TENDYNE

Protocol No. CS-03

EXPANDED CLINICAL STUDY OF TENDYNE MITRAL VALVE SYSTEM

Statistical Analysis Plan

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TABLE OF CONTENTS

1. SYNOPSIS OF STUDY DESIGN AND PROCEDURES 3
1.1 Purpose of the Statistical Analysis Plan 3
1.2 Study Objective 3
1.3 Study Design 3
1.3.1 Primary Endpoints 4
1.3.1.1 Primary Safety Endpoint 4
1.3.1.2 Primary Performance Endpoint 4
1.3.2 Secondary Endpoints 4
1.3.3 Performance Endpoints 5
1.3.3.1 Technical Success 5
1.3.3.2 Device Success 5
1.3.3.3 Individual Patient Success 5
1.3.4 Additional Endpoints 6
1.4 Analysis Populations 6
1.4.1 Treated Population (TP) 6
1.4.2 Implanted Patient Population (IPP) 6
1.5 Clinical Event Committee and Data and Safety Monitoring Board 6
2. STATISTICAL PLAN AND METHODS 7
2.1 Background Characteristics 7
2.1.1 Descriptive Statistics for Continuous Variables 7
2.1.2 Descriptive Statistics for Categorical Variables 7
2.1.3 Subject Disposition 7
2.1.4 Protocol Deviation 8
2.2 Study Endpoint Analyses 8
2.2.1 Primary Safety Endpoint Analyses 8
2.2.2 Primary Performance Endpoint Analyses 8
2.2.3 Secondary Endpoint Analyses 9
2.2.3.1 All-Cause Mortality at 30 Days 9
2.2.3.2 Change from Baseline in KCCQ at 6 Months and 12 Months 10
2.2.3.3 Change from Baseline in Six-Minute Walk Test Distance at 6 Months and 12 Months 11
2.2.4.4 Change in Proportion of NYHA Functional Class I or II at 12 Months 11
2.2.4 Performance Endpoint Analyses 12
2.2.4.1 Technical Success 12
2.2.4.2 Device Success 12
2.2.4.3 Individual Patient Success 12
2.2.5 Analyses of Additional Endpoints 12
2.2.6 Device and Procedure-Related Endpoints 12
2.4 Poolability of Valve Models 13
2.5 Handling of Missing Data 13
2.6 Multiplicity Issues 13
3. REFERENCES 15

1. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is intended to provide a detailed and comprehensive description of the planned methodology and analysis to be used to support conformity requirements for CE Mark of the Tendyne Mitral Valve System with data from the Tendyne CS-03 clinical investigation.

1.2 Study Objective

The objective of the trial is to evaluate the safety and performance of Tendyne Mitral Valve System in the treatment of severe mitral regurgitation in subjects with symptomatic, severe mitral valve regurgitation, who are not suitable for surgical treatment and in whom existing co-morbidities would not preclude the expected benefit from reduction of the mitral regurgitation.

1.3 Study Design

This is a prospective, single-arm, multicenter study designed to evaluate the Tendyne Mitral Valve System in patients with significant mitral regurgitation.

This study is designed in accordance with the Mitral Valve Academic Research Consortium (MVARC) 2015 guidelines and the ISO 5840-3:2013 standard. The study is conducted under ISO 14155-2011 standard.

The data gathered in this study will be used to support conformity requirements for CE Mark of the Tendyne Mitral Valve System and to evaluate long-term safety and performance of Tendyne Mitral Valve in the intended population.

All enrolled subjects will be followed at 30 days, 90 days, 6 months, 12 months, and annually thereafter through 5 years from the index procedure.

A clinical investigation report will be prepared for CE Mark based on clinical data from at least 86 subjects who have completed or crossed the 12-month follow-up.

The study will continue to enroll after the CE Mark and collect long-term safety and performance data as part of the Tendyne post-market follow-up program.

1.3.1 Primary Endpoints

1.3.1.1 Primary Safety Endpoint

The primary safety endpoint is a composite of device success (as defined in **Section 1.3.2.2**) and freedom from the following device- or procedure-related serious adverse events (SAEs) at 30 days post the index procedure, per adjudication by the Clinical Events Committee (CEC):

- Cardiovascular death
- Reintervention caused by valve-related dysfunction
- Disabling stroke
- Myocardial infarction (MI)
- Life-threatening bleeding (BARC Type 2, 3, and 5)
- Major Vascular Complications
- Renal failure requiring dialysis
- Other device-related SAEs: device migration, embolization, fracture, hemolysis, thrombosis or endocarditis
- Other procedure-related SAEs: cardiac tamponade, sepsis

Stroke and MI classifications will be per the Valve Academic Research Consortium – 2 (VARC-2). Life-threatening bleeding classifications will be per the Bleeding Academic Research Consortium (BARC) consensus.

1.3.1.2 Primary Performance Endpoint

The primary performance endpoint is the proportion of subjects with mitral regurgitation (MR) grade ≤ 2, per echocardiography core laboratory, at 30 days post the index procedure. If the 30-day echocardiography data is not available, the data from the next closest visit will be used.

1.3.2 Secondary Endpoints

The secondary endpoints are:

- All-cause mortality at 30 days
- Change from baseline in distance walked on the 6MWT at 6 months and 12 months
- Change from baseline in QoL, as measured by KCCQ at 6 months and 12 months
- Change in proportion of NYHA Functional Classification I or II at 12 months

1.3.3 Performance Endpoints

1.3.3.1 Technical Success

Technical success is a composite endpoint measured at exit from the procedure room, defined as subject is alive with the following:

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

1.3.3.2 Device Success

Device success is a composite endpoint measured at 30 days post the index procedure and all post-procedural time points, defined as subject is alive with the following:

- Disabling stroke free, and
- Original intended device in place, and
- No additional surgical or interventional procedures related to access or the device, and
- Intended performance of the device:
  - [redacted]
  - [redacted]
  - [redacted]

1.3.3.3 Individual Patient Success

Individual patient success is a composite endpoint measured at 1 year post the index procedure, defined as device success (**Section 1.3.2.2**) and all of the following:

- No re-hospitalizations or re-interventions for heart failure
- Improvement in New York Heart Association (NYHA) functional class (≥ 1 compared to baseline)

- Improvement in distance walked, 6 Minute Walk Test (6MWT) (≥ 50 meters compared to baseline)
- Improvement in Kansas City Cardiomyopathy Questionnaire scores (KCCQ) (≥ 10 compared to baseline)

1.3.4 Additional Endpoints

Additional study endpoints include the following:

- Length of hospital stay
- All-cause mortality at 3 months
- A composite endpoint of device success and freedom from device- or SAEs at 2 years post the index procedure. This endpoint is defined similarly as the primary safety endpoint in **Section 1.3.1.1**, except that the endpoint will be measured at 2 years post the index procedure.

1.4 Analysis Populations

[redacted]

1.5 Clinical Event Committee and Data and Safety Monitoring Board

An independent Clinical Events Committee (CEC) has been established. The CEC is responsible for reviewing and classifying all serious adverse events, device- and/or procedure-related adverse events, and deaths.

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

2. STATISTICAL PLAN AND METHODS

Sample size calculations were performed using the Power Analysis and Sample Size Software (PASS) (Version 14, NCSS Statistical Software). All statistical analyses will be performed using Statistical Analysis System (SAS) for Windows (version 9.4, SAS Institute Inc. Cary, NC).

2.1 Background Characteristics

Demographics and baseline characteristics, medical history, echocardiography core laboratory measures, procedural and device data, and treatment results will be summarized using descriptive summary statistics.

2.1.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, LVEF, LVEDV), results will be summarized with the numbers of observations, means, standard deviations, minimums, maximums, and 95% confidence intervals. Change from baseline, if applicable, may be included using these same descriptive statistics. Differences between subgroups, if applicable, will be summarized with differences of the two means, and 95% confidence intervals for the difference between the means.

2.1.2 Descriptive Statistics for Categorical Variables

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

2.1.3 Subject Disposition

The number and percentage of subjects screened, screen failure, enrolled, treated, and completed protocol-required follow-up visits will be summarized. Screen failure percentage is calculated from number of screened subjects and other percentages are calculated among number of enrolled or treated subjects. Subjects who discontinued from the study will be summarized by their primary

reason for discontinuation.

2.1.4 Protocol Deviation

The total number of protocol deviations and total number of subjects with deviations will be provided by deviation type. Number of protocol deviations by site will also be provided.

2.2 Study Endpoint Analyses

2.2.1 Primary Safety Endpoint Analyses

The primary analysis will be based on the TP population. The composite endpoint will be summarized as the proportion of subjects with device success (definition in **Section 1.3.2.2**) and freedom from device- or procedure-related SAEs at 30 days post the index procedure, per CEC adjudication, along with the 95% exact confidence interval. Each component of the primary composite endpoint will also be summarized separately using descriptive statistics.

Similar analyses will be provided for the IPP population.

2.2.2 Primary Performance Endpoint Analyses

The primary performance endpoint is the proportion of subjects with mitral regurgitation (MR) grade ≤ 2, per echocardiography core laboratory, at 30 days post the index procedure. The trial is intended to demonstrate beneficial effects of the study device in reducing the MR severity in subjects treated with the Tendyne Mitral Valve System.

Hypothesis

The null and alternative hypotheses are:

$\mathbf{H_0}$: $P_D \leq P_{PG}$

$\mathbf{H_1}$: $P_D > P_{PG}$

where P_D is the proportion of subjects with MR grade ≤ 2 at 30 days post the index procedure and P_{PG} is the performance goal. The performance goal is set at [redacted]. The hypothesis will be tested at the 2.5% significance level.

[redacted]

[redacted].

Sample Size

[redacted]

Analysis

The primary analysis will be based on the IPP population. The endpoint will be evaluated as a proportion of subjects with MR grade ≤ 2 at 30 days. If the 30-day core lab assessed echocardiography data is not available, the data from the next closest visit will be used. The hypothesis will be tested by comparing the one-sided 97.5% exact lower confidence bound of the observed 30-day MR grade ≤ 2 rate to the performance goal of [redacted]. The null hypothesis will be rejected if this lower bound is greater than [redacted].

Similar analyses will be provided for the TP population.

2.2.3 Secondary Endpoint Analyses

2.2.3.1 All-Cause Mortality at 30 Days

All-cause mortality at 30 days will be assessed to evaluate the acute safety of the Tendyne Mitral Valve System.

Hypothesis

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

H_0: P ≥ [redacted]

H_1: P < [redacted]

where P is the proportion of subjects who died within 30 days post the index procedure and 20% is the performance goal.

Sample Size

[redacted]

Analysis

The primary analysis will be based on the TP population. The number and proportion of subjects who died within 30 days post the index procedure will be summarized along with a 97.5% one-sided exact upper confidence bound. The hypothesis will be tested by comparing the upper bound to the performance goal of [redacted]. The null hypothesis will be rejected if this upper bound is less than [redacted].

[redacted]

2.2.3.2 Change from Baseline in KCCQ at 6 Months and 12 Months

To evaluate the benefit of the Tendyne device, the Quality of Life as measured by the KCCQ scores at 6 and 12 months will be compared with those from baseline.

[redacted]

2.2.3.3 Change from Baseline in Six-Minute Walk Test Distance at 6 Months and 12 Months

To evaluate the benefit of the Tendyne device, the distance walked at 6 months and 12 months as measured by the 6MWT will be compared with those from baseline.

Descriptive statistics will be provided for change from baseline in distance walked on the 6MWT at each follow-up visit. Proportion of subjects with improvement of clinically important differences of at least 24 meters[6] and at least 50 meters (a component of Individual Patient Success, see **Section 1.3.3.3**) at follow-up visit from baseline will also be provided.

2.2.4.4 Change in Proportion of NYHA Functional Class I or II at 12 Months

The proportion of subjects with NYHA Functional Classification I or II at 12 months will be evaluated at one-sided 5% level of significance using the McNemar's test. The primary analysis will be based on the IPP population.

The null and alternative hypotheses are stated as:

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

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

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

Descriptive statistics will be provided for NYHA Functional Classification at baseline each follow-up visit.

2.2.4 Performance Endpoint Analyses

2.2.4.1 Technical Success

The primary analysis will be based on the TP population. The definition of technical success is provided in **Section 1.3.2.1**. The composite endpoint will be summarized as the proportion of subjects with technical success at the end of the index procedure. The count and proportion of subjects that meet the criteria of technical success will be summarized along with the 95% exact confidence interval. The individual components of the composite endpoint will also be provided.

2.2.4.2 Device Success

The primary analysis will be based on the TP population. The definition of device success is provided in **Section 1.3.2.2**. The composite endpoint will be summarized as the proportion of subjects with device success at 30 days post the index procedure and scheduled follow-up visits. The count and proportion of subjects that meet the criteria of device success will be summarized along with the 95% exact confidence interval. The individual components of the composite endpoint will also be provided.

2.2.4.3 Individual Patient Success

The primary analysis will be based on the IPP population. The composite endpoint will be summarized as the proportion of subjects with individual patient success at 1 year (see definition in **Section 1.3.2.3)**. The count and proportion of subjects that meet the criteria of individual patient success will be summarized along with the 95% exact confidence interval. The individual components of the composite endpoint will also be provided.

Similar analyses will be provided for the TP population.

2.2.5 Analyses of Additional Endpoints

The additional study endpoints, described in **Section 1.3.4**, will be reported using descriptive statistics as described in **Section 2.1**.

2.2.6 Device and Procedure-Related Endpoints

The following device and procedure-related acute endpoints will be reported using descriptive statistics:

- Implant Rate: defined as the rate of successful delivery and deployment of Tendyne device

with echocardiographic evidence of leaflet approximation and retrieval of the delivery catheter

- Device Time: defined as the time elapsed from the start of the apex penetration to the time the tether tensioning ends
- Device Procedure Time: defined as the time elapsed from the first incision to the time of skin closure
- Fluoroscopy duration: defined as the duration of exposure to fluoroscopy during the procedure

2.4 Poolability of Valve Models

Two types of Tendyne valves are used in the trial: 1.0 valve and low profile (LP) valve. The LP valve design, the timeline when the LP design was introduced into the trial, and the differences in valve design and anatomical suitability between the 1.0 valve and the LP valve are described in **Section 3.4.2** of the study protocol.

All analyses described in **Section 2.2** above will be performed by pooling data of the two valve models. Analysis will also be conducted to assess poolability of the primary safety and performance endpoints, and the secondary endpoint of 30-day all-cause mortality across the valve [redacted].

2.5 Handling of Missing Data

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

In general, missing values in any of the endpoints will not be imputed when summarizing these endpoints using descriptive statistics. All available data collected will be used in the summaries.

2.6 Multiplicity Issues

[redacted]

[redacted]

3. REFERENCES

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