Severe tricuspid regurgitation or severe right ventricular dysfunction.
11. Any surgical or interventional procedure within the period of 60 days prior to or planned procedure 60 days following subject registration.
12. Implant or revision of CRT device within 90 days prior to intended subject registration.
13. Myocardial infarction within 30 days prior to intended subject registration.
14. Symptomatic, unresolved multi-vessel or unprotected left main coronary artery disease (e.g., active ischemia) requiring stenting or CABG.
15. CVA within 6 months prior to intended subject registration.
16. Unresolved severe symptomatic carotid stenosis (> 70% by ultrasound).

[redacted]

17. Cardiogenic shock or hemodynamic instability requiring inotropes or mechanical support devices at the time of planned implant procedure.
18. Hypertrophic or restrictive cardiomyopathy, or constrictive pericarditis.
19. Any of the following: leukopenia, acute anemia, thrombocytopenia, history of bleeding diathesis, or coagulopathy if cannot be adequately treated.
20. History of endocarditis within 6 months of planned implant procedure.
21. Active systemic infection requiring antibiotic therapy.
22. Known hypersensitivity or contraindication to procedural or post-procedural medications (e.g., contrast solution, anti-coagulation or antiplatelet therapy) that cannot be adequately managed medically.
23. Subjects in whom TEE is contraindicated or high risk.
24. Known hypersensitivity to nickel or titanium.
25. Subject is undergoing hemodialysis due to chronic renal failure.
26. Subject has pulmonary arterial hypertension (fixed PAS >70mmHg).

    Note: If PAS > 70mmHg, site must provide documentation PAS is not fixed in order to be eligible.
27. Subject has COPD requiring continuous home oxygen therapy or chronic outpatient oral steroid use.
28. Subjects with non-cardiac comorbidities that are likely to result in a life expectancy of less than 12 months.
29. Modified Rankin Scale ≥ 4 disability.
30. Status 1 heart transplant or prior orthotopic heart transplantation.
31. Pregnant, lactating, or planning pregnancy during the clinical investigation follow-up period.

    Note: Female subjects of childbearing age should be instructed to use safe contraception (e.g. intrauterine devices, hormonal contraceptives: contraceptive pills, implants, transdermal patches hormonal vaginal devices, injections with prolonged release).
32. Currently participating in an investigational drug or another device trial that has not reached its primary endpoint.

    Note: Trials requiring extended follow-up for products that were investigational, but have since become commercially available, are not considered investigational trials.
33. Presence of other anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements, or impact the scientific soundness of the clinical investigation results.

[redacted]

5.3 Subject Selection

Subjects in this trial must have symptomatic, moderate-to-severe or severe mitral regurgitation or severe MAC. Subjects must be treated per standard of care, meet trial eligibility criteria, and have been assessed by the local site heart team for suitability for mitral valve surgery (see **Section 6 - Subject Screening and Randomization**). Several mechanisms will be employed in this trial to ensure appropriate subjects are registered in the trial:

- Subjects will be selected for inclusion in the SUMMIT trial by a multidisciplinary team at each investigational site involving interventional cardiology, cardiac surgery, imaging (echocardiography and CT) and heart failure personnel, as appropriate.
- All imaging (TEE, TTE, and Cardiac CT) will be submitted to the Sponsor and assessed by independent Echocardiography/CT Core Laboratories. The Sponsor (or imaging core laboratory) may provide echocardiographic and/or cardiac CT training/guidance to sites and assist in the review of screening images to ensure conformance to trial eligibility requirements.
- The SEC must concur with the local site heart team that subjects have been treated per standard of care, meet trial eligibility criteria, and can be treated in the Randomized, Non-repairable, Severe MAC or Severe MAC CAP cohorts of the trial (see **Section 12.11.2 - Subject Eligibility Committee** for more details).

5.4 Subject Registration

Subjects are enrolled in the trial upon providing written informed consent. For the Randomized cohort, subjects will be considered registered in the trial at the time of subject randomization. Sites may not register more than [redacted] of the total of [redacted] in the randomized cohort.

For the Non-repairable, Severe MAC and Severe MAC CAP cohorts, subjects are considered registered in the trial upon Tendyne procedure attempt (initial incision for the Tendyne procedure). Sites may not register more than [redacted] of the total subjects in the Non-repairable [redacted] or Severe MAC [redacted] cohorts.

[redacted]

5.5 Subject Discontinuation

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

- Subject death
- Subject voluntary withdrawal
- Subject lost-to-follow-up as described below
- Subject's follow-up is terminated according to **Section 5.6 - Early Termination of the Clinical Trial**

[redacted]

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

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

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

In case of subject withdrawal of consent, the site should make attempts to schedule the subject for a final clinical investigation visit. At this final follow-up visit, the subject will undergo the following assessments:

- Transthoracic echocardiogram
- Six-minute walk test
- Kansas City Cardiomyopathy Questionnaire
- Any assessments required to complete the Follow Up eCRF
- Any assessments required to complete the Adverse Event or Device Deficiency eCRFs, if applicable

5.5.1 Subject Lost to Follow-up

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

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

  Note: Contact with a general practitioner, non-trial cardiologist or relative will be considered subject contact for the purpose of collecting vital status information. The center shall retain records of the contact.

5.6 Early Termination of the Clinical Trial

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

[redacted]

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

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

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

A Principal Investigator, IRB/EC or regulatory authority may suspend or prematurely terminate participation in the clinical investigation at the investigational site(s) for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If the Sponsor suspends or prematurely terminates the clinical investigation at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators.

If suspension or premature termination occurs, the Sponsor will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following the subjects enrolled in the clinical investigation, and the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her site, if appropriate. Details for such subjects follow up will be provided. The investigator will be requested to return all clinical investigation materials (including devices) to the Sponsor and provide a written statement to the IRB/EC.

If a suspended investigation is to be resumed, approval will be obtained from the EC/IRB and a notification should be sent to the regulatory body or bodies, as applicable, and if subjects were informed of suspension, they shall be informed of the resumption of the clinical investigation.

5.7 Trial Completion

The trial will be completed when all roll-in and registered subjects have either completed a 5-year follow-up visit, have reached a clinical outcome or have withdrawn from the trial. Upon trial completion, the Sponsor and/or its designees will notify the sites and perform trial closeout visits. All unused devices and any unused trial materials and equipment will be collected and returned to the Sponsor and/or its designees. The Sponsor and/or its designees will ensure that the investigator's regulatory files are up to date and complete, that database queries are resolved, and that any outstanding issues from previous monitoring visits have been resolved.

[redacted]

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

Upon completion of the clinical investigation, specific follow-up (regardless of how follow-up was completed, e.g. withdrawal, completion of scheduled follow-ups), subjects should be followed per standard of care for subjects with symptomatic mitral valve disease. Previous participation in this investigation does not require subjects to have any unique follow-up requirements once participation is complete. Investigational device traceability and identification requirements for such follow-up are the same as for commercially approved implants.

6 SUBJECT SCREENING AND RANDOMIZATION

Potential patients presenting at the clinical sites will be fully informed about the clinical investigation, following the established Informed Consent process (described in **Section 5.1**). Once a duly dated and signed Informed Consent form is obtained, the clinical investigation-specific screening procedures may begin. **Section 6.1.2** describes the assessments performed as part of the screening process:

Subjects must be screened for clinical investigation eligibility by a member of the site's clinical investigation team previously trained to the CIP.

If the subject does not meet all inclusion criteria or meets any of the exclusion criteria, the subject is considered a screening failure. The Principal Investigator or the delegated clinical investigation personnel will record the screening failure in the hospital records.

Patients meeting general inclusion criteria and no exclusion criteria will be asked to sign an Informed Consent form if they wish to participate in the clinical investigation. These patients will also be entered into the study electronic database (EDC) system.

Subject data will be collected following enrollment into the clinical investigation.

6.1 Pre-Randomization

6.1.1 Roll-in Subjects

The decision to identify a subject as a roll-in will depend on the level of experience of the investigator with the device. Sites may perform **up to** [redacted] roll-in procedures prior to beginning the registration phase for the trial and subjects will be designated as roll-ins prior to undergoing the procedure. Consideration of roll-ins will be based on the following criteria:

- Investigator does not have prior experience with the Tendyne device; or
- Investigator has not performed a recent Tendyne procedure

The site must receive authorization from the Sponsor for each roll-in case. Each roll-in case must also be presented by the local site heart team to the SEC, and the SEC must confirm subject eligibility.

6.1.2 Screening and Baseline Assessments

Screening of a subject for possible inclusion in the trial may commence once a subject has been identified as potentially having symptomatic, moderate-to-severe or severe mitral regurgitation or severe MAC. Subject's general medical eligibility must be assessed via subject interview and

[redacted]

medical record review prior to subject registration and within the windows stipulated in **Table 3**. Standard of care tests that are performed prior to obtaining informed consent can be used to determine eligibility if those tests meet the requirements of this trial and are within the screening window.

Outlined below is the schedule of tests and assessments that need to be completed prior to registration. For a summary of the screening process, refer to **Appendix III: Subject Screening Flow Chart.**

Baseline Imaging up to 120 Days Prior to Subject Consent

Cardiac CT images obtained within 120 days prior to subject consent or anytime thereafter must be captured per the Cardiac CT Core Laboratory imaging protocol. Similarly, TTE and TEE images must be obtained up to 120 days prior to subject consent or anytime thereafter and must be captured per the Echocardiography Core Laboratory imaging protocol. If any imaging is not standard of care, the subject must provide informed consent prior to obtaining any trial imaging.

Once obtained, Cardiac CT, TTE and TEE images will be submitted to the Sponsor. Both the Sponsor and either the CT Core Laboratory or Echocardiography Core Laboratory will review the images and assess subject's anatomical suitability relevant to valve sizing and to perform procedural planning. The Echocardiography Core Laboratory will confirm the subject's MR severity, LVEF and LVEDD meet eligibility criteria.

If clinically indicated, subject's coronary artery disease status should be assessed via a routine diagnostic coronary angiogram within 60 days prior to subject registration. Any revascularization treatment should be administered prior to subject registration as outlined in the subject eligibility criteria in **Section 5.2.**

Screening Assessments within 90 Days Prior to Registration

Subjects must complete all trial required assessments prior to registration in the randomized cohort and prior to the procedure in roll-in subjects and the non-repairable or severe MAC cohorts.

- Medical history must be obtained, including review of subject's medical records. This review will include history of comorbidities and pre-existing medical conditions; previous cardiovascular and peripheral vascular interventions; symptoms and diagnosis of mitral insufficiency; history of hospitalizations (related to heart failure and mitral valve insufficiency) within the past 12 months.
- A physical exam including an assessment of subject's cardiac status and sitting vital signs (heart rate and blood pressure).
- Blood tests performed, including: BNP or NT-proBNP, plasma free hemoglobin, serum creatinine, serum albumin, International Normalized Ratio (INR), Creatine kinase-MB (CK-MB) if indicated or Troponin (Type I or T) if indicated.
- A 12-lead electrocardiogram (ECG) must be performed.
- Concomitant chronic cardiovascular medications must be documented and may include the following: anticoagulants, antiplatelet agents, ACE inhibitors, angiotensin II receptor blockers or inhibitors, angiotensin receptor-neprilysin inhibitor, I_f channel inhibitor, beta

[redacted]

blockers, calcium channel blockers, diuretics, digitalis preparations, and any medication that may increase the risk of bleeding.

- Modified Rankin Scale must be assessed.
- NYHA Functional Classification must be assessed.
- Canadian Cardiovascular Society (CCS) grading of angina pectoris must be assessed.
- KCCQ, SF-12, and EQ-5D questionnaires must be completed by the subject;
    - **Note:** To minimize bias and undue influence, the QoL questionnaires will be completed by the subject, unless the subject is unable to complete the questionnaire on their own (in such cases a note to file must be completed to document the inability of subject to complete the questionnaire on their own).
- The 6MWT must be administered according to the ATS Statement [77]
- The following assessments will be captured to assist the local site heart team and SEC in determining a subject's risk profile. These assessments include, but are not limited to:
    - STS Predicted Risk of Mortality (PROM) score for <u>both</u> mitral valve replacement and repair
    - Essential Frailty Toolset (see
    - Appendix V: Essential Frailty Toolset
    - Major Organ System Compromise (evaluated on review of subject's medical history)
- Subject is evaluated by the local site heart team to confirm they have been adequately treated per applicable standards, including for coronary artery disease (e.g., revascularization), left ventricular dysfunction (e.g., cardiac resynchronization therapy), and heart failure (e.g., guideline directed medical therapy).
    - Subjects with current or prior symptoms of heart failure and reduced LVEF must be symptomatic, despite being on stable GDMT.
    - GDMT must be documented for a <u>minimum</u> of 30 days prior to intended trial registration and subject must be on appropriate class of medications (per the ACC/AHA/HSFA Heart Failure Guidelines), which typically include: ACE Inhibitor or Angiotensin II Receptor Blocker, Beta-Blocker, and a diuretic as appropriate.

If at any time during the screening process there has been a significant change in the subject's overall condition (e.g., due to recent MI, stroke or worsening heart failure) or the subject has undergone a recent intervention that may impact mitral regurgitation severity (e.g., CRT implant, CABG, PCI), it may be necessary to repeat eligibility assessments and/or imaging to confirm that the subject still meets the eligibility criteria. Subjects with significant changes in condition after approval by the SEC must be re-evaluated by the Committee.

[redacted]

6.2 Randomization / Registration

Prior to a subject being designated to a study cohort, or assigned as a roll-in, the following must be confirmed:

- Echocardiography Core Laboratory must confirm MR severity, LVEF and LVEDD;
- Sponsor must confirm anatomical suitability of subject for the Tendyne device; and
- SEC must concur with local site heart team that the subject has been treated per standard of care, meets trial eligibility criteria, and can be treated in the Randomized, Non-repairable or Severe MAC cohorts of the trial (see **12.11.2 - Subject Eligibility Committee** for more details).

If the screening images are inadequate or the SEC determines a subject requires additional treatment before consideration for the trial, the subject may be deferred and reconsidered for the trial. If a subject is deferred, trial required imaging or assessments may need to be repeated.

Subjects will be assigned to a study cohort, or designated as a roll-in, through the EDC system. If assigned to the randomized cohort, randomization will also occur via the EDC system.

7 TREATMENT AND PRE-DISCHARGE VISITS

For subjects assigned to the Tendyne device (including the Treatment group in the Randomized cohort, any subject in the Non-repairable or Severe MAC cohorts, and all roll-ins), the Tendyne procedure will be performed. For the Control group, TEER with the MitraClip system will be performed.

For subjects in the randomized cohort (Treatment and Control group) the procedure must occur within 14 days from the date of randomization.

7.1 Concomitant Procedures

Concomitant interventional (ex. percutaneous coronary intervention) or surgical procedures are not allowed during implant of the Tendyne device or the Control device in any study cohort, with the exception of balloon mitral valvuloplasty if deemed necessary for device implantation.

7.2 Tendyne Procedure

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

Implantation of the valve will be performed by the local site heart team, with an experienced cardiac surgeon trained to perform transapical procedures. The surgeon may perform the procedure jointly with an experienced interventional cardiologist. Sponsor personnel will be available for procedural support for all Tendyne cases. For a comprehensive description of the Tendyne procedure, refer to the Tendyne Transcatheter Mitral Valve System IFU. If the devices were not used according to the IFU or other instructions in this CIP, complete a Protocol Deviation form.

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

[redacted]

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

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

7.2.1 Tendyne Procedure - Access

An 8 Fr. sheath is placed in the apex at the orthogonal access location predetermined by CT. A balloon tip catheter is then inserted, leading with the inflated balloon tip to establish an entanglement free pathway from the ventricular access site to the left atrium. A 0.035 standard J wire is then advanced into either a pulmonary vein or coiled in the atrium.

Once an entanglement free pathway has been achieved, the balloon tip catheter is deflated and removed. The 8 Fr. sheath is also removed and the Tendyne sheath is inserted.

7.2.2 Tendyne Procedure - Valve Delivery

The delivery system is advanced using echocardiography and fluoroscopy guidance to maintain proper trajectory and to confirm final sheath depth is above the mitral annulus.

Radial orientation of the valve is primarily performed using TEE. The valve is positioned such that the raised anterior aspect is radially oriented toward the aortomitral continuity. Using an X-plane echo image, the Tendyne valve is seated intra-annularly and the deployment of the valve is completed.

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

7.2.3 Tendyne Procedure - Tensioning

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

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

7.2.4 Tendyne Implant Card

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

7.3 Control Group Procedure

Implantation of the Control device will be performed by site investigators (from the local site heart team) that have been trained to perform the Tendyne procedure. Refer to the IFU associated with the Control device (MitraClip) for device implantation.

[redacted]

7.4 Procedural Data Requirements (Tendyne and Control Group)

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

7.4.1 12-Lead ECG

A 12-lead ECG will be performed pre- and post-implant.

7.4.2 Intraoperative Hemodynamic Measurements (Tendyne Only)

Subjects who receive a Tendyne device (including the Treatment group in the Randomized cohort, any subject in the Non-repairable or Severe MAC cohorts, and all roll-ins) will undergo right-heart catheterization to measure hemodynamics intraoperatively. Cardiac output (CO), pulmonary arterial (PA), aortic, and right atrial (RA) pressures will be measured before and after the valve placement. LV pressures should be measured via a pigtail catheter or similar.

7.4.3 Additional Procedural Data Collection

In addition to the intraoperative imaging and hemodynamic measurements, the following Tendyne device and Control group procedural information shall be recorded:

- General procedure information
- Treatment and Control group implant information
- Clinical tests
- Changes in concomitant cardiovascular medications (e.g., heart failure, hypertension, antithrombotic medications)
- Fluoroscopy duration
- Adverse events, if applicable
- Protocol deviations, if applicable
- Device deficiency, if applicable

7.4.4 Immediate Post-Operative Care

Subjects will receive standard post-cardiac transapical (Tendyne device) or transfemoral/transseptal (Control group) care as judged appropriate by the investigator. The subject's ACT should also be monitored in accordance with hospital protocols.

7.4.5 Anticoagulation Regimen

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

For subjects in the Control group, anticoagulation (warfarin) and antiplatelet therapy (aspirin or alternate agent) shall be maintained per the MitraClip IFU.

Notes:

[redacted]

- During the period of CIP required anticoagulation, a subject's anticoagulation regimen may be altered or stopped only if medically indicated, however, it should be restarted as soon as possible per physician's discretion.
- For subjects implanted with the Tendyne device, a TTE must be conducted between 60 and 120 days after anticoagulation stoppage.
    - If the TTE identifies evidence of increased gradient or concerns with leaflet mobility (e.g., mitral valve gradient ≥ 6 mmHg), a cardiac CT must be conducted to evaluate hypoattenuated leaflet thickening or motion. If renal insufficiency precludes a cardiac CT, a TEE must be performed instead.

7.4.6 Pre-Discharge

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

- A physical exam including an assessment of subject's cardiac status and sitting vital signs (heart rate and blood pressure).
- Changes in concomitant cardiovascular medications (e.g., heart failure, hypertension, antithrombotic medications)
- 12-lead ECG
- TTE
- Laboratory and clinical tests: serum creatinine, International Normalized Ratio (INR), Creatine Kinase-MB (CK-MB) if indicated, or Troponin (Type I or T) if indicated
- Adverse events, if applicable
- Protocol deviations, if applicable
- Device deficiency (Tendyne device only), if applicable

8 FOLLOW-UP FOR EVALUATION OF SAFETY AND EFFECTIVENESS

8.1 Clinical Follow-up (All Registered / Roll-in Subjects)

Follow-up evaluations are required at 30 days, 3 months, 6 months, 12 months, and annually thereafter through 5 years (**Table 3**). For all registered and roll-in subjects, follow-up visits will be calculated from the date of the index procedure, or the date of registration if a subject is registered but does not undergo a procedure. Follow-up assessments can be performed at any point in the window, and should be conducted, whenever possible, by the same individual who performed the baseline tests. For a complete schedule of trial assessments occurring at each visit, refer to **Appendix IV: Trial Assessment and Follow-up Schedule**.

Subjects shall be followed at the investigational site where the subject was registered (or designated as a roll-in), and may be followed at another investigational site only with prior agreement from both the new site's Principal Investigator and approval from the Sponsor.

All registered and roll-in subjects should continue to be monitored and treated per applicable standards of care consistent with the subject's condition. Subjects should be followed by the site

[redacted]

investigators at all scheduled follow-up visits. Subjects implanted with the Tendyne or Control device must also be evaluated for device function.

During follow-up, the site Principal Investigator should collaborate with the other site investigators, as applicable, in determining the treatment strategy for all roll-in and registered subjects at their site. Any treatment during follow-up (e.g., due to an adverse event or a change in the subject's condition) should be reported on the appropriate eCRFs.

Note: If a subject has an unsuccessful Tendyne or Control device implant, they should remain in the trial and continue to be followed per the trial follow-up schedule. Additionally, if a subject is randomized to receive either the Treatment or Control device but does not undergo the implant procedure, they should remain in the trial and continue to be followed per the trial follow-up schedule (calculated from the date of randomization).

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

Follow-up visits are required at 30 days, 3 months (phone contact), 6 months, and annually thereafter through 5 years. Subjects must continue to take baseline medications without change during follow-up, unless clinically (medically) necessary. If there are any cardiovascular medication changes, these changes, and the reason for change must be documented on the eCRF. Required tests and procedures are outlined in **Appendix IV: Trial Assessment and Follow-up Schedule**. All visits and tests must be completed within the visit window specified in **Table 3**, even if the subject is in hospital. The following data will be collected for site visits:

- A physical exam including an assessment of subject's cardiac status and sitting vital signs (heart rate and blood pressure).
- Changes in concomitant cardiovascular medications (e.g., heart failure, hypertension, antithrombotic medications)
- NYHA Functional Classification assessment
- Blood tests performed, including: BNP or NT-proBNP, plasma free hemoglobin, serum creatinine, INR, CK-MB if indicated or Troponin (Type I or T) if indicated
- TTE
- 12-lead ECG
- Cardiac CT (**Note:** Only required at 30-day visit)
- KCCQ, SF-12, and EQ-5D questionnaires
- 6-Minute Walk Test
- Modified Rankin Scale (Assessment to be completed after suspected onset of stroke)
- Assess and record adverse events, if applicable
- Assess and record protocol deviations, if applicable
- COVID-19 assessment, if applicable

Note: The 3-month visit will be conducted via telephone. This visit will assess potential adverse events and changes to concomitant cardiovascular medications.

[redacted]

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

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

Every attempt must be made to ensure trial subjects do not miss a scheduled follow-up visit. If a subject is unable to complete a visit, the site may attempt to contact them remotely to document their status (e.g., alive) and to administer trial questionnaires (KCCQ, SF-12, and EQ-5D). This should only be performed in rare instances and the Sponsor should be notified of such instances in advance.

Subjects who do not have a scheduled follow-up visit will be documented as having a missed visit and a protocol deviation (refer to **Section 12.6 - Deviations from Clinical Investigation Plan**) will be completed. The investigator will keep a record of documented follow-up attempts in the subject's file.

Table 3. **Follow-up Schedule* and Windows for Trial Subjects**

Follow-Up Visit	Window Start Day	Target Day	Window Close Day	Follow up Method
Pre-Discharge (Registered and roll-in subjects)	Within 72 hours of discharge	Discharge date	N/A	In hospital or Site visit
30 Days (-3 /+14 days)	27	30	44	Site visit
3 Months (±30 days)	60	90	120	Phone Call
6 Months (±30 days)	152	182	212	Site visit
12 Months (±30 days)	335	365	395	Site visit
2 years (±30 days)	701	731	761	Site visit
3 years (±45 days)	1051	1096	1141	Site visit
4 years (±45 days)	1416	1461	1506	Site visit
5 years (±45 days)	1781	1826	1871	Site visit
* Follow-up visit dates are calculated from the date of the index procedure for registered and roll-in subjects. If a subject in the Randomized cohort does not undergo a Treatment or Control group procedure, follow-up visit dates are calculated from the date of randomization.				

[redacted]

9 ADVERSE EVENTS

To comply with worldwide standards and guidelines on clinical investigation adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

9.1 Definitions / Types of Events

9.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device.

This definition includes events related to the investigational medical device or comparator and/or the procedures involved. This definition includes events related to the procedures involved. For users or other persons, this definition is restricted to events related to the use of investigational medical devices or comparators.

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

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

9.1.2 Serious Adverse Event

Serious Adverse Event (SAE) is an AE that led to any of the following.

a) death,

b) a serious deterioration in the health of the subject, that resulted in any of the following:

1) life-threatening illness or injury

2) permanent impairment of a body structure or a body function

3) hospitalization or prolongation of patient hospitalization

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

5) chronic disease

c) fetal distress, fetal death or a congenital physical or mental impairment or birth defect

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

[redacted]

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

9.1.3 Anticipated Adverse Events

Table 4 summarizes the anticipated events that have been identified as possible complications from the Tendyne Transcatheter Mitral Valve System. Please also refer to the list of anticipated events in the Tendyne Transcatheter Mitral Valve System IFU and package insert for the Control device therapies required per protocol.

Table 4. Anticipated Adverse Events (Tendyne Transcatheter Mitral Valve System)

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

Normal postoperative sequelae or expected postoperative events during the acute perioperative period (72 hours) should not be recorded as SAEs unless they meet the seriousness criteria defined

[redacted]

in Section 9.1.2. A few common examples of normal post-operative sequelae or expected postoperative events include access-site pain, bruising, and events related to general anesthesia.

9.1.4 Unanticipated Adverse Device Effect (UADE)

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

9.2 Device Deficiency

Device deficiency (DD) is defined as any inadequacy in the identity, quality, durability, reliability, usability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in the information supplied by the manufacturer including labeling.

Note: This definition includes device deficiencies related to the investigational medical device or the device comparator

Note: Cybersecurity incidents related to the investigational product, shall be reported as device deficiencies

A device malfunction is the failure of an investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP, or IB

9.3 Device / Procedure Relationship

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

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

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

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

[redacted]

9.4 Adverse Event / Device Deficiency Reporting

9.4.1 AE Reporting

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

For subjects implanted with the Tendyne valve, a TTE must be conducted if signs or symptoms suggestive of valve dysfunction are exhibited. If the TTE indicates evidence of valve dysfunction, a cardiac CT must be performed. If renal insufficiency precludes a cardiac CT, a TEE must be performed instead.

For this clinical investigation, only SAEs, regardless of device and/or procedural relatedness, will be collected on each subject from the time of trial registration through trial completion. A summary of AE reporting requirements is further described in this section and summarized in

Table 5.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

The Sponsor will provide an offline form to allow the investigator to report SAEs in the event entry cannot be made in the EDC. This does not replace the EDC reporting system and sites must still enter all information in the EDC system as soon as feasible.

9.4.2 SAE Reporting to Sponsor and IRB / EC

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

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

The date the site staff became aware the event met the criteria of an SAE must be recorded in the source document. The investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

9.4.3 UADE Reporting to Sponsor and IRB

The Sponsor requires the investigator to report any UADE to the sponsor within three (3) calendar days of the investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB/EC per requirements.

9.4.4 Device Deficiency Reporting

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

[redacted]

The device, if not successfully implanted in the subject, should be returned to the Sponsor. Device deficiencies/malfunctions should be reported to the IRB/EC per the investigative site's local requirements.

9.4.5 Investigational Site AE Reporting Requirements to Sponsor

Investigators are responsible for preparation and submission to the Sponsor of all reportable AEs and DDs identified in the CIP. Adverse event reporting requirements are included in **Table** 5. All reports are subject to inspection and to the retention requirements described in **13.6.1 Investigator Records**.

Table 5. Investigational Site AE Reporting Requirements to Sponsor

Event	Investigational Site	Reporting timelines
SAE	All Sites	SAEs must be reported no later than three (3) calendar days from the day the trial personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.
UADE	All Sites	UADEs must be reported no later than three (3) calendar days from the day the trial personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.
Device Deficiency	All Sites	DDs must be reported no later than three (3) calendar days from the day the trial personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

9.4.6 AE Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report SAEs, UADEs, and DDs to the country regulatory authority, per local requirements.

Note: Reportable device deficiencies include those that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

9.5 Heart Transplants or Subject Death (Tendyne Only)

In the event of heart transplant or subject death, histological and engineering analyses of the *in situ* valve would provide valuable information. The Sponsor must be contacted for shipping and packaging materials and to arrange for transport.

10 STATISTICAL METHODS

The following section describes the statistical methods for the clinical investigation. Additional details are provided in a Statistical Analysis Plan (SAP).

10.1 Analysis Populations

10.1.1 Randomized Cohort

The Intention-to-Treat, modified Intention-to-Treat and Per-Protocol are defined below. For all the analyses, the duration of follow-up will be calculated from the date of registration.

Intention-to-Treat (ITT) Population

[redacted]

Modified Intention-to-Treat (mITT) Population

[redacted]

Per-Protocol (PP) Population

[redacted]

10.1.2 Non-repairable, Severe MAC and Severe MAC CAP Cohorts

Attempted Procedure (AP) Population

The Attempted Procedure population for the Non-repairable and Severe MAC cohorts will consist of subjects in whom a Tendyne procedure is attempted.

[redacted]

10.2 Statistical Analyses

10.2.1 Randomized Cohort

Randomized Cohort – Primary Composite Endpoint

The primary endpoint for the Randomized cohort is freedom from all-cause mortality and heart failure hospitalization (HFH) at 12-months post index procedure. The trial is intended to demonstrate non-inferiority of the Tendyne Transcatheter Mitral Valve System to TEER with MitraClip for the treatment of moderate-to-severe or severe MR.

The null (H_0) and alternative (H_1) hypotheses are:

H_0: $\pi_D - \pi_C \leq -d$

[redacted]

$\mathbf{H_1}$: $\pi_D - \pi_C > -d$

where π_D and π_C are the true event rates for the composite of freedom from all-cause mortality and HFH at 12 months in the Treatment and Control group, respectively, and *d* is the non-inferiority margin. The non-inferiority margin is set at 12.5%.

The primary analysis for the primary endpoint will be performed on the ITT population. The analysis will also be performed on the mITT and PP populations. [redacted] one-sided test with 5% significance level.

[redacted]

Randomized Cohort – Secondary Endpoints

The following secondary endpoints will be evaluated. These endpoints will be evaluated for labeling claims if the primary endpoint for the randomized cohort is met.

Effectiveness: Freedom from MR > mild in severity at 30 days post index procedure among survivors

Subjects treated with the Tendyne device are expected to experience greater reduction in MR severity than subjects in the Control group. The proportion of subjects with MR ≤ mild (1+) at 30 days will be compared between the Treatment and Control groups.

The null and alternative hypotheses are stated as:

$\mathbf{H_0}$: $P_D - P_C \leq 0$

$\mathbf{H_1}$: $P_D - P_C > 0$

where P_D and P_C represent the proportion of subjects with MR ≤ 1+ at 30 days in the Treatment and Control groups, respectively. [redacted] at one-sided 2.5% significance level. The primary analysis for this secondary endpoint will be performed on the ITT population.

Safety: Freedom from all-cause mortality and MV reintervention at 12 months

The Tendyne device may reduce the risk for surgical reintervention and subjects in the Treatment group are expected to experience greater reduction in MR severity than subjects in the Control group. The proportion of subjects alive and without MV reintervention at 12 months will be compared between the Treatment and Control groups.

The null and alternative hypotheses are stated as:

$\mathbf{H_0}$: $\pi_D - \pi_C \leq -d$

$\mathbf{H_1}$: $\pi_D - \pi_C > -d$

[redacted]

where π_D and π_C are the true event rates for the composite of freedom from all-cause mortality and MV reintervention or reoperation at 12 months in the Treatment and Control group, respectively, and *d* is the non-inferiority margin of 10%. [redacted] a one-sided test with 2.5% significance level. [redacted]

Improvement in KCCQ by at least 10 points at 12 months from baseline

To evaluate the benefit of the Tendyne device, the change from baseline in Quality of Life as measured by the KCCQ score will be compared between Tendyne and MitraClip groups at 12 months for non-inferiority.

The null and alternative hypotheses are stated as:

H_0: $P_D - P_C \leq -d$

H_1: $P_D - P_C > -d$

where P_D and P_C represent the proportion of subjects who improved at least 10 points in KCCQ score at 12 months from baseline in the Treatment and Control groups, respectively, and *d* is the non-inferiority margin of 15%. [redacted] at one-sided 2.5% significance level. [redacted]

Proportion of Patients with NYHA Functional Classification I or II at 12 months

To evaluate improvement in heart failure symptoms, the proportion of NYHA Functional Classification I or II at 12 months between Tendyne and MitraClip groups will be tested for non-inferiority.

The null and alternative hypotheses are stated as:

H_0: $P_D - P_C \leq -d$

H_1: $P_D - P_C > -d$

where P_D and P_C represent the proportion of subjects who have NYHA Functional Classification I/II at 12 months in the Treatment and Control groups, respectively, and *d* is the non-inferiority margin of 15%. [redacted] at one-sided 2.5% significance level. [redacted]

Improvement in Six-Minute Walk Test Distance by at least 50 meters at 12 months from baseline

To evaluate the benefit of the Tendyne device, the change from baseline in distance walked as measured by the 6MWT will be compared between Tendyne and MitraClip groups at 12 months for non-inferiority.

The null and alternative hypotheses are stated as:

H_0: $P_D - P_C \leq -d$

H_1: $P_D - P_C > -d$

[redacted]

where P_D and P_C represent the proportion of subjects who improved at least 50 meters in 6MWT distance at 12 months from baseline in the Treatment and Control groups, respectively, and *d* is the non-inferiority margin of 15%. [redacted] at one-sided 2.5% significance level. The justification of the non-inferiority margin *d* of 15% is provided in the SAP.

10.2.2 Non-Repairable Cohort

Non-Repairable Cohort – Primary Endpoint

The primary endpoint for the Non-repairable cohort is freedom from all-cause mortality and heart failure hospitalization at 12 months post index procedure. The trial is intended to demonstrate that the primary endpoint event rate in subjects treated with the Tendyne Transcatheter Mitral Valve System is greater than a pre-specified performance goal (PG).

The null and alternative hypotheses are:

$\mathbf{H_0}$: $\pi_D \leq \pi_{PG}$

$\mathbf{H_1}$: $\pi_D > \pi_{PG}$

where π_D is the true rate of freedom from all-cause mortality and heart failure hospitalization at 12 months post index procedure, and π_{PG} is the performance goal. The PG is set at 45% [redacted] The null hypothesis will be tested at the one-sided 2.5% level of significance [redacted].

Subjects who have not experienced mortality or heart failure hospitalization, within 12 months, will be censored at the date of last information available.

[redacted]

Non-Repairable Cohort – Secondary Endpoints

The following secondary endpoints will be evaluated in the Non-repairable cohort. These endpoints will be evaluated for labeling claims if the primary endpoint for the Non-repairable cohort is met. Details about statistical methods are described in the SAP.

Change in Quality of Life, as measured by the KCCQ through 12 months

To evaluate the benefit of the Tendyne device, the change in Quality of Life as measured by the KCCQ scores at 6-month and 12-month follow-up visits from baseline will be tested separately. Details about hypotheses, statistical methods, and the significance level are described in the SAP.

Improvement of NYHA Functional Classification I or II at 12 months

To evaluate improvement in heart failure symptoms, the proportion of NYHA Functional Classification I or II at 12 months will be compared with that at baseline.

The null and alternative hypotheses are stated as:

$\mathbf{H_0}$: $P_{M12,\ NYHA\ I/II} \leq P_{B,\ NYHA\ I/II}$ vs.

$\mathbf{H_1}$: $P_{M12,\ NYHA\ I/II} > P_{B,\ NYHA\ I/II}$

[redacted]

where $P_{M12, NYHA I/II}$ and $P_{B, NYHA I/II}$ represent the proportion of subjects with NYHA Classification I/II at 12 months and baseline, respectively.

Change in Six Minute Walk Test Distance through 12 Months

To evaluate the long-term benefit of the Tendyne device, the change in distance walked as measured by the 6MWT at 6-month and 12-month follow-up visits from baseline will be tested separately. Details about hypotheses, statistical methods, and the significance level are described in the SAP.

10.2.3 Severe MAC Cohort

Severe MAC Cohort – Primary Endpoint

The primary endpoint for the Severe MAC cohort is freedom from all-cause mortality and heart failure hospitalization at 12 months post index procedure.

The null and alternative hypotheses are:

$\mathbf{H_0}: \pi_D \leq \pi_{PG}$

$\mathbf{H_1}: \pi_D > \pi_{PG}$

where π_D is the true event rate for the composite of freedom from all-cause mortality and heart failure hospitalization at 12 months and π_{PG} is the performance goal. The PG is set at 43% [redacted] The null hypothesis will be tested at the one-sided 2.5% level of significance [redacted].

[redacted]

Severe MAC Cohort – Secondary Endpoints

The following secondary endpoints will be evaluated in the Severe MAC cohort. These endpoints will be evaluated for labeling claims if the primary endpoint for the Severe MAC cohort is met.

Freedom from MR > mild in severity at 30 days post index procedure

To evaluate whether the Tendyne system is more effective at reducing MR than a pre-specified performance goal [redacted], freedom from MR > mild (1+) at 30 days post index procedure will be tested against a PG.

The null and alternative hypotheses are stated as:

$\mathbf{H_0}: P_{MR \leq 1+} \leq P_{PG}$
$\mathbf{H_1}: P_{MR \leq 1+} > P_{PG}$

where $P_{MR \leq 1+}$ is the proportion of subjects who have MR ≤ 1+ at 30 days post index procedure. P_{PG} is set at 75%.

[redacted]

[redacted] The null hypothesis will be rejected at the one-sided 2.5% significance level [redacted].

Change in Quality of Life, as measured by the KCCQ through 12 months

To evaluate the benefit of the Tendyne device, the change in Quality of Life as measured by the KCCQ scores at 6-month and 12-month follow-up visits from baseline will be tested separately. Details about hypotheses, statistical methods, and the significance level are described in the SAP.

Improvement of NYHA Functional Classification I or II at 12 months

To evaluate improvement in heart failure symptoms, the proportion of NYHA Functional Classification I or II at 12 months will be compared with that at baseline.

The null and alternative hypotheses are stated as:

$\mathbf{H_0}$: $P_{M12,\ \text{NYHA I/II}} \leq P_{B,\ \text{NYHA I/II}}$

$\mathbf{H_1}$: $P_{M12,\ \text{NYHA I/II}} > P_{B,\ \text{NYHA I/II}}$

where $P_{M12,\ \text{NYHA I/II}}$ and $P_{B,\ \text{NYHA I/II}}$ represent the proportion of subjects with NYHA Classification I/II at 12 months and baseline, respectively. The SAP specifies the details of this hypothesis test.

Change in Six Minute Walk Test Distance through 12 Months

To evaluate the long-term benefit of the Tendyne device, the change in distance walked as measured by the 6MWT at 6-month and 12-month follow-up visits from baseline will be tested separately. Details about hypotheses, statistical methods, and the significance level are described in the SAP.

10.2.4 Severe MAC CAP Cohort

Endpoints will be descriptively summarized and compared to the results in the Severe MAC primary analysis cohort. Data from the Severe MAC CAP Cohort may be used to support the PMA application for Severe MAC.

10.3 Sample Size Calculations and Assumptions

10.3.1 Randomized Cohort

The sample size for the Randomized cohort is determined based on the primary endpoint of freedom from all-cause mortality and heart failure hospitalizations (HFH) at 12 months. The primary endpoint will be analyzed based on the ITT population in which the Tendyne group is tested against the MitraClip group for non-inferiority. The null and alternative hypotheses are stated in Section 10.2.1. [redacted]

[redacted]

10.3.2 Non-Repairable Cohort

The sample size for the Non-repairable cohort is determined based on the primary endpoint of freedom from all-cause mortality and HFH at 12 months. The primary endpoint will be analyzed based on the AP Population and tested against a pre-specified performance goal of 45%. The null and alternative hypotheses are stated in Section 10.2.2. [redacted]

10.3.3 Severe MAC Cohort

The sample size for the Severe MAC cohort is determined based on the primary endpoint of freedom from all-cause mortality and heart failure hospitalizations (HFH) at 12 months. The primary endpoint will be analyzed based on the AP Population and tested against a pre-specified performance goal of 43%. The null and alternative hypotheses are stated in Section 10.2.3. [redacted]

10.3.4 Severe MAC CAP Cohort

After enrollment has been completed for the Severe MAC Cohort, additional patients with severe MAC will be enrolled in the Severe MAC CAP. Up to an additional [redacted] subjects upon FDA approval may be enrolled into the Severe MAC CAP, until the PMA review is complete for the Tendyne system. [redacted]

10.4 Timing of Analysis

The primary and secondary endpoints in the Randomized, Non-repairable and Severe MAC cohorts will be analyzed when all registered subjects in the corresponding cohorts complete 12 months of follow-up.

10.5 Subgroup Analysis

Subgroup analysis will be provided for the primary endpoint of the Randomized, Non-repairable and Severe MAC cohorts. [redacted]

10.6 Multiplicity Adjustments

Since the three cohorts (Randomized, Non-repairable and Severe MAC) are independent and mutually exclusive, the primary and secondary endpoints for the three cohorts will be evaluated separately and need no multiplicity adjustment among the cohorts. Data from subjects enrolled in the Severe MAC CAP will be independently analyzed from the primary study cohorts.

[redacted]

The primary endpoint of each cohort must be met for individual cohort success. The secondary endpoints for each cohort will be evaluated for labeling claims if the primary endpoint of that cohort is met. [redacted]

10.7 Procedures for Accounting for Missing Data

Analyses will be performed on all evaluable data. [redacted]

10.8 Statistical Criteria for Termination

There are no statistical criteria for termination of this clinical investigation.

10.9 Trial Success

Randomized Cohort

The Randomized cohort will be considered successful if the primary endpoint is met. Additional labeling claims may be made based on the secondary endpoints.

Non-Repairable Cohort

The Non-repairable cohort will be considered successful if the primary endpoint is met. Additional labeling claims may be made based on the secondary endpoints.

Severe MAC Cohort

The Severe MAC cohort will be considered successful if the primary endpoint is met. Additional labeling claims may be made based on the secondary endpoints.

Severe MAC CAP Cohort

No pre-specified success criteria will be set for the Severe MAC CAP; the primary and secondary endpoints will be descriptively summarized.

10.10 Deviations from Statistical Plan

Any major changes to the statistical plan will be documented in an amendment to the statistical plan. Less significant changes to the planned analyses will be documented in the final report.

11 DIRECT ACCESS TO SOURCE DATA / DOCUMENTS

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

Subjects providing informed consent are agreeing to allow clinical investigation monitors or regulatory agencies, including foreign countries, to review, in confidence, any records identifying the subjects in this clinical investigation. This information may be shared with regulatory agencies; [redacted]

however, Sponsor undertakes not to otherwise release the subject's personal and private information.

12 QUALITY CONTROL AND QUALITY ASSURANCE

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

12.1 Selection of Clinical Sites and Investigators

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

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

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

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

12.1.1 Investigator Experience Requirements

Implantation of the Tendyne device must include an operator (e.g., cardiothoracic surgeon) who is experienced in transapical access.

Implantation of the Control device will be performed by the same site investigators that have been trained to perform the Tendyne procedure.

The responsibilities of the various roles/specialties on the multidisciplinary team at the site are summarized in **Table 6** below:

Table 6. Investigator Responsibilities

Role / Specialty	Responsibility
Interventional Cardiologist	• Evaluates all potential subjects • Performs Tendyne and Control group procedure* • May present potential subjects to SEC

[redacted]

Role / Specialty	Responsibility
Cardiothoracic Surgeon	• Evaluates all potential subjects • Performs Tendyne and Control group procedure* • May present potential subjects to SEC
Echocardiographer	• Evaluates potential subjects for echocardiographic eligibility criteria • Participates in the Tendyne procedure
Note: Interventional Cardiologists or Cardiothoracic Surgeons can be Tendyne implanters as long as they have undergone the Tendyne Transcatheter Mitral Valve System training and are authorized by the Sponsor to perform the procedure. A total of three operators are required to complete the implant procedure; however, only the primary two operators require prior authorization by the sponsor. Training of the third operator can occur at, or just prior to, the day of the procedure and does not require pre-authorization from Abbott.	

12.1 Clinical Investigation Finances and Agreements

The clinical investigation will be financed by Abbott. Investigational sites will be compensated by Abbott for participation in the clinical investigation per the conditions of agreement between the Sponsor and the Investigational site.

12.2 Site Principal Investigator Responsibilities

The role of the Site Principal Investigator is to implement, oversee the management of the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety and well-being of the subjects involved in the clinical investigation. The principal investigator shall support monitoring and reporting to IRB/EC and local competent authorities as necessary, throughout the conduct of the clinical investigation.

The principal investigator is responsible for ensuring adequate training and qualification of the investigation site team and for maintaining oversight of their activities. The Principal Investigator may delegate tasks to members of the investigation site team but retains responsibility for the clinical investigation. This also applies when activities are outsourced to an external organization by the principal investigator in which case he/she shall exercise oversight to ensure the integrity of all tasks performed and any data generated by this external organization.

12.3 Clinical Investigation Plan Amendments

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

The Sponsor will submit the CIP Amendment to regulatory bodies per applicable regulation and await regulatory approval before implementing the CIP amendment.

[redacted]

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

12.4 Trial Training

[redacted]

12.5 Monitoring

The Sponsor and/or designee will monitor the trial over its duration according to the CIP-specific Monitoring Plan, which will include the planned extent of source data verification.

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The investigator understands and accepts the obligation to conduct the clinical investigation according to the CIP and applicable regulations, and has signed the Investigator Agreement.
- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical investigation and should have access to an adequate number of appropriate subjects to conduct the clinical investigation.
- Source documentation (including original medical records) must be available to substantiate proper informed consent procedures, adherence to CIP procedures, adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.
- The Investigator/site will permit access to such records. A monitoring visit sign-in log will be maintained at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of clinical investigation-related documents

[redacted]

12.6 Deviations from Clinical Investigation Plan

The investigator will not deviate from the CIP for any reason without prior written approval from Sponsor except in cases of medical emergencies, when the deviation is necessary to protect the rights, safety and well-being of the subject or eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing. All deviations must be reported to the Sponsor. No waivers for CIP deviations will be granted by Sponsor. All deviations must be reported to the Sponsor using the Deviation CRF. The occurrence of CIP deviations will be monitored by the Sponsor for evaluation of investigator compliance to the CIP and regulatory requirements and dealt with according to written procedures. Investigators will determine the cause of deviations, implement corrective actions and inform their IRB/EC or equivalent committee of CIP deviations in accordance with their specific IRB/EC or equivalent committee reporting policies and procedures.

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

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

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

12.6.1 Deviations with Expedited Reporting Requirements

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

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

Notification to the Sponsor and/or the IRB/EC shall be documented and maintained in the clinical trial file at the site and by the Sponsor.

12.6.2 Non-Critical Deviations

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

12.7 Measures Taken to Avoid and Minimize Bias

Due to the nature of the treatment in the Treatment and Control groups, site personnel and some Sponsor personnel will be aware of treatment assignment. The following steps will be taken to minimize bias in the conduct of the trial and analyses of clinical data.

[redacted]

12.7.1 Subject Recruitment and Randomization

Investigational sites will attempt to recruit consecutive subjects who meet trial eligibility criteria, with the following considerations:

- Candidates will be considered for the trial after they have been informed of trial requirements and have signed the informed consent form. See **Section 5 - Subject Selection and Withdrawal** for additional details on subject screening and informed consent process.
- Imaging (TEE, TTE, and Cardiac CT) for trial eligibility will be confirmed by an independent core laboratory.
- All baseline tests and assessments must be completed prior to registration.
- Subjects will be randomized or treated only after the investigational site personnel have confirmed and documented that the subject has met all eligibility criteria, the imaging core labs have confirmed eligibility, and the SEC has concurred with the local site heart team that the subject has been treated per applicable standards and can be treated in either the Randomized, Non-repairable or Severe MAC cohorts of the trial.
- Randomization will be stratified by site, assigned in permuted block sizes, and block sizes will not be disclosed to the sites.

12.7.2 Maintaining Similar Levels of Follow-up

The follow-up schedule for all registered subjects (Treatment and Control groups), including those that have been designated as a roll-in subject, is identical. Subjects will be followed by the local site heart team and will continue to be treated per standard of care consistent with the subject's condition prior to trial registration.

12.7.3 Review of Trial Imaging Assessments

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

12.7.4 Safety and Effectiveness Monitoring

All SAEs will be reviewed by the Sponsor (and/or designee). SAEs requiring adjudication will be submitted to an independent CEC. Every effort will be made to keep the CEC blinded to the subject's treatment assignment.

12.7.5 Follow-up Compliance

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

- During site initiation and training, the Sponsor will emphasize the importance of subject follow-up to the site, and that the site should communicate this importance to each subject.
- Sites will be informed to promptly reschedule any missed subject visits, and to reinforce the necessity of a follow-up visit.
- If a scheduled visit is missed due to subject illness, transportation issues, or travel, the site will be advised to:

[redacted]

  - Reinforce the necessity of follow-up visits;
  - Identify alternate transportation sources, and involve the Sponsor if necessary

- Sites will be instructed to ask subjects who withdraw during the trial to provide the reason for withdrawal and ask them if the investigator may contact them at the end of the trial follow-up.
- Subject follow-up rates will be monitored closely so that problems may be identified and addressed as soon as possible.
- For subjects who are lost-to-follow-up, sites may be requested to examine the Social Security Death Index to determine subject survival status (only the status will be sent to Sponsor, not any subject identifying information).

In addition to aforementioned steps, investigational sites will be educated on the importance of maintaining low rates of withdrawals for all registered subjects, including those that have been designated as a roll-in, and will be expected to make every effort to maintain low withdrawals during trial conduct. Withdrawals from the trial will require discussion between the investigator and the Sponsor.

12.8 Quality Assurance Audit

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

12.9 Sponsor Support for Regulatory Body Inspection

In the event an investigator is contacted by a Regulatory Agency regarding this clinical trial, the Investigator shall notify the Sponsor immediately. The investigator and research coordinator must be available to respond to reasonable requests and inspection queries made during the inspection process. The investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current clinical trial (e.g., Form FDA 483, Inspectional Observations, and warning letters). As necessary, the Sponsor may provide any assistance in preparing and/or responding to regulatory inspections.

12.10 Sponsor Auditing

The Sponsor may conduct periodic Quality Assurance audits (on-site audits) at various investigational sites. These audits will be conducted as follows:

- The Sponsor shall prepare an audit plan as well as the operating procedures for the related duties, and conduct audits in accordance with the audit plan and the operating procedures.
- Individual engaged in auditing (hereinafter referred to as "auditor") shall be different than those in charge of medical device development or monitoring.
- The auditor shall prepare an audit report documenting the matters confirmed in the audit to certify and verify that the audit has been conducted, and submit them to the Sponsor.

[redacted]

12.11 Committees

12.11.1 Steering Committee (SC)

The Steering Committee is responsible for providing trial leadership and overseeing the scientific and operational aspects of the trial. This committee will meet regularly to monitor subject enrollment and registration, general data collection and non-compliance with the CIP at individual sites, to review and act upon recommendations of the DSMB, to review operational issues that may arise and warrant a CIP amendment or other corrective action, and to determine policy regarding any publications arising from data generated from the performance of the trial.

12.11.2 Subject Eligibility Committee (SEC)

The SEC will confirm that each subject is symptomatic despite being on GDMT, has been adequately treated per applicable standards (e.g., coronary artery disease and left ventricular dysfunction), and meets trial entrance criteria. The committee will also confirm whether the subject is appropriate for TEER as well as the appropriate cohort of the trial.

The SEC will be comprised of, at a minimum, representatives from the following specialties: cardiothoracic surgery (with expertise in mitral valve surgery), interventional cardiology (with expertise in mitral valve therapies, including MitraClip) and may include cardiology (with expertise in heart failure). The composition, guiding policies, and operating procedures governing the SEC are described in a separate SEC Charter.

12.11.3 Publications Committee

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

12.11.4 Data and Safety Monitoring Board (DSMB)

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

The DSMB may consider a recommendation for modifications or termination of the clinical investigation based on any perceived safety concerns regardless of statistical significance. The recommendations of the DSMB are not binding, and all final decisions related to clinical investigations modifications rest with the Sponsor.

12.11.5 Clinical Events Committee (CEC)

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

[redacted]

13 DATA HANDLING AND RECORD KEEPING

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation.

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

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

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

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

For the clinical trial duration, the investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical trial progress records, laboratory reports, eCRFs, signed ICFs, device accountability records, correspondence with the IRB/EC and clinical trial monitor/Sponsor, AE reports, and information regarding subject discontinuation or completion of the clinical trial.

13.1 Data Management

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

13.2 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a 'need to know' basis, including periodic review of access rights, and revocation of access when an individual's employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to transfer into Sponsor's data management systems only pseudonymous Personal Information (key-coded) necessary to conduct the Clinical Investigation, such as the patient's medical condition, treatment, dates of treatment, etc. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of

[redacted]

the participating physicians on the device implant or procedures, monitoring and quality control purposes. Confidentiality of Personal Information will be observed by all parties involved at all times throughout the clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

13.3 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies. If appropriate, the DMP may be updated throughout the duration of the clinical investigation. All revisions will be tracked and document controlled.

13.4 Source Documentation

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

- Medical history/physical condition of the subject before involvement in the trial sufficient to verify CIP entry criteria.
- Dated and signed notes on the day of entry into the trial referencing the Sponsor, CIP number, subject ID number and a statement that informed consent was obtained.
- Dated and signed notes from each subject visit (for specific results of procedures and exams).
- Adverse events reported and their resolution including supporting documents such as discharge summaries, imaging, ECGs, and lab results; including documentation of site awareness of SAEs and of investigator assessment of device/procedure relationship.
- Trial required laboratory reports and 12-lead ECGs, signed and dated for review and annotated for clinical significance of out of range results.

[redacted]

Note: With electronic medical records some clinical sites may be able to annotate that the labs or ECG have been reviewed in the system. For those sites that do not have such capability, the labs or ECG may be able to be printed or signed.

- Notes regarding CIP required and/or prescription medications taken during the trial (including start and stop dates).
- Subject's condition upon completion of or withdrawal from the trial.
- Patient reported outcome measures may be completed using CRF worksheets. These serve as the source documentation.
- Any other data required to substantiate data entered into the eCRF.

13.5 Electronic Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the CIP and eCRF completion. eCRF data will be collected for all subjects that are enrolled into the trial. The investigator will ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. An electronic audit trail will be used to track any subsequent changes of the entered data.

13.6 Record Retention

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

The investigator will maintain all CRFs, essential trial documents, and any source documentation that supports data collected on trial subjects, in compliance with regulations and their local IRB/EC requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical investigation records.

The investigator will take measures to ensure essential documents are not accidentally damaged or destroyed. If for any reason the investigator withdraws responsibility for maintaining these essential documents, custody must be transferred to an individual who will assume responsibility. In such an event, the Sponsor must receive written notification of this custodial change.

13.6.1 Investigator Records

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

- Trial-related correspondence with another investigator, an IRB/EC, the Sponsor, monitors, subjects, or regulatory agencies, including required reports that relate to this trial
- Device Accountability log
- Delegation of Authority log
- Subject's case history records

[redacted]

- Signed informed consent form
- Signed HIPAA authorization (if separate from the consent form)
- Relevant subject complaints
- Protocol required CRFs and data sets
- Documentation of the dates and reasons for any trial deviation
- Clinical investigation plan and amendments
- Trial personnel training records
- Signed investigator agreement and clinical trial reimbursement agreement
- Current curriculum vitae (current by address)
- Current medical license (current by date)
- Financial disclosure
- IRB approvals, renewals and correspondence

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

13.6.2 Sponsor Records

The Sponsor will maintain the following records:

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

[redacted]

14 ETHICAL CONSIDERATIONS

IRB/EC approval for the CIP and ICF or other written information provided to the subject will be obtained by the Principal Investigator at each investigational site prior to participation in this clinical trial. The approval letter must be received prior to the start of the trial and a copy must be provided to the Sponsor. No changes will be made to the CIP or ICF or other written information provided to the subject without appropriate approvals, including IRB/EC, the Sponsor, and/or the regulatory agencies/competent authorities. Any amendments to the CIP as well as associated ICF changes will be submitted to the IRB/EC and written approval obtained prior to implementation, according to each institution's IRB/EC requirements. No changes will be made to the CIP or ICF or other written information provided to the patient without appropriate approvals, including IRB/EC, the Sponsor, and the regulatory agencies (if applicable).

Until the clinical trial is completed, the investigator will update the IRB/EC of the progress of this clinical trial, per IRB/EC requirements. Written approval must be obtained from the IRB/EC annually to continue the clinical trial, or according to each institution's IRB/EC requirements. Further, any amendments to the CIP as well as associated ICF changes will be submitted to the IRB/EC and written approval obtained prior to implementation, according to each institution's IRB/EC requirements.

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

15 CLINICAL INVESTIGATION CONCLUSION

The clinical investigation will be concluded when:

- All sites are closed AND
- The final report has been provided to investigators or the Sponsor has provided formal documentation of clinical investigation closure. The final report will be submitted within six months of the end of the investigation.

16 PUBLICATION POLICY

[redacted]

The Sponsor will register the clinical trial on www.clinicaltrials.gov, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. The Sponsor shall be responsible for any such registration and results posting as required by

[redacted]

ClinicalTrials.gov. Investigational sites shall not take any action to register the trial. A full report of the pre-specified outcomes, including any negative outcomes, will be made public through www.clinicaltrials.gov according to the requirements of Section 801 of the FDA Amendments Act. If this clinical investigation is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through www.clinicaltrials.gov.

17 RISK ANALYSIS

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

17.1 Anticipated Clinical Benefits

[redacted]

17.2 Foreseeable Adverse Events and Anticipate Adverse Device Effects

As previously described, **Table 4** indicates all anticipated AEs/risks associated with the use of the Tendyne Transcatheter Mitral Valve System. Risks associated with the specified device and procedure are described in the Instructions for Use. There may be risks related to the device under investigation that are unknown at present. Likewise, the exact frequency of the risk may be unknown.

17.3 Residual Risks Associated with the Device Under Investigation, as Identified in the Risk Analysis Report

Risk analysis of the Tendyne Transcatheter Mitral Valve has been performed in accordance with the risk management plant and Failure Mode Effect Analysis (FMEA) (Ref: RM0004) to systemically identify potential hazards associated with the design and use of this device. Based upon bench testing and prior clinical studies data, all risks have been identified and determined to be within acceptable levels.

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

- [redacted]

17.6 Steps Taken to Control or Mitigate the Risks

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

[redacted]

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

Risks associated with the use of the device during this clinical trial are minimized through device design, investigator selection and training, pre-specified subject eligibility requirements, trial monitoring to ensure adherence to the CIP and the use of a DSMB. Stopping rules will be discussed with the DSMB and applied for subject safety through enrollment. A steering committee will provide operational and scientific oversight. All SAEs and device deficiencies will be reported to the Sponsor and will be monitored internally for safety surveillance purposes.

17.7 Risk to Benefit Rationale

The Tendyne Transcatheter Mitral Valve System represents a novel, state-of-the-art technology that provides the unique benefit of treatment of mitral regurgitation. The potential risks are well tolerated when compared with other treatment options for symptomatic, severe MR. Therefore, the incremental benefits of the Tendyne Transcatheter Mitral Valve System outweigh the risks associated with this product.

[redacted]

APPENDIX I: ABBREVIATIONS AND ACRONYMS

Acronym	Definition	Acronym	Definition
6MWD/T	Six Minute Walk Distance/Test	IFU	Instructions for Use
ACC	American College of Cardiology	IMR	Ischemic Mitral Regurgitation
AE	Adverse Event	INR	International Normalized Ratio
AHA	American Heart Association	IRB	Institutional Review Board
CABG	Coronary Artery Bypass Grafting	KCCQ	Kansas City Cardiomyopathy Questionnaire
CAP	Continued Access Plan	LV	Left Ventricle
CCS	Canadian Cardiovascular Society	LVEDD	Left Ventricular End Diastolic Dimension
CEC	Clinical Events Committee	LVEDV	LVEDV Left Ventricle End Diastolic Volume
CFR	Code of Federal Regulations	LVEF	Left Ventricular Ejection Fraction
CIP	Clinical Investigational Plan	LVESD	Left Ventricular End Systolic Dimension
COPD	Chronic Obstructive Pulmonary Disease	LVESV	Left Ventricular End Systolic Volume
CRO	Contract Research Organization	LVOT	Left Ventricular Outflow Tract
CRT	Cardiac Resynchronization Therapy	MAC	Mitral Annular Calcification
CT	Computerized Tomography	MI	Myocardial Infarction
CV	Cardiovascular	MR	Mitral Regurgitation
CVA	Cerebrovascular Accident	MS	Mitral Stenosis
DD	Device Deficiency	MV	Mitral Valve
DAOH	Days Alive and Out of Hospital	MVARC	Mitral Valve Academic Research Consortium
DSMB	Data and Safety Monitoring Board	MVR	Mitral Valve Replacement
EACTS	European Association for Cardio-Thoracic Surgery	NYHA	New York Heart Association
EC	Ethics Committee	PAS	Pulmonary Artery Systolic pressure
ECG	Electrocardiogram	PCI	Percutaneous Coronary Intervention
EDC	Electronic Data Capture	PG	Performance Goal
EFT	Essential Frailty Toolset	PROM	Predicted Risk of Mortality
EROA	Effective Regurgitant Orifice Area	QoL	Quality of Life
ESC	European Society of Cardiology	RCT	Randomized Control Trial
FDA	U.S. Food and Drug Administration	RVSP	Right Ventricular Systolic Pressure
GCP	Good Clinical Practices	SAE	Serious Adverse Event
GDMT	Guideline Directed Medical Therapy	SEC	Subject Eligibility Committee
HF	Heart Failure	SF-12	Short Form Health Survey
HFH	Heart Failure Hospitalization	STS	Society of Cardiothoracic Surgeons
HIPAA	Health Insurance Portability and Accountability Act	TEE	Transesophageal Echocardiogram
ICD	Implantable Cardioverter Defibrillator	TEER	Transcatheter Edge-to-Edge Repair
ICF	Informed Consent Form	TTE	Transthoracic Echocardiogram
ICH	International Council for Harmonization	TMVR	Transcatheter Mitral Valve Replacement
IDE	Investigational Device Exemption	UADE	Unanticipated Adverse Device Effect

[redacted]

APPENDIX II: DEFINITIONS

The following definitions will be used in the SUMMIT trial Clinical Investigational Plan. All events constituting primary or secondary endpoints will be adjudicated by the independent Clinical Events Committee, along with relationship to the Treatment or Control group device and/or procedure.

Bleeding

Bleeding is defined per MVARC, which is based on the modified VARC-2 and modified Bleeding Academic Research Consortium (BARC) [69]. For this trial, the CEC will adjudicate bleeding events based on the tables below.

MVARC Primary Bleeding Scale (Modified VARC-2)

I. Minor

Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that meets ≥1 of the following:

- requiring nonsurgical medical intervention by a health care professional
- leading to hospitalization or increased level of care
- prompting evaluation; or requires 1 or 2 U of whole blood or packed RBC transfusion; and
- does not meet criteria for major, extensive, or life-threatening bleeding.

II. Major

Overt bleeding either associated with:

- a drop in the hemoglobin of ≥3.0 g/dl or requiring transfusion of ≥3 U of whole blood or packed RBCs, and
- does not meet criteria of life-threatening or extensive bleeding.

III. Extensive

Overt source of bleeding with:

- a drop in hemoglobin of ≥4 g/dl or whole blood or packed RBC transfusion ≥4 U within any 24-h period, or
- drop in hemoglobin of ≥6 g/dl or whole blood or packed RBC transfusion ≥4 U (BARC type 3b) within 30 days of the procedure.

IV. Life-threatening

Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating surgery or intervention, or intramuscular with compartment syndrome OR bleeding causing hypovolemic shock or hypotension (systolic blood pressure <90 mm Hg lasting >30 min and not responding to volume resuscitation) or requiring significant doses of vasopressors or surgery.

V. Fatal

Bleeding adjudicated by the CEC as being a proximate cause of death. Severe bleeding adjudicated as being a major contributing cause of a subsequent fatal complication, such as MI or cardiac arrest, is also considered fatal bleeding.

Modified BARC Bleeding Scale (Secondary Use)

Type 0

[redacted]

No bleeding.

Type 1

Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a health care professional. May include episodes leading to self-discontinuation of medical therapy by the patient without consulting a health care professional

Type 2

Any overt, actionable sign of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria:

- requiring nonsurgical, medical intervention by a healthcare professional
- leading to hospitalization or increased level of care, or
- prompting evaluation

Type 3

Type 3a

- Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed)
- Any transfusion with overt bleeding

Type 3b

- Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed)
- Cardiac tamponade
- Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid)
- Bleeding requiring intravenous vasoactive agents

Type 3c

- Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal)
- Subcategories confirmed by autopsy or imaging or lumbar puncture
- Intraocular bleed compromising vision

Type 4 (periprocedural)

- Perioperative intracranial bleeding within 48 h
- Reoperation after closure of sternotomy for the purpose of controlling bleeding
- Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period†
- Chest tube output ≥2L within a 24-h period

Type 5 (fatal bleeding)

Type 5a

- Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious

Type 5b

- Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

[redacted]

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

CCS Angina Classification is defined by the Canadian Cardiovascular Society [79] as:

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

Cardiovascular Death

Cardiovascular death is defined by VARC II [80], as any one of the following:

- 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 device, the implant procedure or the patient's condition. It should be established for both the Tendyne and Control device, based on the following categories:

Relatedness	Definition
Device-related	Any AE involving the function of the device, or the presence of the device in the body. Included in this category are events that are directly attributed to the device or the use of the device system.

[redacted]

Relatedness	Definition
Procedure-related	Any AE that results from the implant procedure. Events in this category are directly related to the general procedural sequelae.
Patient condition-related	Any AE that results from the worsening of a pre-existing condition or cannot be attributed to the device procedure.

Chronic Kidney Disease

The following definitions of Chronic Kidney Disease will be utilized in the trial, as stated from National Institute for Health & Clinical Excellence [81]:

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

Coronary Artery Disease

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

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

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

[redacted]

Endocarditis

Defined as a diagnosis of endocarditis based on the following Duke criteria [82]:

Criteria	Definition
Pathological Criteria	• **Microorganisms**: culture or histology in a vegetation, in a vegetation that has embolized, or in an intracardiac abscess, or • **Pathological lesions:** vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis; or
Major Clinical Criteria	• Persistently positive blood cultures: o Typical organisms for endocarditis: *Streptococcus viridans, S bovis*, "HACEK" group, community acquired *Staphylococcus aureus* or enterococci, in the absence of a primary focus • Persistent bacteremia: o ≥ 2 positive cultures separated by ≥12 hours or ≥ 3 positive cultures ≥ 1 h apart or 70% blood culture samples positive if ≥ 4 are drawn • Evidence of endocardial involvement o Positive echocardiogram ▪ Oscillating vegetation ▪ Abscesses ▪ Valve perforation ▪ New partial dehiscence of prosthetic valve o New valvular regurgitation
Minor Clinical Criteria	• Predisposing heart condition: MVP, bicuspid aortic valve, rheumatic or congenital heart disease, intravenous drug use • Fever • Vascular phenomena: Major arterial emboli, septic pulmonary emboli, mycotic aneurysm, intracranial hemorrhage, Janeway lesions • Immunologic phenomena: Glomerulonephritis, Osler's nodes, Roth spots, and rheumatoid factor • Positive blood culture: not meeting major criteria • Echocardiogram: positive but not meeting major criteria
Note: Clinical Diagnosis of Endocarditis is based on: • 2 major criteria; or • 1 major + 3 minor criteria; or • 5 minor criteria	

Guideline Directed Medical Therapy (GDMT)

Guideline Directed Medical Therapy (GDMT) is defined per the ACC/AHA/HFSA Heart Failure Guidelines [83]. GDMT must be documented for a minimum of 30 days prior to intended trial registration and subject must be on appropriate class of medications, which typically include: ACE Inhibitor or Angiotensin II Receptor Blocker, Beta-Blocker, and diuretic as appropriate.

[redacted]

Hospitalization (All-cause)

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

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

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

Hospitalization (Heart Failure): Any inpatient unit or ward hospitalization for at least 24 hours including emergency stay that requires treatment for heart failure. This definition also includes any event that meets all of the following criteria:

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

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

Index Procedure

The procedure in which the Tendyne or Control (MitraClip) device implant is first attempted.

Left Ventricular Dysfunction

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

- An implantable cardioverter-defibrillator is recommended as secondary prevention to prolong survival in subjects with current or prior symptoms of HF and reduced LVEF who have a history of cardiac arrest, ventricular fibrillation, or hemodynamically destabilizing ventricular tachycardia.
- Implantable cardioverter-defibrillator therapy is recommended for primary prevention of sudden cardiac death to reduce total mortality in subjects with non-ischemic dilated cardiomyopathy or ischemic heart disease at least 40 days post-MI, a LVEF less than or equal to 35%, and NYHA Functional Class II or III symptoms while receiving chronic optimal medical therapy, and who have reasonable expectation of survival with a good functional status for more than 1 year

[redacted]

- Subjects with LVEF of less than or equal to 35%, sinus rhythm, left bundle-branch block (LBBB), a QRS duration of ≥ 150 ms, and NYHA Functional Class III or ambulatory class IV symptoms despite recommended optimal medical therapy, should receive cardiac resynchronization therapy, with or without an ICD, unless contraindicated

Local Site Heart Team

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

Mitral Regurgitation Etiology

Defined in **Figure 2,** adapted from the 2017 ACC Expert Consensus Decision Pathway for MR [84].

[redacted]

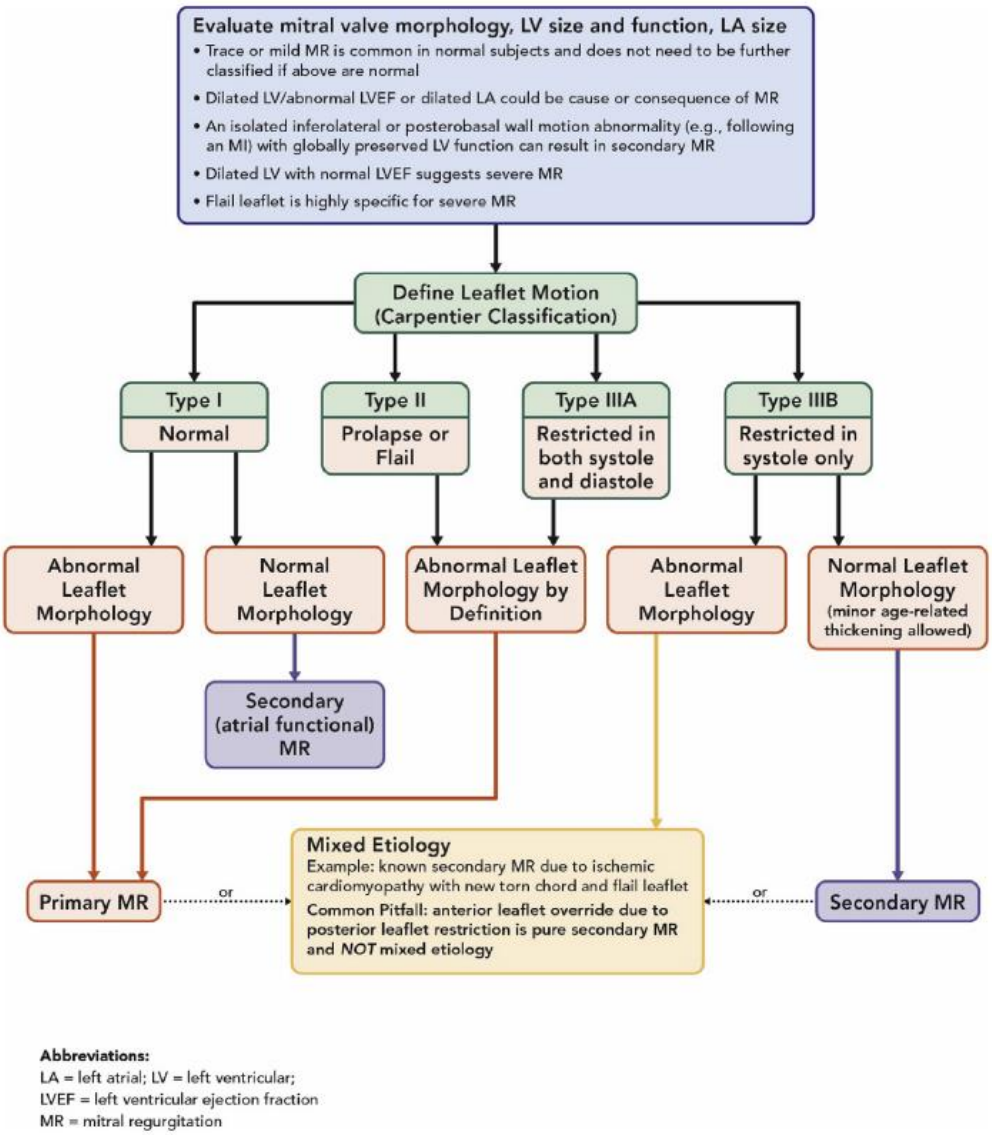


Figure 2. Decision Tree for Determining MR Etiology

Modified Rankin Scale Score

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

Score	Definition
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Disabling stroke: an mRS score ≥2 with an increase in ≥1 mRS category from a subject's pre-stroke baseline at 90 days.

Non-disabling stroke: an mRS score of < 2 at 90 days or one that does not result in an increase in at least one mRS category from an individual's pre-stroke baseline

Mitral Valve Academic Research Consortium (MVARC)

The following MVARC endpoints will be captured for the Tendyne device and Control group in the study cohorts [72].

MVARC (Tendyne)	MVARC (Control Group)
Technical Success Measured at exit from procedure room: 1) Absence of procedural mortality; and 2) Successful access, delivery and retrieval of the device delivery system; and 3) Successful deployment and correct positioning of the intended device; and 4) Freedom from emergency surgery or reintervention related to the device or access procedure **Note**: Criterion #3 above has been modified from the MVARC guidelines since the Tendyne device is designed to be fully retrievable, and thus allows the use of	**Technical Success** Measured at exit from operating room: 1) Absence of procedural mortality; and 2) Successful access, delivery and retrieval of the device delivery system; and 3) Successful deployment and correct positioning of the intended device; and 4) Freedom from emergency surgery or reintervention related to the device or access procedure **Note**: Criterion #3 above has been modified from the MVARC guidelines as either a single or multiple MitraClip devices may be attempted and/or

[redacted]

MVARC (Tendyne)	MVARC (Control Group)
additional devices during the index procedure.	ultimately implanted, and thus allows the use of additional devices during the index procedure.
Device Success Measured at 30 days and at all later post-procedural intervals: 1) Absence of procedural mortality or stroke; and 2) Proper placement and positioning of the device 3) Freedom from unplanned surgical or interventional procedures related to the device or access procedure; and 4) Continued intended safety and performance of the device, including: a) No evidence of structural or functional failure b) No specific device-related technical failure issues or complications c) Reduction of MR to either optimal* or acceptable levels without structural valve dysfunction (see **Appendix II: Definitions**), and with no greater than mild (1+) paravalvular MR (and without associated hemolysis). **Note**: Criterion #4c above has been modified from the MVARC guidelines, to align with the structural valve dysfunction definition used in this CIP.	**Device Success** Measured at 30 days and at all later post-procedural intervals: 1) Absence of procedural mortality or stroke; and 2) Proper placement and positioning of the device 3) Freedom from unplanned surgical or interventional procedures related to the device or access procedure; and 4) Continued intended safety and performance of the device, including: a) No evidence of structural or functional failure b) No specific device-related technical failure issues or complications. c) Reduction of MR to either optimal* or acceptable levels without significant mitral stenosis (i.e., post-procedure EOA is >1.5 cm^2) with a transmitral gradient <5 mm Hg). **Note:** Criterion #4c above has been modified from the MVARC guidelines, as paravalvular leak is not applicable to MitraClip.
Procedural Success All of the following must be present (measured at 30 days): 1) Device success (either optimal or acceptable*); and 2) Absence of major device or procedure related serious adverse events, including: a) Death b) Stroke c) Life-threatening bleeding (MVARC scale)	**Procedural Success** All of the following must be present (measured at 30 days): 1) Device success (either optimal or acceptable*); and 2) Absence of major device or procedure related serious adverse events, including: a) Death b) Stroke c) Life-threatening bleeding (MVARC scale)

[redacted]

MVARC (Tendyne)	MVARC (Control Group)
d) Major vascular complications e) Major cardiac structural complications f) Stage 2 or 3 acute kidney injury (includes new dialysis) g) Myocardial infarction or coronary ischemia requiring PCI or CABG h) Severe hypotension, heart failure, or respiratory failure requiring intravenous pressors or invasive or mechanical heart failure treatments such as ultrafiltration or hemodynamic assist devices, including intra-aortic balloon pumps or left ventricular or biventricular assist devices, or prolonged intubation for ≥ 48 hours. i) Any structural valve dysfunction, migration, thrombosis, or other complication requiring surgery or repeat intervention.	d) Major vascular complications e) Major cardiac structural complications f) Stage 2 or 3 acute kidney injury (including new dialysis) g) Myocardial infarction or coronary ischemia requiring PCI or CABG h) Severe hypotension, heart failure, or respiratory failure requiring intravenous pressors or invasive or mechanical heart failure treatments such as ultrafiltration or hemodynamic assist devices, including intra-aortic balloon pumps or left ventricular or biventricular assist devices, or prolonged intubation for ≥ 48 hours i) Any device detachment, migration, thrombosis, or other complication requiring surgery or repeat intervention. **Note**: Criterion #2i above has been modified from the MVARC guidelines as structural valve dysfunction is not applicable to MitraClip.
Patient Success All of the following must be present (measured at 12 months): 1) Device success (either optimal or acceptable*); and 2) Subject returned to the pre-procedural setting; and 3) No re-hospitalizations or reinterventions for the underlying condition (e.g., mitral regurgitation, heart failure); and 4) Improvement from baseline symptoms (NYHA improvement by ≥ 1 Functional Classification); and 5) Improvement from baseline in functional status (6MWD improvement by ≥ 50 meters); and 6) Improvement from baseline in Quality of Life (KCCQ improvement by ≥ 10 points).	**Patient Success** All of the following must be present measured at 12 months): 1) Device success (either optimal or acceptable*); and 2) Subject returned to the pre-procedural setting; and 3) No re-hospitalizations or reinterventions for the underlying condition (e.g., mitral regurgitation, heart failure); and 4) Improvement from baseline symptoms (NYHA improvement by ≥ 1 Functional Classification); and 5) Improvement from baseline in functional status (6MWD improvement by ≥ 50 meters); and 6) Improvement from baseline in quality of life (KCCQ improvement by ≥ 10 points).

[redacted]

MVARC (Tendyne)	MVARC (Control Group)
*MR reduction is considered optimal when post-procedure MR is reduced to trace or absent. MR reduction is considered acceptable when post-procedure MR is reduced by at least 1 class or grade from baseline and to no more than moderate (2+) in severity.	

Myocardial Infarction

Myocardial infarction (MI) classification and criteria for diagnosis is defined by MVARC, which incorporates elements of the Third Universal definition of MI [72], [85].

MI Type	Definition
Periprocedural MI (≤48 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 • The peak CK-MB measured within 48 h of the procedure rises to ≥ 10x the local laboratory ULN plus new ST-segment elevation or depression of ≥1 mm in ≥2 contiguous leads (measured 80 ms after the J-point), or to ≥5x ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB, OR in the absence of CK-MB measurements and a normal baseline cTn, a cTn (I or T) level measured within 48 h of the PCI rises to ≥70x the local laboratory ULN plus new ST-segment elevation or depression of ≥1 mm in ≥2 contiguous leads (measured 80 ms after the J-point), or ≥35x ULN with new pathological Q waves in ≥2 contiguous leads or new persistent LBBB.
Spontaneous MI (>48 hours after the index procedure)	• 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: o ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block (LBBB)) o New pathological Q-waves in at least two contiguous leads o Imaging evidence of a new loss of viable myocardium or new wall motion abnormality o 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.

[redacted]

MI Type	Definition
	○ Pathological findings of an acute myocardial infarction.

New York Heart Association Classification (NYHA Class):

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

Principal Investigator (from ISO 14155)

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

Randomization (from ISO 14155)

Process of assigning subjects to the investigational medical device or comparator groups using an established, recognized statistical methodology to determine the assignment in order to reduce bias.

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.

Single Leaflet Device Attachment (SLDA)

The loss of insertion of a single leaflet from the MitraClip device with ongoing insertion of the opposing leaflet [65].

Stroke and TIA (from VARC II)

The following stroke and TIA diagnostic criteria will be used in this trial, per VARC II [80]:

- 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

[redacted]

affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke.

- **Stroke:** Duration of a focal or global neurological deficit ≥24 hours; OR <24 hours if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death.
- **TIA:** Duration of a focal or global neurological deficit <24 hours, any variable neuroimaging does not demonstrate a new hemorrhage or infarct.
- No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with the designated neurologist.
- Confirmation of the diagnosis by one of the following:
  - Neurologist or neurosurgical specialist
  - Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone.

Stroke Classification

The following stroke definitions will be used, per VARC II [77].

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

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

Structural Valve Dysfunction

Structural valve dysfunction will apply to Tendyne only, and will be defined as hemodynamic dysfunction (moderate or severe) in the presence of morphologic dysfunction. These definitions were adapted based on the EAPCI Consensus Statement [86] and the ASE Guidelines [87]:

Type of Valve Dysfunction	Definition
Moderate hemodynamic dysfunction	• Mean transvalvular gradient 6-10 mmHg OR • Moderate transvalvular regurgitation (grade 2-3+)
Severe hemodynamic dysfunction	• Mean transvalvular gradient >10 mmHg OR • Severe transvalvular regurgitation (grade 4+)
Morphologic dysfunction	• Leaflet abnormalities resulting in stenosis and/or central regurgitation, including: o *Integrity* – torn or flail o *Structure* – thickening or calcification o *Function* – impaired mobility

[redacted]

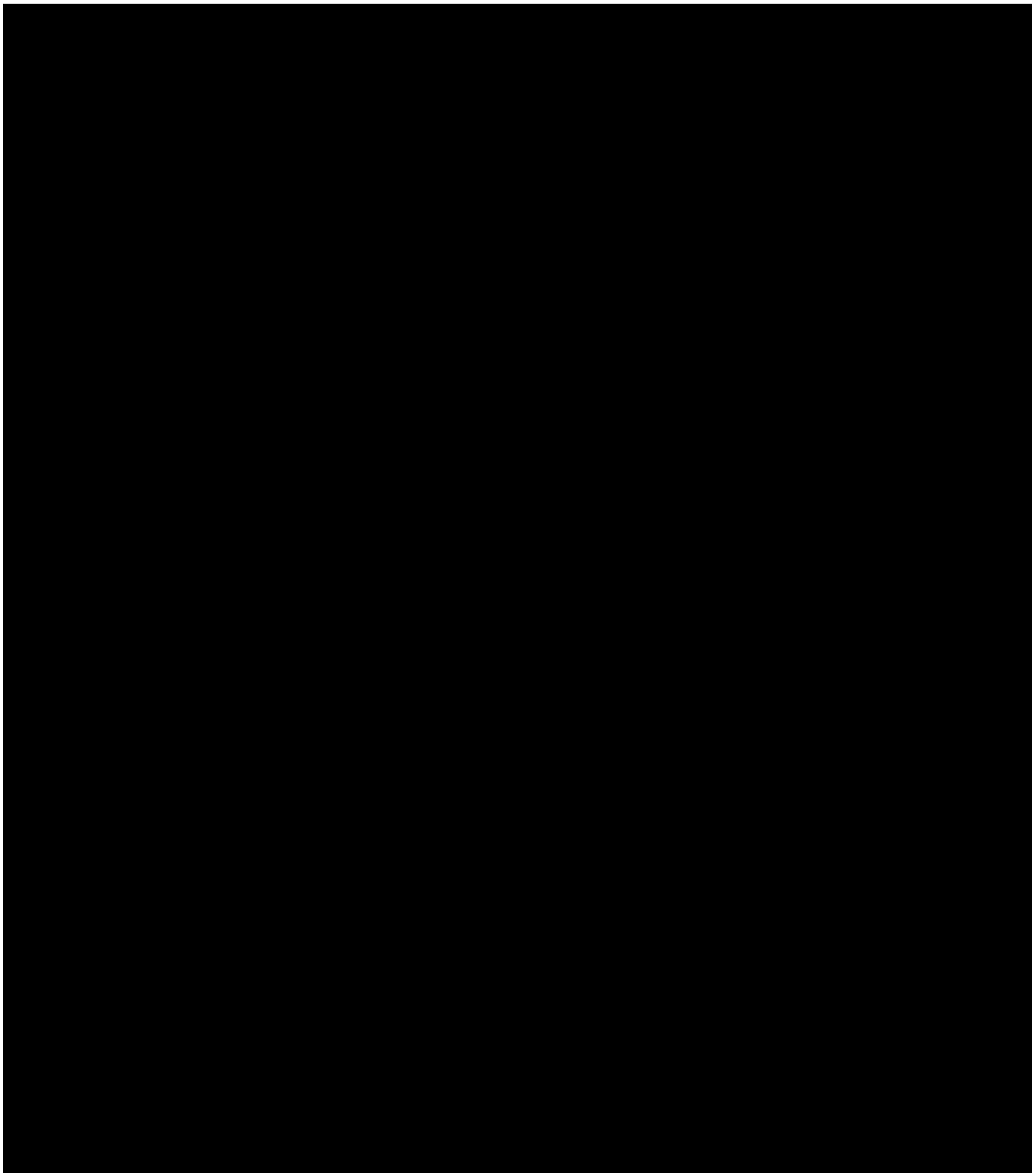
Type of Valve Dysfunction	Definition
	• Strut/frame fracture • Tether rupture • Apical pad deterioration

Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (PROM) Score

STS PROM scores for both "MV Replacement Only" and "MV Repair" will be calculated in the trial for the Tendyne device and Control group subjects. The risk calculators can be completed online at http://riskcalc.sts.org/.

[redacted]

APPENDIX III: SUBJECT SCREENING FLOW CHART



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APPENDIX IV: TRIAL ASSESSMENT AND FOLLOW-UP SCHEDULE

Exams, Tests and Data Collection	Screening / Baseline	Procedure	Pre-discharge	1 Month	3 Months*	6 Months	1 and 2 years	Annual visits (3-5 years)
Visit Window		**Before and After Implant**	**72 hours prior to discharge**	**-3 days +14 days**	**±30 days**	**±30 days**	**±30 days**	**±45 days**
Informed Consent	X							
Inclusion/Exclusion Screening	X							
Medical history with Demographics	X							
Physical Exam including Vital Signs while sitting	X		X	X		X	X	X
Cardiovascular Medications	X	X	X	X	X	X	X	X
Essential Frailty Toolset (EFT)	X							
STS PROM Risk Score	X							
CCS Angina Classification	X							
NYHA Classification	X			X		X	X	X
Modified Rankin Scale (mRS‡)	X							
Six Minute Hall Walk Test	X			X		X	X	X
KCCQ	X			X		X	X	X
EQ-5D	X			X		X	X	X
SF-12	X			X		X	X	X
CLINICAL LABORATORY TESTS								
Pregnancy Test	X							
Creatinine	X		X	X		X	X	X
Plasma–free Hemoglobin	X			X		X	X	X
BNP or NT pro-BNP	X			X		X	X	X
International Normalized Ratio (INR)	X		X	X		X	X	X
Creatine Kinase-MB (CK-MB) if indicated	X		X	X		X	X	X
Troponin (Type I or T) if indicated	X		X	X		X	X	X
Serum albumin	X							
INTRAOPERATIVE HEMODYNAMICS – (Tendyne Only)								
Cardiac Output		X						
PA Pressures		X						
RA Pressures		X						
Aortic pressures		X						
LV Pressures		X						
EXAMS AND TESTS								
Coronary Angiogram (if clinically indicated)	X							
Cardiac CT^	X			X				
ECG (12-Lead)	X	X	X	X		X	X	X
TEE	X	X						
TTE^	X		X	X		X	X	X
OTHER								
Device Deficiencies		X						
Adverse Events		X	X	X	X	X	X	X
Protocol Deviations	X	X	X	X	X	X	X	X
COVID-19 Assessment	X	X	X	X	X	X	X	X

*The 3 month visit will be conducted via telephone.

‡Modified Rankin Scale is also to be completed after suspected onset of stroke^

^TTE imaging must be conducted between 60 and 120 days after anticoagulation stoppage for subjects implanted with the Tendyne valve. If the TTE identifies suspected valve dysfunction, contrast-enhanced cardiac CT imaging is also required. If renal insufficiency precludes a cardiac CT, a TEE must be performed instead.

Note: Baseline imaging for Cardiac CT, TEE and TTE must be acquired no earlier than 120 days prior to subject consent.

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APPENDIX V: ESSENTIAL FRAILTY TOOLSET

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APPENDIX VI: CONTACT INFORMATION

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APPENDIX VII: ACCOMPANYING INFORMATION

Investigational device labels, case report forms, and informed consent form template have all been provided under separate cover and are available on request from the Sponsor.

A copy of the monitoring plan can be obtained on request from the Sponsor clinical project manager.

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APPENDIX VIII: NON-SUITABILITY CRITERIA FOR TEER

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APPENDIX IX: CLINICAL INVESTIGATION PLAN REVISIONS

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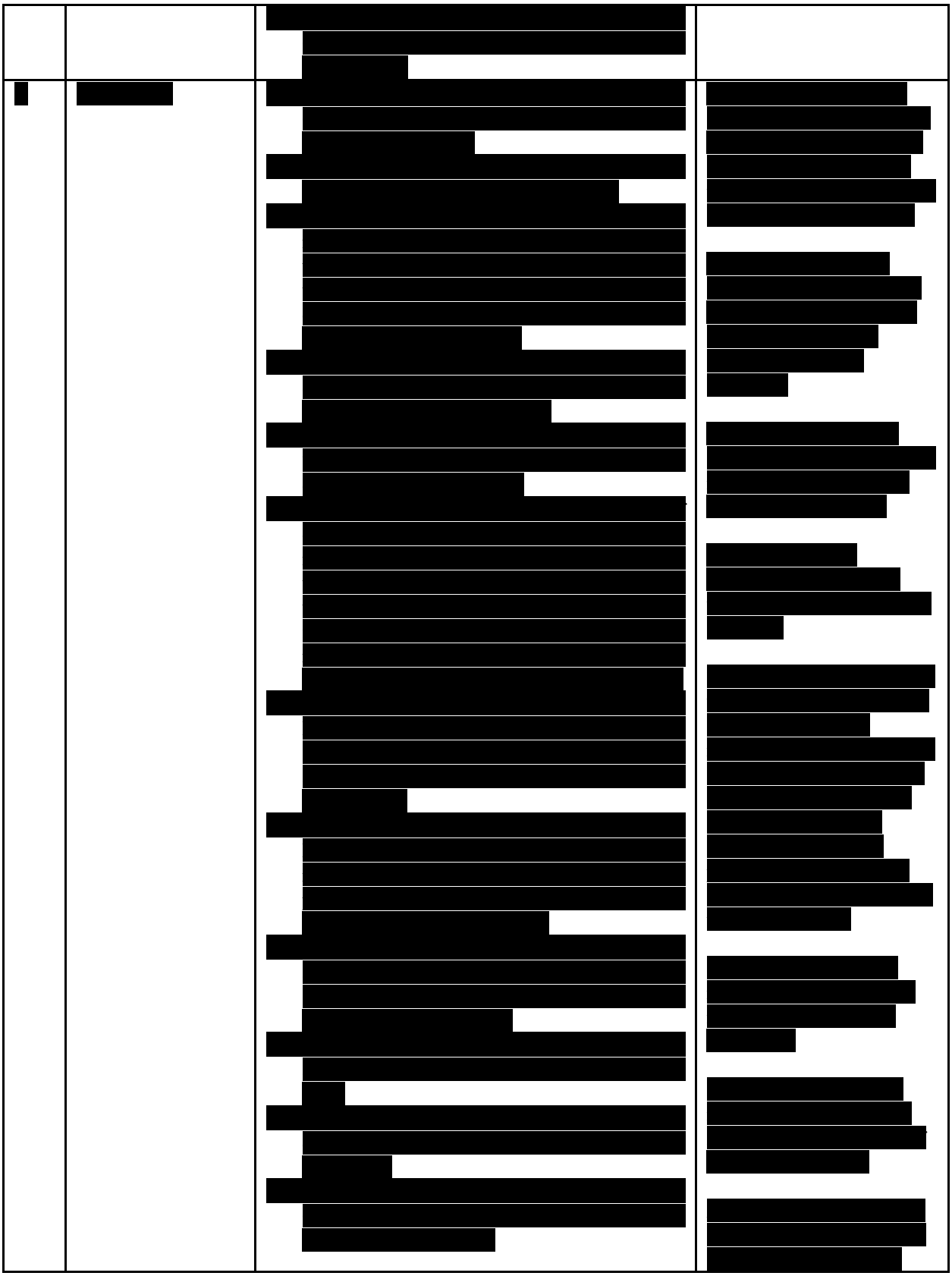

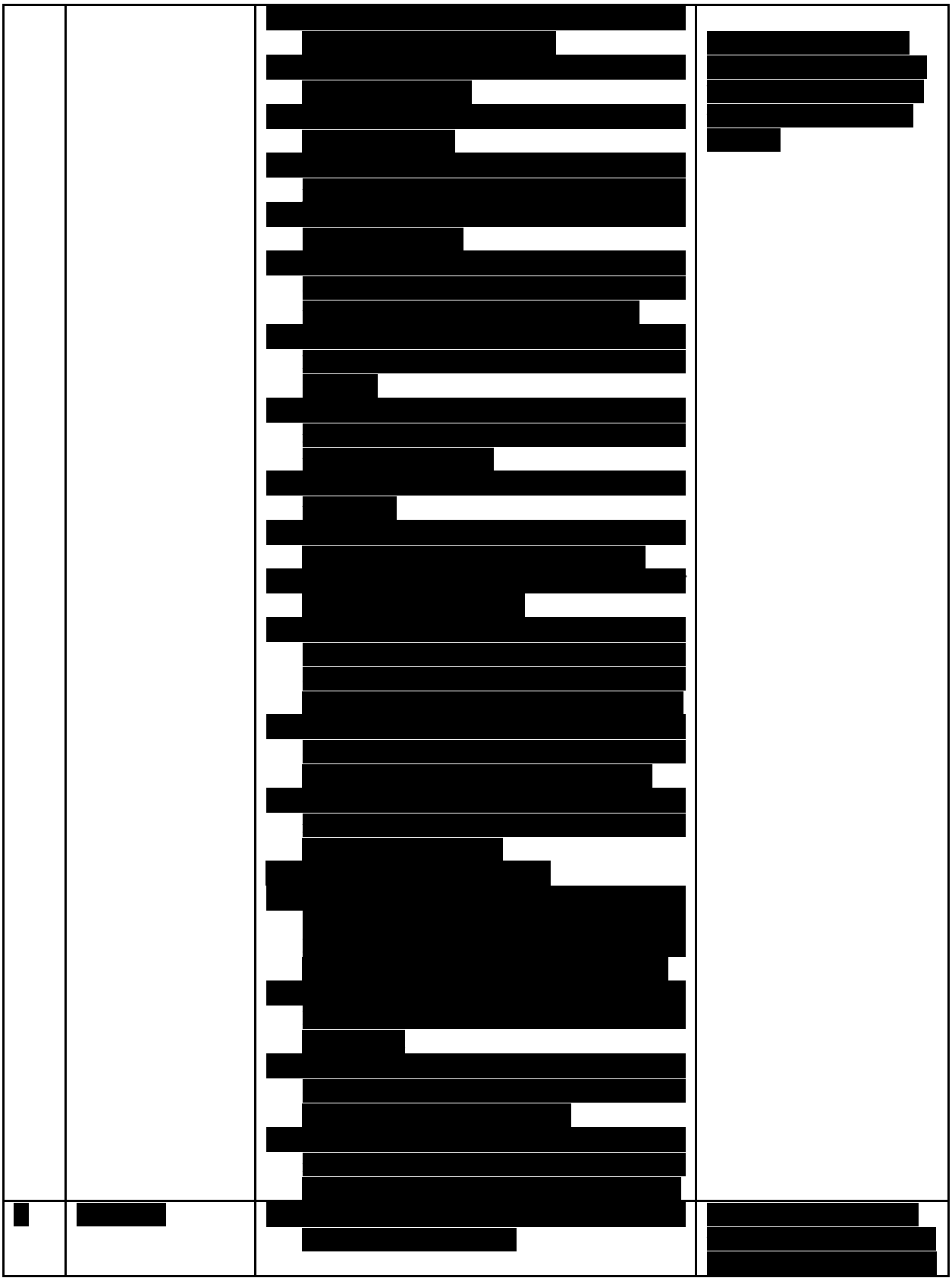

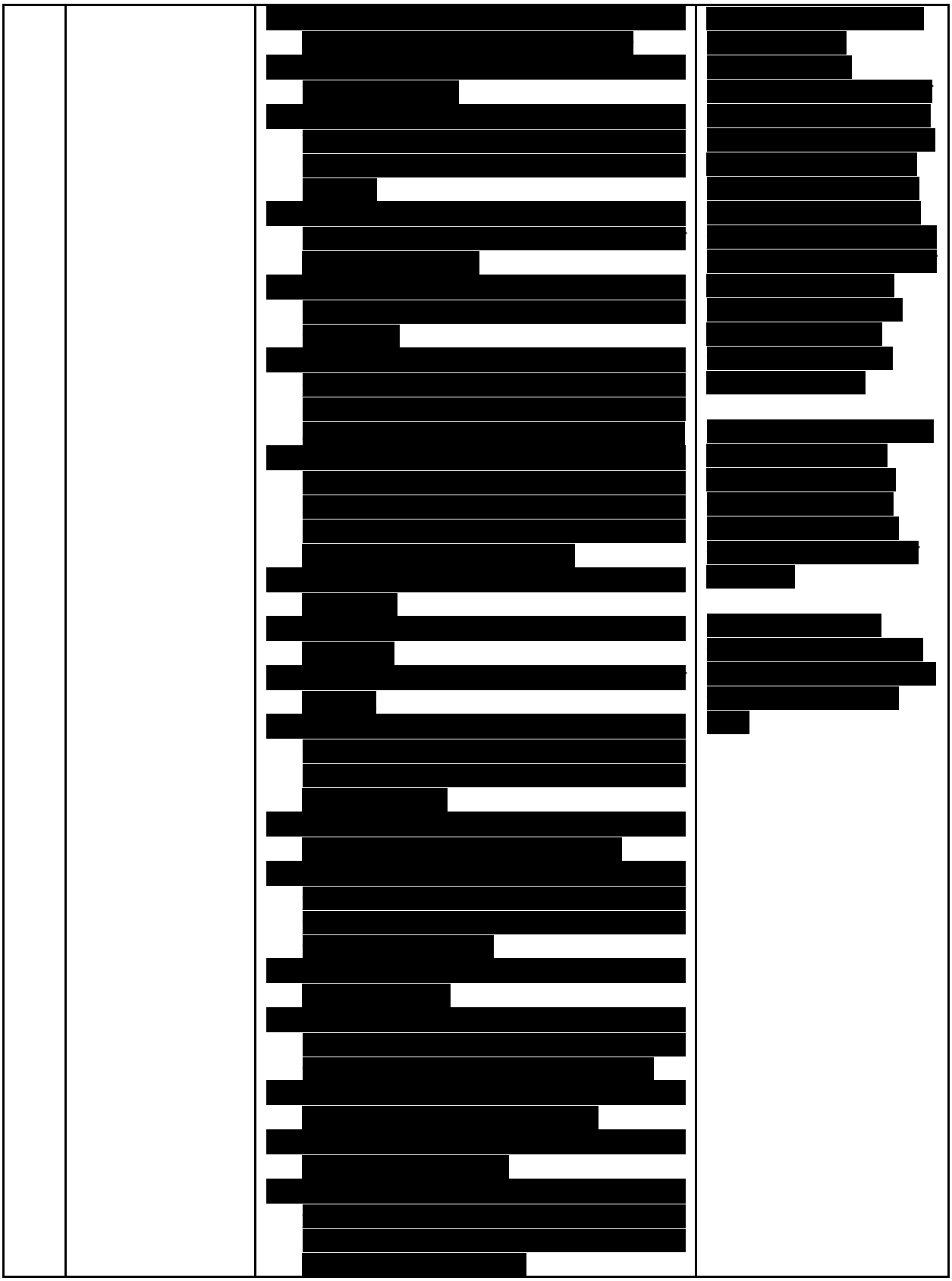

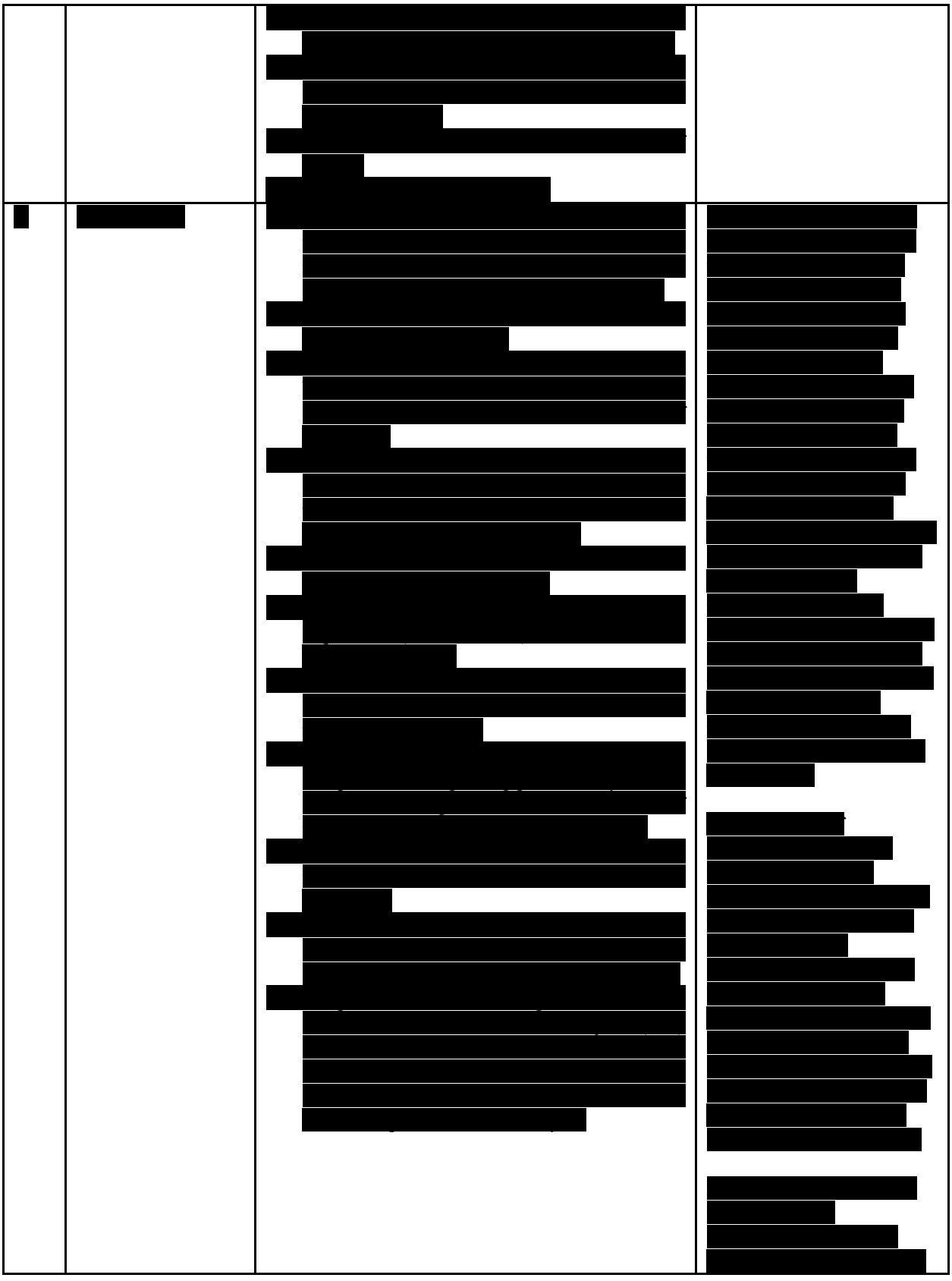

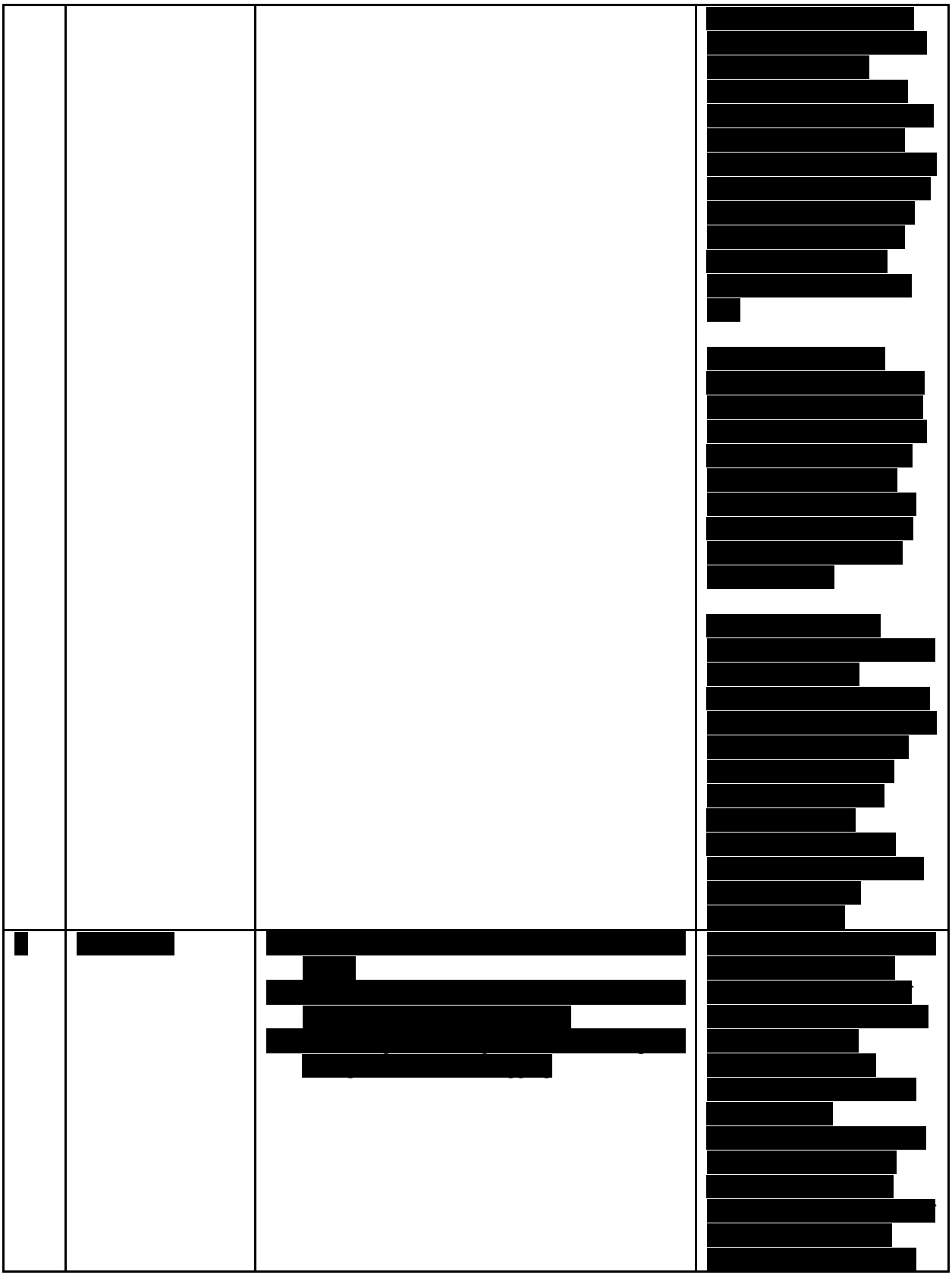

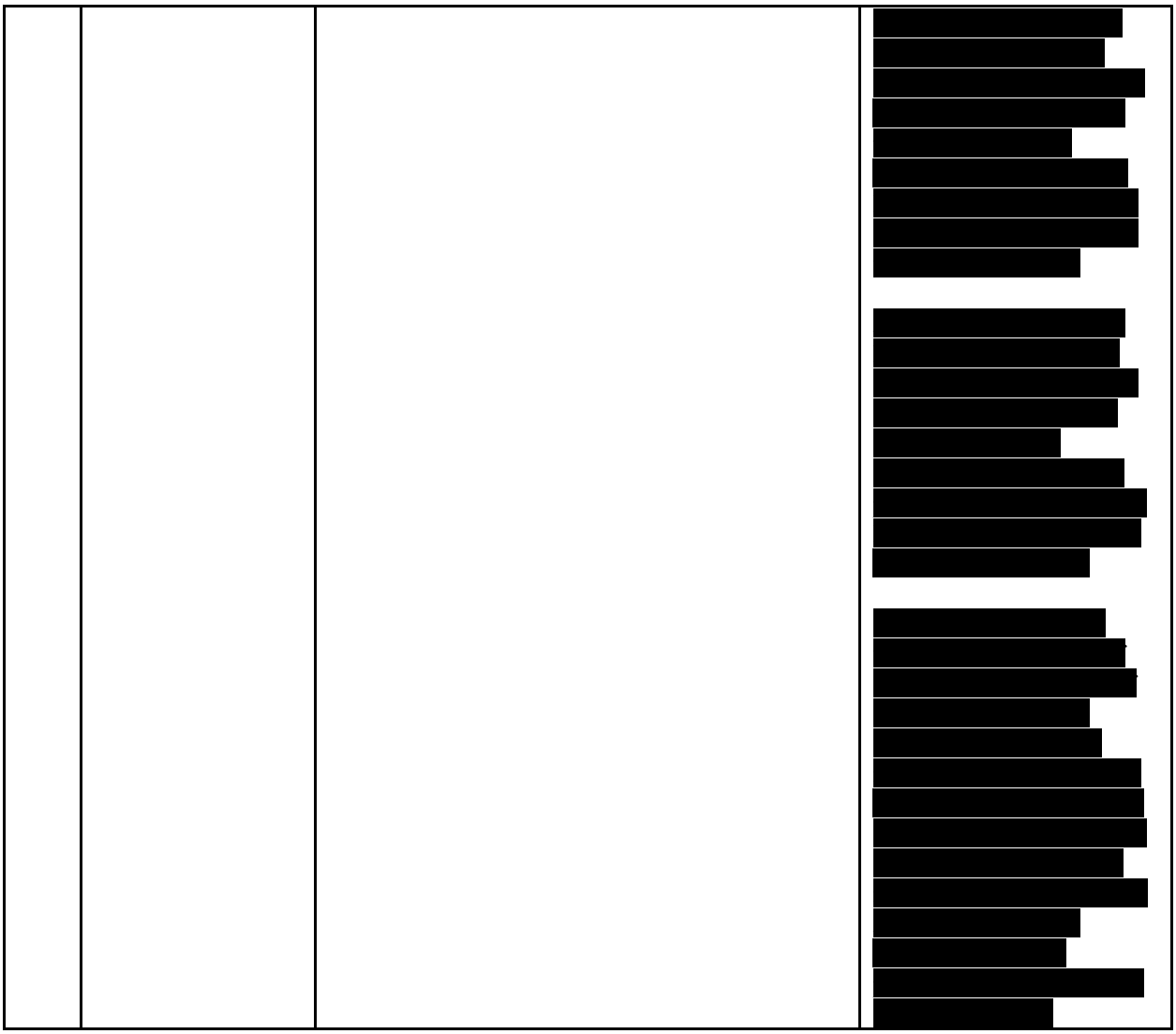

APPENDIX X MITRACLIP INDICATION FOR USE

- The MitraClip™ NTR/XTR Clip Delivery System is indicated for the percutaneous reduction of significant symptomatic mitral regurgitation (MR ≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.
- The MitraClip™ NTR/XTR Clip Delivery System, when used with maximally tolerated guideline-directed medical therapy (GDMT), is indicated for the treatment of symptomatic, moderate-to-severe or severe secondary (or functional) mitral regurgitation (MR; MR ≥ Grade III per American Society of Echocardiography criteria) in patients with a left ventricular ejection fraction (LVEF) ≥ 20% and ≤ 50%, and a left ventricular end systolic diameter (LVESD) ≤ 70 mm whose symptoms and MR severity persist despite maximally tolerated GDMT as determined by a multidisciplinary heart team experienced in the evaluation and treatment of heart failure and mitral valve disease.

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