Statistical Analysis Plan

Protocol #ABT-CIP-10249
TRILUMINATE PIVOTAL

Clinical **TRI**al to Eva**LU**ate Cardiovascular Outco**M**es **IN** P**A**tients Treated with the **T**ricuspid Valv**E** Repair System Pivotal

Statistical Analysis Plan (SAP)

Version G

July 01, 2022

Qian Ren

Statistical Analysis Plan

TABLE OF CONTENTS

Statistical Analysis Plan

Statistical Analysis Plan

Statistical Analysis Plan

1.0 SYNOPSIS OF STUDY DESIGN

1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is to provide a detailed and comprehensive description of the planned methodology and analysis to be used for ABT-CIP-10249, the TRILUMINATE PIVOTAL clinical investigation. This plan is based on the Version F of Clinical Investigation Plan.

1.2 Clinical Investigation Objectives

The objective of this trial is to evaluate the safety and effectiveness of the TriClip™ device in improving clinical outcomes in symptomatic patients with severe tricuspid regurgitation (TR) who have been determined by the site's local heart team to be at intermediate or greater estimated risk for mortality or morbidity with tricuspid valve surgery.

1.3 Clinical Investigation Design

TRILUMINATE Pivotal trial is a prospective, multicenter, randomized, controlled, clinical trial of the TriClip™ device in symptomatic subjects with severe TR, who have been determined by the site's local heart team to be at intermediate or greater estimated risk of mortality or morbidity with tricuspid valve surgery.
The trial consists of two cohorts: Randomized cohort and Single-arm cohort. Determination as to whether a patient is placed in the Randomized cohort or Single-arm cohort will be made by the independent eligibility committee. Patients will be placed in the Single-arm cohort if they meet the following criteria:

- The likelihood of achieving TR reduction of at least 1 grade (as assessed using a 5-grade scale) is high, and
- The likelihood of achieving TR reduction to moderate or less (≤ 2) is low

All other patients will be randomized.
Randomization will occur in a minimum of 350 eligible subjects in a 1:1 ratio to receive either the TriClip™ device or medical therapy (control group), at up to 80 sites as follows:

- **TriClip™ Device (Device) Group:** Eligible subjects will undergo the TriClip procedure and will continue to be managed on medical therapy, per physician discretion.
- **Medical Therapy (Control) Group:** Eligible subjects will not undergo the TriClip procedure but will continue to be managed on medical therapy, per physician discretion.

The Single-arm cohort will enroll approximately 200 eligible subjects and all subjects will receive the TriClip™ device.

Additionally, up to 3 roll-in subjects will be permitted per implanter without prior experience of transcatheter treatment of the tricuspid valve. The trial will be conducted in US, Canada and Europe, with a minimum of 50% of the subjects in each cohort enrolled in the US.
Following the completion of enrollment of the TRILUMINATE Pivotal trial, subjects from eligible sites will be enrolled into a continued access study (CAS). Details of the analysis plan to continued access study is included in Appendix B.
An independent Clinical Events Committee (CEC) will adjudicate events including cause of death, HF hospitalization and components of major adverse events. The independent ECL will assess echocardiographic endpoints.

1.4 Endpoints

1.4.1 Endpoints – Randomized Cohort

1.4.1.1 Primary Endpoint – Randomized Cohort

The primary endpoint is a hierarchical composite of all-cause mortality or tricuspid valve (TV) surgery, heart failure hospitalizations, and quality of life improvement assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 12 months. The endpoint will be evaluated in a hierarchical order as follows:

- Time to all-cause death or TV surgery
- Number of Heart Failure (HF) Hospitalizations
- An Improvement of ≥15 points in KCCQ from baseline

The primary endpoint must be met for study success.

[redacted]

1.4.1.2 Secondary Endpoints – Randomized Cohort

The following secondary endpoints will be assessed at the same time of the primary endpoint for labeling claims:

- TR Reduction to moderate or less at 30-day visit post procedure. The endpoint will be assessed as the proportion of subjects who have moderate or less TR at 30 days.

- Freedom from major adverse events (MAE) occurring after procedure attempt (femoral vein puncture) at 30 days. Components of MAE consist of the following:
  - Cardiovascular Mortality,
  - New Onset Renal Failure,
  - Endocarditis Requiring Surgery, and
  - Non-Elective Cardiovascular Surgery for TriClip™ device-related AE post-index procedure.
- Change in KCCQ at 12 months
- Change in 6MWT at 12 months

The following secondary endpoints will be assessed after all randomized subjects complete 24-month follow-up:

- Recurrent HF hospitalizations at 24 months
- Freedom from all-cause mortality, tricuspid valve surgery and tricuspid valve intervention at 24 months

1.4.1.3 Descriptive Endpoints – Randomized Cohort

The following descriptive endpoints will be assessed and reported:

- Technical Success at exit from procedure room: [redacted]
- Device Success at 30-day post-procedure: [redacted]
- Procedural Success at 30-day post-procedure: [redacted]
- Incidence of peripheral edema requiring hospitalization at 12 months, and annually through 24, 36, 48, and 60 months
- Incidence of ascites at 12 months, and annually through 24, 36, 48, and 60 months
- Incidence of IV diuretic administration (including outpatient clinics) at 12 months, and annually through 24, 36, 48, and 60 months
- Change in KCCQ score from baseline through 30 days, 6 months, 12 months and 24, 36, 48, and 60 months

- SF-36 QoL scores at baseline, 30 days, 12 months and 24 months (and change from baseline to follow-up)
- Change in NYHA Functional Class (III/IV to I/II) from baseline through 30 days, 6 months, 12 months and 24, 36, 48, and 60 months
- Change in 6MWT from baseline through 30 days, 6 months, 12 months and 24, 36, 48, and 60 months
- Change in BNP/NT-proBNP from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months
- Change in gamma-GGT from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months
- Change in patient weight from baseline through 30 days, 6 months, 12 months and 24, 36, 48, and 60 months
- Change in kidney function (assessed using eGFR) from baseline through 30 days, 6 months, 12 months and 24, 36, 48, and 60 months
- Change in liver function (assessed using the MELD score) from baseline through 30 days, 6 months, 12 months and 24, 36, 48, and 60 months
- Echocardiographic endpoints assessed from baseline through 30 days, 6 months, 12 months and 24, 36, 48, and 60 months post procedure, as follows:
    - TR severity grade
    - Tricuspid valve annulus diameter
    - Effective Regurgitant Orifice Area (EROA)
    - Regurgitant Volume
    - Vena Contracta Width
    - Right Ventricular End Diastolic Dimension (RVEDD)
    - Right Ventricular Fractional Area Change
    - Left Ventricular End Diastolic Volume (LVEDV)
    - Left Ventricular End Systolic Volume (LVESV)
    - Tricuspid Annular Plane Systolic Excursion (TAPSE)
    - Cardiac Output
    - Forward Stroke Volume (Left Ventricle)
    - Inferior Vena Cava Dimension

1.4.2 Endpoints – Single-arm Cohort

1.4.2.1 Primary Endpoint – Single-arm Cohort

Statistical Analysis Plan

The primary endpoint of the Single-arm cohort is survival at 12 months with a quality of life improvement (assessed using KCCQ overall score) of at least 10 points compared to baseline.

1.4.2.2 Secondary Endpoints – Single-arm Cohort

The following secondary endpoints will be assessed at the same time of the primary endpoint:

- TR Reduction by at least one grade at 30-day post procedure as compared to baseline.
- Freedom from MAE occurring after procedure attempt (femoral vein puncture) at 30 days. Components of MAE consist of the following:
  - Cardiovascular Mortality,
  - New Onset Renal Failure,
  - Endocarditis Requiring Surgery, and
  - Non-Elective Cardiovascular Surgery for TriClip™ device-related AE post-index procedure.
- Change in 6MWT at 12 months, as compared to baseline
- Recurrent HF hospitalizations at 12 months compared to the rate of heart failure hospitalizations in the prior 12 months
- Freedom from all-cause mortality and tricuspid valve surgery at 12 months

1.4.2.3 Descriptive Endpoints – Single-arm Cohort

The following descriptive endpoints will be assessed and reported:

- Technical Success at exit from procedure room: [redacted]
- Device Success at 30-day post-procedure: [redacted]
- Procedural Success at 30-day post-procedure: [redacted]
- Incidence of peripheral edema requiring hospitalization at 12 months, and annually through 24, 36, 48, and 60 months
- Incidence of ascites at 12 months, and annually through 24, 36, 48, and 60 months
- Incidence of IV diuretic administration (including outpatient clinics) at 12 months, and annually through 24, 36, 48, and 60 months

Statistical Analysis Plan

- Change in KCCQ score from baseline through 30 days, 6 months, 12 months and 24, 36, 48, and 60 months
- SF-36 QoL scores at baseline, 30 days, 12 months and 24 months (and change from baseline to follow-up)
- Change in NYHA Functional Class (III/IV to I/II) from baseline through 30 days, 6 months, 12 months and 24, 36, 48, and 60 months
- Change in 6MWT from baseline through 30 days, 6 months, 12 months and 24, 36, 48, and 60 months
- Change in BNP/NT-proBNP from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months
- Change in gamma-GGT from baseline through 30 days, 6 months, 12 months, and annually through 24, 36, 48, and 60 months
- Change in patient weight from baseline through 30 days, 6 months, 12 months and 24, 36, 48, and 60 months
- Change in kidney function (assessed using eGFR) from baseline through 30 days, 6 months, 12 months and 24, 36, 48, and 60 months
- Change in liver function (assessed using the MELD score) from baseline through 30 days, 6 months, 12 months and 24, 36, 48, and 60 months
- Echocardiographic endpoints assessed from baseline through 30 days, 6 months and 12 months post procedure, as follows:
    - TR severity grade
    - Tricuspid valve annulus diameter
    - Effective Regurgitant Orifice Area (EROA)
    - Regurgitant Volume
    - Vena Contracta Width
    - Right Ventricular End Diastolic Dimension (RVEDD)
    - Right Ventricular Fractional Area Change
    - Left Ventricular End Diastolic Volume (LVEDV)
    - Left Ventricular End Systolic Volume (LVESV)
    - Tricuspid Annular Plane Systolic Excursion (TAPSE)
    - Cardiac Output
    - Forward Stroke Volume (Left Ventricle)
    - Inferior Vena Cava Dimension

Statistical Analysis Plan

1.4.3 Descriptive analyses - Imaging Sub-Study

Descriptive analyses will be performed on the imaging sub-study data. These analyses will be exploratory and will investigate quantitative assessments of TR as well as right ventricular function. This data will be compared descriptively between MRI/CT and TTE at baseline and at follow-up.

1.5 Randomization

[redacted]

1.6 Blinding

[redacted]

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Population

2.1.1 Randomized Cohort

The Intention-to-Treat, As-Treated, Per-Protocol and Attempted Procedure populations are defined below. For all the analysis, the duration of follow-up will be calculated from the date of the Treatment visit.

Statistical Analysis Plan

Intent-to-Treat (ITT) Population

[redacted]

Per-Protocol Population

[redacted]

Attempted Procedure (AP) Population

[redacted]

2.1.2 Single-Arm Cohort

Attempted Procedure Population

[redacted]

2.1.3 Imaging Sub-Study

Imaging Population

[redacted]

2.1.4 Roll-In Cohort

Attempted Procedure Population

[redacted]

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, 6MWT), results will be summarized with the number of observations, means, and standard deviations, and, in addition, with medians, quartiles, minimums, maximums, and 95% confidence intervals for the means, when specified.

2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables (e.g. sex, TR Severity), results will be summarized with subject counts and percentages/rates, with exact 95% Clopper-Pearson[1] confidence intervals when specified. Differences between the two subgroups, when specified, will be summarized with the difference in percentages and the Newcombe[2] score 95% confidence interval for the difference of two percentages.

2.2.3 Survival Analyses

Survival analysis will be conducted to analyze time-to-event variables. Subjects without events will be censored at their last known event-free time point when they stay in the study. Survival curves will be

constructed using Kaplan-Meier estimates.

2.3 Endpoint Analysis

As the Coronavirus Disease 2019 (COVID-19) pandemic has spread around the globe, the following analysis mechanism will be implemented to minimize the potential confounding effect from this emerging infectious disease for the trial primary and secondary endpoints set forth in assessing the trial success and labeling claims. In alignment with the guidance documents by FDA and EU as follows, additional considerations were given to the impact of the COVID-19 pandemic on the primary and secondary endpoint analyses for this study:

- "Statistical Considerations for Clinical Trials During the COVID-19 Public Health Emergency – Guidance for Industry" published in June 2020
- "FDA Guidance on Conduct of Clinical Trials of Medical Products during the COVID-19 Public Health Emergency" updated on 03-June-2020
- EU "Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) pandemic" updated on 28-April-2020

As such, prespecified methods are included in the sections that follow to indicate the handling of any outcomes impacted by COVID-19 as well as effects to minimize missing endpoint data COVID-19 pandemic. Unless otherwise specified, the impact of COVID-19 on the primary analysis of the primary and secondary endpoints of each cohort will be as follows:

For subjects who have experienced any hospitalization or death related to COVID-19 (relatedness adjudicated by CEC), all subsequent follow-up period for those subjects, after their first CEC adjudicated COVID-19 related hospitalization admission date or death event, will be censored. The first adjudicated COVID-19 related hospitalization or death event along with the subsequent follow-up data (KCCQ, 6MWT, MAE, hospitalizations, etc.) will not contribute towards any primary analysis for the primary or secondary endpoints analyses, except for the echo parameters (e.g. TR). Any subject who had a COVID-19 infection but did not experience a CEC-adjudicated COVID-19 related hospitalization or death will not be censored.

2.3.1 Randomized Cohort

2.3.1.1 Randomized Cohort – Primary Endpoint

The primary endpoint for the randomized study is a hierarchical composite of all-cause mortality or tricuspid valve surgery, heart failure (HF) hospitalizations, and quality of life improvement assessed using

Statistical Analysis Plan

the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 12 months. The endpoint will be compared between the Device group and the Control group in a hierarchical fashion using the Finkelstein-Schoenfeld[3] methodology as follows:

- Time to all-cause death or tricuspid valve surgery
- Number of HF hospitalizations
- Improvement of ≥15 points in KCCQ from baseline

The null and alternative hypotheses are stated as:

H_0: None of the components are different between the Treatment and Control group

H_1: At least one components are different between the Treatment and Control group

The primary endpoint will be analyzed using the Finkelstein-Schoenfeld method and the null hypothesis will be rejected at a two-sided 5% level of significance.

The primary analysis for the primary endpoint will be performed on the ITT population. [redacted]

Statistical Analysis Plan

[redacted]

$$T = \sum_{i=1}^{n} U_i D_i$$

[redacted]

$$U_i = \sum_{i \neq j} u_{ij}$$

[redacted]

$$V = \frac{n_D(n - n_D)}{n(n-1)} \sum_{i=1}^{n} U_i^2$$

[redacted] $\overline{V}$ [redacted] $\overline{2}$ [redacted]

[redacted].

Statistical Analysis Plan

[redacted]

2.3.1.2 Randomized Cohort – Secondary Endpoints

The following six secondary endpoints will be used as secondary measures of safety and effectiveness for the TriClip™ system. The secondary endpoints will be tested at a two-sided 5% level of significance unless otherwise specified. The primary analysis population of the secondary endpoints will be the ITT population. Additional analyses may be performed on the PP and AT populations.

2.3.1.2.1 TR Reduction to Moderate or Less at 30-Day Visit

Subjects in the randomized Device group are expected to experience greater reduction in TR severity than subjects in the Control group. The null and alternative hypotheses are stated as:

H_0: $P_{D,TR \leq 2} - P_{C,TR \leq 2} = 0$ vs.

H_1: $P_{D,TR \leq 2} - P_{C,TR \leq 2} \neq 0$

where $P_{D,TR \leq 2}$ and $P_{C,TR \leq 2}$ represent the proportion of subjects with TR reduced to moderate or less at 30-day visit in the Device and Control groups respectively. [redacted]

[redacted] The null hypothesis will be rejected at a two-sided 5% level of significance.

2.3.1.2.2 Freedom from Major Adverse Events (MAE) at 30 Days Post Procedure

A composite of cardiovascular mortality, new onset renal failure, endocarditis requiring surgery, and non-elective cardiovascular surgery for TriClip™ device-related adverse event post-index procedure will be

used as a secondary measure of safety. The analysis of this secondary endpoint is a one-group test against a performance goal (PG) for the proportion of subjects in the Attempted Procedure population free from the composite of this secondary endpoint of MAE at 30-day post procedure.

The null and alternative hypotheses are stated as:

H₀: $P_{30D}(MAE) \leq 90\%$

H₁ $P_{30D}(MAE) > 90\ \%$

where $P_{30D}(MAE)$ is the probability of freedom from any MAE at 30-day post procedure. [redacted]

[redacted] E

The null hypothesis will be rejected at a one-sided 2.5% level of significance.

[redacted]

2.3.1.2.3 Change in Quality of Life (Kansas City Cardiomyopathy Questionnaire, KCCQ) at 12 Months over Baseline

Improvement in quality of life as measured by the KCCQ test at 12 months from baseline will be a secondary effectiveness endpoint in the comparison of the Device group to the Control group.

The null and alternative hypotheses are stated as:

H₀: $\mu_{D,\,\Delta\mathrm{KCCQ}} - \mu_{C,\,\Delta\mathrm{KCCQ}} = 0$

H₁: $\mu_{D,\,\Delta\mathrm{KCCQ}} - \mu_{C,\,\Delta\mathrm{KCCQ}} \neq 0$

where $\mu_{D,\,\Delta\mathrm{KCCQ}}$ and $\mu_{C,\,\Delta\mathrm{KCCQ}}$ represent the mean change in quality of life score between 12 months and baseline in the Device and Control groups respectively.

The analysis will be performed in subjects with paired KCCQ data at baseline and 12 months. Subjects who experience an adjudicated heart failure related cardiovascular death or receive the Tricuspid Valve surgery prior to completing the 12 months follow-up will also be included in the analysis. Their KCCQ score at 12 months will be imputed as 0 points.

ANCOVA will be used to compare the mean changes in KCCQ score between 12 months and baseline in the two groups, while adjusting for the baseline KCCQ score. The null hypothesis will be rejected a two-sided 5% level of significance.

Statistical Analysis Plan

2.3.1.2.4 Change in 6MWT (Six Minute Walk Test) Distance at 12 Months over Baseline

Improvement in the 6MWT distance at 12 months from baseline is an important secondary effectiveness endpoint in the comparison of the Device group to the Control group.

The null and alternative hypotheses are stated as:

H_0: $\mu_{D,\,\Delta 6\mathrm{MWD}} - \mu_{C,\,\Delta 6\mathrm{MWD}} = 0$

H_1: $\mu_{D,\,\Delta 6\mathrm{MWD}} - \mu_{C,\,\Delta 6\mathrm{MWD}} \neq 0$

where $\mu_{D,\,\Delta 6\mathrm{MWD}}$ and $\mu_{C,\,\Delta 6\mathrm{MWD}}$ represent the mean change in 6MWT distance between 12 months and baseline in the Device and Control groups respectively.

The analysis will be performed in subjects with paired 6MWT data at baseline and 12 months. [redacted] The null hypothesis will be rejected at a two-sided 5% level of significance.

2.3.1.2.5 Recurrent HF Hospitalizations at 24 Months

Treatment with the TriClip™ device is expected to reduce the risk of recurrent HF hospitalizations. The null and alternative hypotheses are stated as:

H_0: $HR(24M) > 1$

H_1: $HR(24M) \leq 1$

where $HR(24M)$ is the hazard ratio of recurrent HF hospitalization between the Device and Control groups. Hospitalizations that are adjudicated by the CEC as related to heart failure using the pre-specified Clinical Investigational Plan definition will be included as events in the analysis.

[redacted] Beneficial treatment effect is established if the upper one-sided 95% confidence limit of the hazard ratio is smaller than 1.

Statistical Analysis Plan

2.3.1.2.6 Freedom from All-Cause Mortality, Tricuspid Valve Surgery, and Tricuspid Valve Intervention at 24 Months

The difference in risk of all-cause mortality or Tricuspid Valve surgery or intervention at 24 months between the Device and Control groups is a secondary measure of safety. The null and alternative hypothesis are stated as:

H_0: Survival curves of the two groups through 24 months are the same.

H_1: Survival curves of the two groups through 24 months are different.

[redacted] The null hypothesis will be rejected with a two-sided 5% level of significance.

2.3.2 Single-Arm Cohort

2.3.2.1 Single-Arm Cohort – Primary Endpoint

The primary endpoint of the Single-arm Cohort is survival at 12 months with a quality of life improvement (assessed using KCCQ overall score) of at least 10 points compared to baseline. This endpoint will be assessed as a proportion of subjects meeting the definition of the endpoint.

The null and alternative hypotheses are stated as:

H_0: $P(12M) \leq 30\%$ vs.

H_1: $P(12M) > 30\%$

where $P(12M)$ represents the proportion of subject survival at 12 months with a quality of life improvement (assessed using KCCQ overall score) of at least 10 points compared to baseline. [redacted] The primary analysis will be performed on the Attempted Procedure population and the null hypothesis will be rejected at a one-sided 2.5% level of significance.

The performance goal was set based on the following clinical assumptions:

- [redacted]

Statistical Analysis Plan

[redacted]

2.3.2.2 Single-Arm Cohort – Secondary Endpoint

2.3.2.2.1 TR Reduction by at least 1 Grade at 30-Day Follow-up

The TR reduction by at least 1 grade at 30-day post procedure is the secondary measure of effectiveness for TriClip™ in the Single-Arm Cohort. The analysis of this secondary endpoint is a one-group test against an objective performance goal of 50%.

The null and alternative hypotheses are stated as:

H_0: $P_{30D,TR} \leq 50\%$

H_1 $P_{30D,TR} > 50\ \%$

where $P_{30D,TR}$ represents the proportion of subjects in the Single-Arm Cohort with TR reduction by at least 1 grade at 30-day follow-up. [redacted]

An exact test for a binomial proportion will be used to test the null hypothesis at a one-sided 2.5% level of significance.

2.3.2.2.2 Freedom from Major Adverse Events (MAE) at 30 Days Post Procedure

The freedom from MAE occurring after procedure attempt (femoral vein puncture) at 30 days is the secondary measure of safety for TriClip™ in the Single-Arm Cohort. The analysis of this secondary endpoint is a one-group test against an objective performance goal of 80%.

The null and alternative hypotheses are stated as:

H_0: $P_{30D} \leq 80\%$

H_1: $P_{30D} > 80\%$

where P_{30D} is the probability of freedom from any MAE at 30-day post procedure. A[redacted]

Statistical Analysis Plan

[redacted]

The null hypothesis will be rejected at a one-sided 2.5% level of significance.

2.3.2.2.3 Change in 6MWT (Six Minute Walk Test) Distance at 12 Months over Baseline

Improvement in the 6MWT distance at 12 months from baseline is an important secondary effectiveness endpoint.

The null and alternative hypotheses are stated as:

H_0: $\mu_{\Delta 6MWD} \leq 0$ vs.

H_1: $\mu_{\Delta\ 6MWD} > 0$

where $\mu_{\Delta\ 6MWD}$ represents the mean change in 6MWT distance at 12 months from baseline.

The analysis will be performed in subjects with paired 6MWT data at baseline and 12 months. [redacted] Paired t test will be used to compare the mean change to 0 and the null hypothesis will be rejected at a one-sided 2.5% level of significance.

2.3.2.2.4 Recurrent HF Hospitalizations at 12 Months

The null and alternative hypotheses are stated as:

H_0: $\lambda_{12\mathrm{M}}(\mathrm{PRE}) \leq \lambda_{12\mathrm{M}}(\mathrm{POST})$ vs.

H_1: $\lambda_{12\mathrm{M}}(\mathrm{PRE}) > \lambda_{12\mathrm{M}}(\mathrm{POST})$

where $\lambda_{12\mathrm{M}}(\mathrm{PRE})$ and $\lambda_{12\mathrm{M}}(\mathrm{POST})$ represent the annualized event rates for recurrent HF hospitalizations within 12 months prior to (PRE) and on or after (POST) study enrollment.

[redacted]

The null hypothesis will be rejected at a one-sided 2.5% level of significance.

2.3.2.2.5 Freedom from All-Cause Mortality and Tricuspid Valve Surgery at 12 Months

The null and alternative hypotheses are stated as:

H_0: $P_{12M}(\text{Survival}) \leq 65\%$ vs.

H_1: $P_{12M}(\text{Survival}) > 65\%$

where $P_{12M}(\text{Survival})$ is the freedom from all-cause mortality and tricuspid valve surgery (survival rate) at 12 months.

[redacted]

The null hypothesis will be rejected at a one-sided 2.5% level of significance.

2.3.3 Imaging Sub-Study

The imaging endpoints will be compared descriptively among MRI, CT and TTE at baseline, 30-days and 12 months on the imaging population.

2.4 Sample Size Calculations

2.4.1 Randomized Cohort

2.4.1.1 Primary Endpoints

Detailed simulations were conducted in order to determine the appropriate sample size to adequately power the study. The following assumptions were made to evaluate the power to demonstrate the superiority of the Device group to the control group:

- [redacted]

Statistical Analysis Plan

[redacted]

A simulation with 10,000 iterations was performed to determine the sample size and power for the primary endpoint. A total sample size of 350 randomized subjects provides approximately 83% power at the two-sided 5% significance level for the primary endpoint.

The assumptions for each component of the primary endpoint in the sample size calculation are determined collectively based on published literature on the use of the MitraClip device for the treatment of TR and preliminary data derived from the TRILUMINATE. Since the TRILUMINATE study is still ongoing with limited data available, the information from the COAPT PMA submission is also used to leverage the assumptions.

[redacted]

Statistical Analysis Plan

[redacted]

2.4.1.2 Secondary Endpoints

2.4.1.2.1 TR Reduction to Moderate or Less at 30-Day Post Procedure

The power calculation for the TR reduction to moderate or less at 30-day post-procedure is based on the following assumptions:

- [redacted]

Ten thousand (10,000) simulations were performed. Based on the assumptions, with 350 randomized subjects, the power is approximately 93% to reject the null hypothesis at a two-sided 5% level of significance.

Statistical Analysis Plan

The assumption for the secondary endpoint of TR reduced to moderate or less at the 30-day visit is determined collectively based on the preliminary data derived from TRILUMINATE as well as the trending of reduction in Mitral regurgitation at 30-day visit in COAPT:

- [redacted]
- [redacted]

Therefore, for the TRILUMINATE PIVOTAL study, the rates of TR reduction to moderate or less at the 30-day visit were conservatively assumed to be 70% vs 50% for the Device vs Control groups respectively.

2.4.1.2.2 Freedom from Major Adverse Events (MAE) at 30-Day Post Procedure

The power calculation for the major adverse events at 30-day post procedure is based on the following assumptions:

- [redacted]
- [redacted]

Ten thousand (10,000) simulations were performed to calculate the sample size and power for this secondary endpoint. Based on the assumptions, with approximately 175 subjects randomized to the Device arm, the power is > 95% to reject the null hypothesis against the performance goal of 90% at a one-sided 2.5% level of significance.

The event rate of MAE is determined based on the preliminary result of MAE from TRILUMINATE study as of the data cut-off date (November 29, 2018). There were 1.2% (1/85) of subjects with an MAE for new onset renal failure at 30 days. The 95% one-sided upper confidence limit is 5.5%.

Statistical Analysis Plan

2.4.1.2.3 Change in Quality of Life (Kansas City Cardiomyopathy Questionnaire, KCCQ) at 12 Months over Baseline

The power calculation for the change in KCCQ overall summary score at 12 months over baseline is based on the following assumptions:

[redacted]

Ten thousand (10,000) simulations were performed to calculate the sample size and power for this secondary endpoint. Based on the assumptions, with 350 randomized subjects, the power is above 90% to reject the null hypothesis at a two-sided 5% level of significance.

2.4.1.2.4 Change in 6MWT (Six Minute Walk Test) Distance at 12 Months over Baseline

The power calculation for the change in 6MWT distance at 12 months over baseline is based on the following assumptions:

[redacted]

Ten thousand (10,000) simulations were performed to calculate the sample size and power for this secondary endpoint. Based on the assumptions, with 350 randomized subjects, the power is above 90% to reject the null hypothesis at a two-sided 5% level of significance.

The clinical assumptions for the changes in 6MWT distance are derived collectively from data from TRILUMINATE I as well as COAPT:

[redacted]

2.4.1.2.5 Recurrent HF Hospitalizations at 24 Months

The power calculations for the recurrent HF hospitalizations at 24 months is based on the following assumptions:

[redacted]

Ten thousand (10,000) simulations were performed to calculate the sample size and power for this secondary endpoint. Based on the assumptions, with 450 randomized subjects, the power is approximately 80% to reject the null hypothesis at a one-sided 5% level of significance.

2.4.1.2.6 Freedom from All-Cause Mortality, Tricuspid Valve Surgery, and Tricuspid Valve Intervention at 24 Months

The power calculations for all-cause mortality or tricuspid valve surgery or intervention at 24 months is based on the following assumptions:

[redacted]

Ten thousand (10,000) simulations were performed to calculate the sample size and power for this secondary endpoint. Based on the assumptions, with 450 randomized subjects, the power is approximately 80% to reject the null hypothesis at a two-sided 5% level of significance.

2.4.2 Single-Arm Cohort

2.4.2.1 Single-Arm Cohort – Primary Endpoint

The power calculation for the proportion of survival subjects with at least 10-point improvement in KCCQ overall summary score at 12 months over baseline for the Single-Arm Cohort is based on the following assumptions:

- [redacted]

Statistical Analysis Plan

[redacted]

Based on the assumptions, with 100 subjects, the power is about 90% to reject the null hypothesis; and with 200 subjects the overall power is more than 95% at a one-sided 2.5% level of significance. The details of the group sequential design can be found in Section 2.5.2.

2.4.2.2 Single-arm Cohort – Secondary Endpoints

The secondary endpoints of the Single-arm cohort will be evaluated only if the primary endpoint of the Single-arm cohort is met. Hence, the following secondary endpoints are adequately powered (≥ 80%) with a sample size of 100 at the interim analysis for primary endpoint.

2.4.2.2.1 TR Reduction by at least 1 Grade at 30-Day Follow-up

The power calculation for TR reduction by at least 1 grade at 30-day post procedure for the Single-Arm Cohort is based on the following assumptions:

[redacted]

Ten thousand (10,000) simulations were performed to calculate the sample size and power for this secondary endpoint. Based on the assumptions, with 100 subjects, the power is about 90% to reject the null hypothesis at a one-sided 2.5% level of significance.

Statistical Analysis Plan

2.4.2.2.2 Freedom from MAE Occurring after Procedure Attempt (Femoral Vein Puncture) at 30 Days

The power calculation for MAE occurring after procedure attempt (femoral vein puncture) at 30-day post

[redacted]

to calculate the sample size and power for this secondary endpoint. Based on the assumptions, with 100 subjects, the power is > 95% to reject the null hypothesis against the performance goal of 80% at a one-sided 2.5% level of significance.

2.4.2.2.3 Change in 6MWT (Six Minute Walk Test) Distance at 12 Months over Baseline

The power calculation for the change in 6MWT distance at 12 months over baseline for the Single-Arm Cohort is based on the following assumptions:

[redacted]

Ten thousand (10,000) simulations were performed to calculate the sample size and power for this secondary endpoint. Based on the assumptions, with approximately 100 subjects, the power is above 90% to reject the null hypothesis at a one-sided 2.5% level of significance.

2.4.2.2.4 Recurrent HF Hospitalizations at 12 Months

The power calculations for recurrent HF hospitalizations at 12 months for the Single-Arm Cohort is based on the following assumptions:

[redacted]

[redacted]

Ten thousand (10,000) simulations were performed to calculate the sample size and power for this secondary endpoint. Based on the assumptions, with approximately 100 subjects, the power is approximately 83% to reject the null hypothesis at a one-sided 2.5% level of significance.

2.4.2.2.5 Freedom from All-Cause Mortality and Tricuspid Valve Surgery at 12 Months

The power calculations for freedom from all-cause mortality and tricuspid valve surgery at 12 months for the Single-Arm Cohort is based on the following assumptions:

[redacted]

Ten thousand (10,000) simulations were performed to calculate the sample size and power for this secondary endpoint. Based on the assumptions, with 100 subjects, the power is approximately 83% to reject the null hypothesis at a one-sided 2.5% level of significance.

[redacted]

[redacted]

2.5 Interim Analysis

2.5.1 Sample Size Re-estimation for Randomized Cohort

[redacted]

2.5.2 Group Sequential Design for Single-arm Cohort

[redacted]

Statistical Analysis Plan

2.6 Timing of Analysis

2.6.1 Randomized Cohort

The analysis of the primary endpoints and the following secondary endpoints will be assessed when the 350th subject completes 12 months follow-up if there is no sample size increment, or the last subject resulted by the sample size re-estimation reaches 12 months follow-up.

- TR reduction to moderate or less at 30-day post procedure
- Freedom from MAE at 30 days
- Change in KCCQ at 12 months over baseline
- Change in 6MWT distance at 12 months over baseline

The analysis of the following secondary endpoints for the Randomized cohort will be assessed when all randomized subjects complete 24 months follow up.

- Recurrent HF hospitalizations at 24 months
- Freedom from All-cause mortality, tricuspid valve surgery, and tricuspid value intervention at 24 months

2.6.2 Single-arm Cohort

If the primary endpoint of the Single-arm cohort is met at the interim analysis, the secondary endpoints of the Single-arm cohort will be evaluated for the same cohort as the primary endpoint. The Single-arm cohort endpoints of all additional subjects enrolled after the first 100 will be summarized descriptively. If the primary endpoint is not met at the interim analysis, then it will be re-analyzed when all enrolled subjects in the Single-Arm cohort complete 12 months follow-up.

2.7 Study/Trial Success

Trial success will be declared when the primary endpoint for the Randomized cohort is met.

2.8 Subgroups for Analysis

2.8.1 Subgroups for Analysis for the Randomized Cohort

2.8.1.1 Sex (Male vs. Female)

Subgroup analyses of sex will be performed for analysis of the primary endpoint components in the Randomized Cohort. Major baseline and clinical characteristics will be summarized by treatment groups and sex.

Statistical Analysis Plan

[redacted]

2.8.1.2 Baseline TR Grading (Grade 3 vs. > Grade 3)

Subgroup analyses of baseline TR grading will be performed for the analysis of the primary endpoint components in the Randomized Cohort. Major baseline and clinical characteristics will be summarized by treatment group and TR grading at baseline.

[redacted]

2.8.1.3 Baseline NYHA Functional Class (I/II vs. III/IV)

Subgroup analyses of the baseline NYHA functional class (I/II vs. III/IV) will be performed for analysis of the primary endpoint components in the Randomized Cohort. Major baseline and clinical characteristics will be summarized by treatment groups and device type.

[redacted]

Statistical Analysis Plan

[redacted]

2.8.1.4 Baseline Etiology of TR (Primary TR vs. Secondary TR)

If there were at least 10% of subjects in each of the subgroups, the subgroup analyses of baseline etiology of TR (primary TR vs. secondary TR) will be performed for analysis of the primary endpoint components for the Randomized Cohort. Major baseline and clinical characteristics will be summarized by treatment group and baseline etiology of TR.

[redacted]

2.8.2 Subgroups for Analysis for the Single-arm Cohort

2.8.2.1 Sex (Male vs. Female)

Subgroup analyses of sex will be performed for analysis of the primary endpoint for the Single-Arm Cohort. Major baseline and clinical characteristics will be summarized by sex.

[redacted]

2.8.2.2 Baseline TR Grading (≤ Grade 4 vs. Grade 5)

If there were at least 20 subjects in each of the subgroups, the subgroup analyses of baseline TR grading will be performed for analysis of the primary endpoint for the Single-Arm Cohort. Major baseline and clinical characteristics will be summarized by baseline TR grading subgroup.

[redacted]

2.8.2.3 Baseline NYHA Functional Class (I/II vs. III/IV)

Subgroup analyses of baseline NYHA functional class (I/II vs. III/IV) will be performed for analysis of the primary endpoint for the Single-Arm Cohort. Major baseline and clinical characteristics will be summarized by device type.

[redacted]

2.8.2.4 Baseline Etiology of TR (Primary TR vs. Secondary TR)

Subgroup analyses of baseline etiology of TR will be performed for analysis of the primary endpoint for the Single-Arm Cohort. Major baseline and clinical characteristics will be summarized for each subgroup at baseline.

[redacted]

2.8.3 Subgroup Analysis for TriClipTM System vs. TriClipTM G4 System

Subgroup analyses for TriClip™ system vs. TriClip™ G4 system will be performed. Subjects in the Randomized Device group and Single-Arm cohort who have the TriClip™ index procedure attempted with the TriClip™ system will be included in the TriClip™ system subgroup, while subjects in the Randomized Device group and Single-Arm cohort who have the TriClip index procedure attempted with the TriClip™ G4 system will be included in the TriClip™ G4 system subgroup. Baseline and echocardiographic characteristics, procedure outcome and TR grading over time will be summarized descriptively in these two subgroups.

Statistical Analysis Plan

2.9 Handling of Missing Data

[redacted]

2.10 Poolability Issue

2.10.1 Poolability Issue of the Randomized Cohort

Analysis will be performed pooling data across study sites.

[redacted]

2.10.2 Poolability Issue of the Single-Arm Cohort

[redacted]

2.11 Multiplicity Issues

Since the analysis population for the Randomized Cohort and Single-Arm Cohort are mutually exclusive, the primary and secondary endpoints for the Randomized Cohort and Single-Arm Cohort will be evaluated separately and need no multiplicity adjustment. Within each cohort, sequential testing will be performed for the pre-specified endpoints. Therefore, the overall type I error is under control.

Statistical Analysis Plan

2.11.1 Multiplicity – Randomized Cohort

The secondary endpoints for the Randomized Cohort will be evaluated for labeling claims if the primary endpoint is met. The secondary endpoints for the Randomized Cohort will be tested sequentially in the following order:

- Freedom from major adverse events (MAE) occurring after procedure attempt (femoral vein puncture) at 30 days.
- Change in KCCQ at 12 months over baseline (superiority of Device vs. Control)
- TR Reduction to moderate or less at 30 days post procedure (superiority of Device vs. Control)
- Change in 6MWT at 12 months over baseline (superiority of Device vs. Control)
- Recurrent HF hospitalizations at 24 months (superiority of Device vs. Control)
- Freedom from all-cause mortality, tricuspid valve surgery, and tricuspid valve intervention at 24 months (superiority of Device vs. Control)

The two secondary endpoints assessed at 24 months (recurrent HF hospitalizations and freedom from all-cause mortality, tricuspid valve surgery and tricuspid valve intervention) will be evaluated when all randomized subjects complete 24-month follow-up for additional labeling claims.

2.11.2 Multiplicity – Single-Arm Cohort

The secondary endpoints for the Single-Arm Cohort will be evaluated for labeling claims if the primary endpoint of the Single-Arm Cohort is met. The secondary endpoints for the Single-Arm Cohort will be tested sequentially in the following order:

- TR Reduction by at least one grade at 30-day post procedure as compared to baseline.
- Freedom from major adverse events (MAE) occurring after procedure attempt (femoral vein puncture) at 30 days.
- Change in 6MWT at 12 months, as compared to baseline
- Freedom from all-cause mortality and tricuspid valve surgery at 12 months
- Recurrent HF Hospitalizations at 12 Months

Statistical Analysis Plan

2.12 Sensitivity Analysis

[redacted]

Statistical Analysis Plan

[redacted]

Statistical Analysis Plan

[redacted]

2.12.2 Primary Endpoint for the Randomized Cohort Evaluated in All Randomized Subjects

A sensitivity analysis for the primary endpoint of the Randomized cohort will be performed based on all the randomized subjects. The same hypothesis test and statistical method will be implemented as specified in Section 2.3.1.1.

2.12.3 COVID-19 Relatedness

To understand the impact of COVID-19 pandemic on the clinical outcomes, sensitivity analysis for the primary endpoint of the randomized and single-arm will be performed to include all the adjudicated events and follow-up periods for each endpoint regardless the status of COVID-19 infection.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

All endpoints in this section will be reported with descriptive statistics. Continuous endpoints will be summarized using the following: mean, standard deviation, median, the first and third quartiles, range, and the 95% confidence interval for the population mean using the normal approximation, when specified. Categorical endpoints will be summarized as proportions in the form of fractions and percentages. The 95% confidence interval for a population proportion will be constructed using the Clopper-Pearson exact method[1]. The 95% confidence interval for the difference of two proportions will be constructed using the Newcombe[2] score method. Other analyses are specified under each category of additional descriptive endpoints.

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized for the subjects enrolled: gender, age, ethnicity, race, medical history, baseline echocardiographic measurements, etc.

3.2 Adverse Events

All adverse device effects, serious adverse device effects, UADEs, and USADEs will be summarized for all enrolled subjects in terms of the number of events, the percentage of subjects with events per MedDRA coding. Procedure related AEs may also be summarized.

Statistical Analysis Plan

All CEC adjudicated adverse events will be summarized for all subjects who enrolled in the trial by treatment group in terms of the number of events, and the percentage of subjects with events. Moreover, COVID-19 related AEs will be summarized in terms of number of events, the percentage of subjects with events per AE term.

3.3 Subject Early Termination

Subject early termination reasons including death, withdrawal, lost-to-follow-up, etc. will be summarized by treatment group at all scheduled visits.

3.4 Protocol Deviation

Protocol deviations will be summarized for subjects with reported protocol deviations in the Randomized cohort, Single-arm cohort and Roll-In cohort separately. COVID-19 related protocol deviations will also be summarized.

3.5 Descriptive Endpoints

The descriptive endpoints for the Randomized Cohort will be summarized with descriptive statistics for the Device and Control groups respectively.

The descriptive endpoints for the Single-arm cohort will be summarized with descriptive statistics.

4.0 DOCUMENTATION AND OTHER CONSIDERATIONS

All analyses will be performed using SAS® for Windows, version 9.2 or higher.

Statistical Analysis Plan

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
6MWT	Six Minute Walk Test
CAS	Continued Access Study
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CMH	Cochran-Mantel-Haenszel
CRF	Case Report Form
COVID-19	2019 Novel Coronavirus
EC	Eligibility Committee
ECL	Echocardiography Core Laboratory
EROA	Effective Regurgitant Orifice Area
GDMT	Guideline Directed Medical Therapy
HF	Heart Failure
HR	Hazard Ratio
JFM	Joint Frailty Model
KCCQ	Kansas City Cardiomyopathy Questionnaire
MAE	Major Adverse Event
MRI	Cardiac Magnetic Resonance Imaging
CT	Computed Tomography
NT-pro BNP	N-terminal prohormone of Brian Natriuretic Peptide
NYHA	New York Heart Association
RVEDD	Right Ventricular End Diastolic Dimension
LVEDV	Left Ventricular End Diastolic Volume
LVEDV	Left Ventricular End Diastolic Volume
TAPSE	Tricuspid Annular Plane Systolic Excursion
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TEE	Trans-Esophageal Echocardiogram
TR	Tricuspid Regurgitation

Statistical Analysis Plan

6.0 REFERENCES

1. Clopper C. J., Pearson E. S., “The Use of the Confidence or Fiducial Limits Illustrated in the Case of the Binomial.” *Biometrika*, 1934, 26, 404-413.

2. Newcombe, R. G., “Interval estimation for the difference between independent proportions: comparison of eleven methods”, *Statistics in Medicine*, 1998, 17, 873-890.

3. Dianne M. Finkelstein, David A. Schoenfeld, “Combining Mortality and Longitudinal Measures in Clinical Trials”, *Statistics in Medicine*, 1999;18: 1341-1354.

4. Pocock, S.J., et.al., “The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities.” *European Heart Journal*, 2012, 33, 176-182.

5. Kilic, A., et.al. “Trends and Outcomes of Tricuspid Valve Surgery in North America: An Analysis of More Than 50,000 Patients from The Society of Thoracic Surgeons Database”, *Annuals of Thoracic Surgery*

6. Rondeau V, Mathoulin-Pelissier S, Jacqmin-Gadda H, Brouste V, Soubeyran P. “Joint frailty models for recurring events and death using maximum penalized likelihood estimation: application on cancer events.” *Biostatistics* 2007;8(4):708-21

7. Besler, C, et al. “Predictors of Procedural and Clinical Outcomes in Patients With Symptomatic Tricuspid Regurgitation Undergoing Transcatheter Edge-to-Edge Repair.” *JACC Cardiovasc Interv*. 2018 Jun 25;11(12):1119-1128.

8. Nath, J, et al. “Impact of tricuspid regurgitation on long-term survival.” *J Am Coll Cardiol*. 2004 Feb 4;43(3):405-9.

9. Kalbacher, D. et.al. “Impact of tricuspid valve regurgitation in surgical high-risk patients undergoing MitraClip implantation: results from the TRAMI registry.” *EuroIntervention*. 2017 Feb 3;12(15):e1809-e1816.

10. Topilsky, Y, et al. “Clinical outcome of isolated tricuspid regurgitation.” JACC Cardiovasc Imaging. 2014 Dec;7(12):1185-94.

11. Pocock, S.J., et. al., “Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems.” *Statistics in Medicine,* 2002, 21, 2917-2930.

12. Pocock, S.J., et. al., “Regression to the mean in SYMPLICITY HTN-3, Implications for Design and Reporting of Future Trials.” *JACC,* 2016, Vol. 68, No. 18, 2016-2025.

Statistical Analysis Plan

13. SAS/STAT® 9.3 User's Guide, SAS Institute Inc., Cary, NC, 2011.

14. Dmitrienko, A. et. al., Analysis of Clinical Trials Using SAS: A Practical Guide, SAS Institute, Cary, NC, 2005.

15. Hausleiter, Jörg, et al. "Patient selection, echocardiographic screening and treatment strategies for interventional tricuspid repair using the edge-to-edge repair technique." EuroIntervention: journal of EuroPCR in collaboration with the Working Group on Interventional Cardiology of the European Society of Cardiology 14.6 (2018): 645-653.

16. Ho, Edwin C., Geraldine Ong, and Neil P. Fam. "Transcatheter tricuspid valve intervention: a practical algorithm for patient selection." Current opinion in cardiology 34.2 (2019): 164-172.

17. Sorajja, Paul, et al. "Transcatheter repair of tricuspid regurgitation with MitraClip." Progress in cardiovascular diseases (2019).

18. Taramasso, Maurizio, et al. "Outcomes of TTVI in Patients With Pacemaker or Defibrillator Leads: Data From the TriValve Registry." JACC: Cardiovascular Interventions (2020).

19. Mehr, Michael, et al. "1-year outcomes after edge-to-edge valve repair for symptomatic tricuspid regurgitation: results from the TriValve Registry." JACC: Cardiovascular Interventions 12.15 (2019): 1451-1461.

20. Fam, Neil P., et al. "Compassionate use of the PASCAL transcatheter valve repair system for severe tricuspid regurgitation: A multicenter, observational, first-in-human experience." *JACC: Cardiovascular Interventions* 12.24 (2019): 2488-2495.

21. Taramasso M, Benfari G, van der Bijl P, Alessandrini H, Attinger-Toller A, Biasco L, Lurz P, Braun D, Brochet E, Connelly KA, de Bruijn S, Denti P, Deuschl F, Estevez-Loureiro R, Fam N, Frerker C, Gavazzoni M, Hausleiter JR, Ho E, Juliard JM, Kaple R, Besler C, Kodali S, Kreidel F, Kuck KH, Latib A, Lauten A, Monivas V, Mehr M, Muntane-Carol G, Nazif T, Nickening G, Pedrazzini G, Philippon F, Pozzoli A, Praz F, Puri R, Rodes-Cabau J, Scha Fer U, Schofer J, Sievert H, Tang GHL, Thiele H, Topilsky Y, Rommel KP, Delgado V, Vahanian A, Von Bardeleben RS, Webb JG, Weber M, Windecker S, Winkel M, Zuber M, Leon MB, Hahn RT, Bax JJ, Enriquez-Sarano M and Maisano F. Transcatheter versus medical treatment of symptomatic severe tricuspid regurgitation. J Am Coll Cardiol. 2019.

Statistical Analysis Plan

7.0 APPENDICS

APPENDIX A: POWER AND SAMPLE SIZE CALCULATIONS

The R and SAS code will be provided in a separate document.

Statistical Analysis Plan

APPENDIX B: STATISTICAL ANALYSIS PLAN FOR CONTINUED ACCESS STUDY

B.1 Study Design

The TriClip™ Continued Access Study (CAS) of the TRILUMINATE Pivotal trial will be initiated upon the completion of enrollment of both the randomized and single-arm cohorts. The objective of this CAS will be to ensure continued access to the TriClip™ G4 device for eligible patients, while also providing additional experience for operators and supplementary safety and effectiveness data on the TriClip™ G4 device.

All subjects enrolled into the CAS will receive the TriClip™ G4 device. Enrollment into the CAS will continue until up to 600 subjects are enrolled or commercial approval is received, whichever occurs first. All subjects enrolled in the CAS will be followed for 5 years.

The same independent Clinical Events Committee (CEC) and Data Monitoring Committee (DMC) used for the randomized-arm and single-arm cohorts will adjudicate events for the CAS including cause of death, HF hospitalization and components of major adverse events. The same echo core lab (ECL) will be used for screening and evaluation of echocardiographic endpoints.

B.2 Study Endpoints

The following endpoints will be assessed and reported for the CAS.

- Technical Success at exit from procedure room: Alive with successful access, delivery and retrieval of the device delivery system, and deployment and correct positioning of a Clip, and no need for additional unplanned or emergency surgery or re-intervention related to the device or access procedure
- Device Success at 30-day post-procedure: Alive with original intended Clip(s) in place, and no additional surgical or interventional procedures related to access or device since completion of the original procedure, and intended performance of the Clip(s) (i.e. ≥1 grade improvement in TR severity, no embolization, single leaflet device attachment, absence of para-device complications)
- Procedural Success at 30-day post-procedure: Device success, and no device or procedure related SAE
- TR Reduction by at least one grade at 30-day post procedure as compared to baseline.
- Freedom from MAE occurring after procedure attempt (femoral vein puncture) at 30 days. Components of MAE consist of the following:
    - Cardiovascular Mortality,
    - New Onset Renal Failure,
    - Endocarditis Requiring Surgery, and
    - Non-Elective Cardiovascular Surgery for TriClip™ device-related AE post-index procedure.
- Recurrent HF hospitalizations at 12 months compared to the rate of heart failure hospitalizations in the prior 12 months
- Freedom from all-cause mortality and tricuspid valve surgery at 12 months

- Incidence of peripheral edema requiring hospitalization at 12 months, and annually through 24, 36, 48, and 60 months
- Incidence of ascites at 12 months, and annually through 24, 36, 48, and 60 months
- Incidence of IV diuretic administration (including outpatient clinics) at 12 months, and annually through 24, 36, 48, and 60 months
- Change in KCCQ score from baseline through 30 days, 12 months and annually through 24, 36, 48, and 60 months
- Change in NYHA Functional Class (III/IV to I/II) from baseline through 30 days 12 months and annually through 24, 36, 48, and 60 months
- Echocardiographic endpoints assessed from baseline through 30 days, 12 months and annually through 24, 36, 48, and 60 months post procedure, as follows:
    - TR severity grade
    - Tricuspid valve annulus diameter
    - Effective Regurgitant Orifice Area (EROA)
    - Regurgitant Volume
    - Cardiac Output
    - Forward Stroke Volume (Left Ventricle)

B.3 Analysis Consideration

B.3.1 Analysis Population

The analysis for the CAS will include all continued access subjects that receive treatment with the TriClip™ G4 device. The Attempted Procedure population will be used for the endpoint analysis for the continuous access study, which will consist of subjects in whom a TriClip™ G4 procedure is attempted, i.e., undergo femoral vein puncture.

B.3.2 Endpoints Analysis

All the analysis for the CAS endpoints will be descriptive. Continuous endpoints will be summarized using the following: mean, standard deviation, median, the first and third quartiles, range, and the 95% confidence interval for the population mean using the normal approximation, when specified. Categorical endpoints will be summarized as proportions in the form of fractions and percentages. The 95% confidence interval for a population proportion will be constructed using the Clopper-Pearson exact method[1]. The 95% confidence interval for the difference of two proportions will be constructed using the Newcombe score method. Other analyses are specified under each category of additional descriptive endpoints. Survival analysis will be conducted to analyze time-to-event variables. Subjects without events will be censored at their last known event-free time point when they stay in the study. Survival curves will be constructed using Kaplan-Meier estimates.

Statistical Analysis Plan

B.3.3 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized for the subjects enrolled: gender, age, ethnicity, race, medical history, baseline echocardiographic measurements, etc.

B.3.4 Adverse Events

All adverse device effects, serious adverse device effects, UADEs, and USADEs will be summarized for all enrolled subjects in terms of the number of events, the percentage of subjects with events per MedDRA coding. Procedure related AEs may also be summarized.
All CEC adjudicated adverse events will be summarized for all subjects who enrolled in the trial in terms of the number of events, and the percentage of subjects with events. Moreover, COVID-19 related AEs will be summarized in terms of number of events, the percentage of subjects with events per AE term.

B.3.5 Protocol Deviation

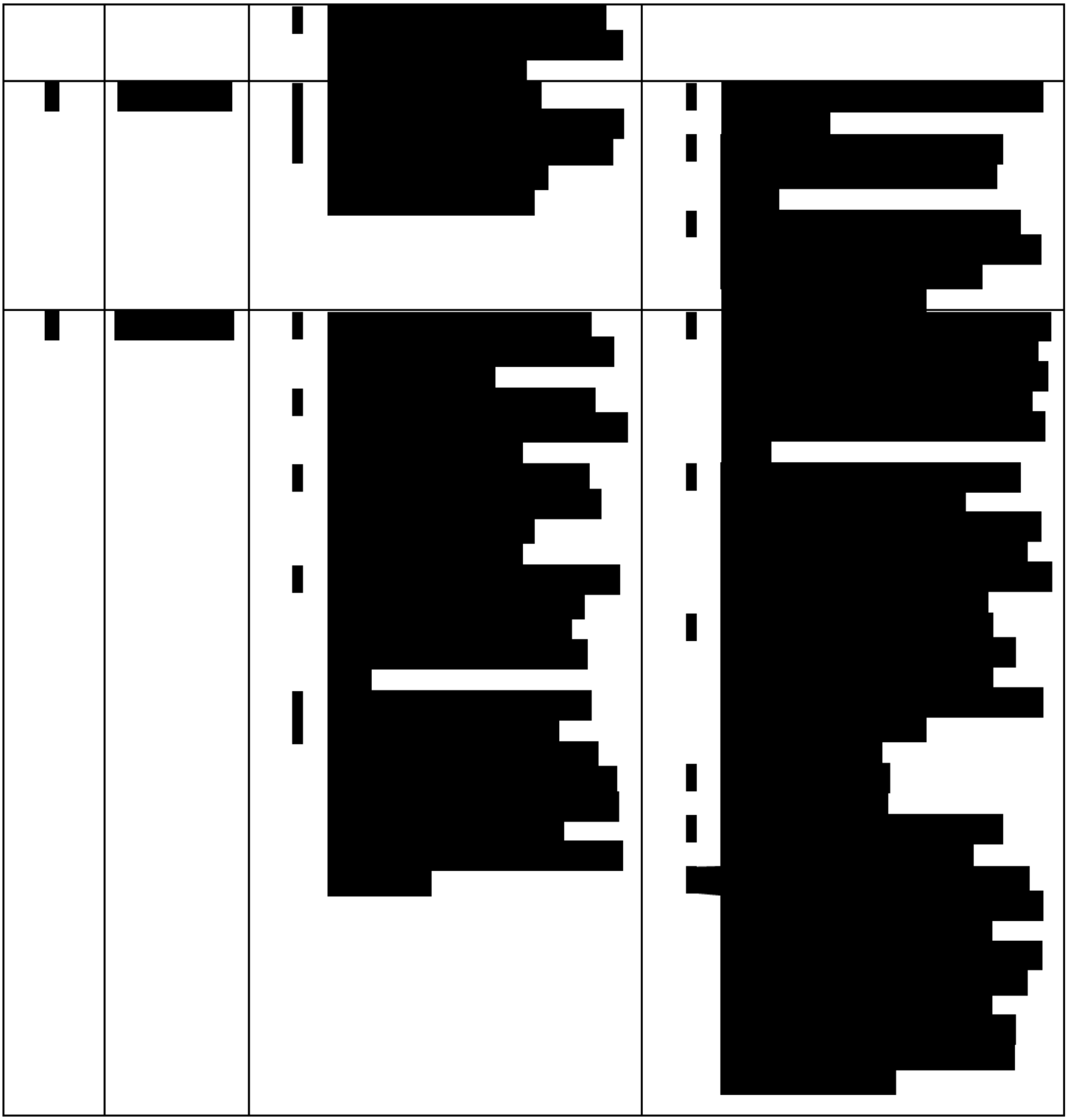
Protocol deviations will be summarized for subjects with reported protocol deviations. COVID-19 related protocol deviations will also be summarized.

Statistical Analysis Plan

APPENDIX C: MAJOR STATISTICAL ANALYSIS PLAN REVISIONS

Version	Date	Details	Rationale
[redacted]	[redacted]	[redacted]	[redacted]

Statistical Analysis Plan



Statistical Analysis Plan