Statistical Analysis Plan

[redacted]

Assessment of the Portico™ Transcatheter Aortic Valve for Valve-in-Valve Use

Retrospective Assessment of the Portico™ Transcatheter Aortic Valve for Valve-in-Valve Use

Statistical Analysis Plan (SAP)

[redacted]

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[redacted]

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1.0 SYNOPSIS OF STUDY DESIGN

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 for Portico Valve-in-Valve Retrospective Registry clinical investigation plan (CIP) [redacted]. This plan is based on [redacted] of the CIP.

1.2 Clinical Investigation Objectives

The objective of this data-collection study is to evaluate the safety and clinical performance of the Portico transthoracic aortic valve (sizes 23-29 mm) for Valve-in-Valve (ViV) treatment of a failed aortic surgical bioprosthetic valve in patients who are considered at increased surgical risk for a redo surgical aortic valve replacement.

1.3 Clinical Investigation Design

This is a multi-center, international, single-arm, retrospective data-collection study. The study will use a Core Laboratory for echocardiogram analysis and a Clinical Events Committee (CEC). The study includes the primary study arm and an exploratory registry arm; both study arms will follow all timepoints and data-collection requirements outlined in Figure 2 of the CIP. This study may include up to 100 patients for the primary analysis population.

[redacted] Patients must have met the sizing requirements of the Portico™ transthoracic aortic valve sizing specification (≥19 mm and ≤27 mm). Patients must meet all inclusion and exclusion criteria to be eligible for enrollment.

In addition, an exploratory registry arm will collect data for patients that were treated for a failed surgical bioprosthetic aortic valve true inner diameter size of <19 mm or >27 mm. There will be no enrollment limit in the exploratory registry arm.

[redacted]

1.4 Endpoints

1.4.1 Primary Safety Endpoint

Composite of all-cause mortality, disabling stroke, life threatening bleeding requiring transfusion, Acute Kidney Injury (AKI) requiring dialysis, and major vascular complications at 30 days.

[redacted]

1.4.2 Primary Performance Endpoint

Composite of all-cause mortality or disabling stroke at 1 year.

1.4.3 Descriptive Endpoints

1. Procedure success defined as:
   - Absence of procedural mortality AND
   - Successful access, delivery of the valve, and retrieval of the delivery system

2. Evaluation of adverse event rates

   At 30 days and one year:
   - All-cause mortality
   - Cardiovascular-related mortality
   - All Stroke (by severity)
   - Transient Ischemic Attacks (TIA)
   - Myocardial infarction (MI)
   - New pacemaker implant (PPI)
   - Coronary obstruction

   At 30 days:
   - Minor, Major, and Life-threatening bleeding
   - Major vascular, major non-vascular access-related, or cardiac structure complication
   - Acute Kidney Injury (AKI) stages 1-4

3. Evaluation of adverse event rates annually through 5 years:
   - All-cause mortality
   - Cardiovascular-related mortality
   - All Stroke (by severity)
   - TIA

The following will be collected if standard of care or if available:

4. Echocardiographic assessment of valve performance at discharge, 30 days, 1 year, and annually through 5 years including:
   - Transvalvular mean gradient
   - Indexed Effective orifice area (iEOA)
   - Doppler velocity index (DVI)
   - Aortic Valve Area (AVA)
   - Non-structural valve dysfunction:
     - Prosthetic patient mismatch (PPM) per body mass index (BMI)
     - Degree of aortic valve regurgitation (transvalvular and paravalvular leak (PVL)) as none/trace, mild, mild-moderate, moderate, moderate/severe, or severe per VARC-3; and per VARC-2 none/trace, mild, moderate, or severe).

5. Valve Integrity at 1 year and annually through 5 years as assessed by:

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- Structural Valve Deterioration (SVD) (by hemodynamic valve deterioration (HVD) stages 1-3 per VARC-3)
  Confirmed intrinsic permanent changes to the prosthetic valve, including:
  - Wear and tear
  - Leaflet disruption
  - Flail leaflet
  - Leaflet fibrosis and/or calcification
  - Strut fracture or deformation

- Non-structural Valve Dysfunction other than PVL and PPM (HVD stages 1-3 per VARC-3)
  Any abnormality not intrinsic to the prosthetic valve resulting in valve dysfunction other than PVL and PPM, including:
  - Leaflet entrapment by pannus or tissue
  - Inappropriate positioning or sizing
  - Embolization

- Clinically Significant Thrombosis
  Meeting either of the following criteria:
  - Clinical sequelae of thromboembolic event or worsening AS/transvalvular AR **and** HVD Stage 2-3 or confirmatory imaging of thrombosis
    Or
  - In the absence of clinical sequelae, **both** HVD Stage 3 **and** confirmatory imaging

- Endocarditis (by HVD stages 1-3 per VARC-3)
  Meeting at least one of the following criteria:
  - Fulfilment of the Duke endocarditis criteria
  - Evidence of abscess, pus, or vegetation confirmed as secondary to infection by histological or microbiological studies during re-operation
  - Evidence of abscess, pus or vegetation confirmed on autopsy.

The following definitions of HVD Stages (1-3) will be used when assessing valve integrity.

- Stage 1 (Morphological Valve Deterioration):
  Evidence of SVD, non-structural valve dysfunction (other than paravalvular or PPM), thrombosis or endocarditis without significant hemodynamic changes.

- Stage 2 (Moderate hemodynamic valve deterioration):
  Increase in mean transvalvular gradient ≥10 mmHg resulting in mean gradient ≥20 mmHg with concomitant decrease in EOA ≥0.3 cm^2 or ≥25% and/or decrease in Doppler velocity index ≥0.1 or ≥20% compared with echocardiographic assessment performed 1-3 months post-procedure, OR new occurrence or increase of ≥1 graded of intra-prosthetic AR resulting in ≥ moderate AR

- Stage 3 (Severe hemodynamic valve deterioration):
  Increase in mean transvalvular gradient ≥20 mmHg resulting in mean gradient ≥30 mmHg with concomitant decrease in EOA ≥0.6 cm^2 or ≥50% and/or decrease in Doppler velocity index ≥0.2 or ≥40% compared with echocardiographic assessment performed 1-3 months

post-procedure, OR new occurrence, or increase of ≥2 grades, of intra-prosthetic AR resulting in severe AR.

- Any need for Portico TAVI re-intervention after implant through 5 years

6. Clinical benefit endpoints defined as improvement from baseline to 30 days, 1 year, and annually through 5 years from index procedure, including:
   - New York Heart Association (NYHA) functional classification

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Population

2.1.1 Primary Analysis Population

The primary analysis population will include patients who have signed an Informed Consent Form (ICF), or for those patients deceased at the time of study screening, all local and national regulatory requirements were met for consent, and at minimum, the Portico delivery system entered his/her vasculature for an attempted Portico ViV implant. Subjects that are enrolled and later determined to be screen failures (those that do not meet all inclusion criteria or meet any exclusion criteria) will not be included in any analysis. Subjects that are enrolled in the Exploratory Arm of the study will not be included in the primary arm of the study.

2.1.2 Exploratory Registry Arm

Subjects enrolled that were treated for a failed surgical bioprosthetic aortic valve true inner diameter size of < 19 mm or > 27 mm will be included in a separate exploratory analysis.

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, BMI, heart rate, etc.), results will be summarized with the numbers of observations, means, and standard deviations, with 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. gender, diabetic status, etc.), results will be summarized with subject counts and percentages/rates, with exact 95% Clopper-Pearson confidence intervals, when specified.

2.2.3 Survival Analyses

Survival analysis will be conducted to analyze time-to-event variables. Subjects without events will be censored at the time of analysis. Survival curves will be constructed using Kaplan-Meier estimates and Greenwood standard errors.

2.2.4 Analysis in Response to COVID-19 Impact

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 endpoints set forth in assessing the trial success and labeling claims. In alignment with the EU guidance document "Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic" updated on 28-April-2020, and "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" updated on 03-June-2020, additional consideration was given to the impact of the COVID-19 pandemic on the primary endpoint analyses for this study. 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 efforts to minimize missing endpoint data during the COVID-19 pandemic. Specific analyses to address COVID-19 impacts are included in relevant subsections in Section 2.3.

2.3 Endpoint Analysis

2.3.1 Primary Endpoints

2.3.1.1 Primary Safety Endpoint

The primary safety composite endpoint is all-cause mortality, disabling stroke, life threatening bleeding requiring transfusion, AKI requiring dialysis, and major vascular complications at 30 days, as adjudicated by the CEC. COVID-19 relatedness of mortality, disabling stroke, life threatening bleeding requiring transfusion, AKI requiring dialysis, and major vascular complications will be adjudicated by the CEC, and any 30-day mortality, disabling stroke, life threatening bleeding requiring transfusion, AKI requiring dialysis, and major vascular complications that is adjudicated as COVID-19 related will be excluded from the primary analysis. The proportion of subjects experiencing a primary safety endpoint will be estimated from the binomial model. The 95% confidence intervals will be calculated using the exact Clopper-Pearson method.

The analysis population will include subjects enrolled in the study that is described in Section 2.1.1, including subjects who withdraw or are lost to follow-up prior to 30-day visit.

2.3.1.2 Primary Performance Endpoint

The primary performance composite endpoint is all-cause mortality or disabling stroke at 1 year, adjudicated by the CEC. COVID-19 relatedness of mortality and disabling stroke will be adjudicated by the CEC, and any 1-year death or disabling stroke that is adjudicated as COVID-19 related will be excluded and subjects' follow-up will be censored at the first COVID-19 related event from the primary analysis. The proportion of subjects experiencing a primary performance endpoint will be estimated using the Kaplan-Meier (KM) method, and the standard error of KM estimate will be calculated with Greenwood method.

The analysis population will include subjects enrolled in the study that is described in Section 2.1.1.

2.3.2 Descriptive Endpoints

Descriptive endpoints are listed in Section 1.4.3. Study results will be summarized using descriptive statistics including mean, standard deviation, median and range for continuous data and count and percentage for categorical data. All analyses will be performed on available data.

2.3.3 Exploratory Registry Arm

The data collected from subjects in the exploratory arm will not be included in the primary analysis but will be analyzed using descriptive statistics. Data from this analysis may be used to explore future research, specifically on valve sizing and echocardiogram measurements (eg. PVL, TVL, etc.).

The analysis population will include subjects enrolled in the study that is described in Section 2.1.2.

2.4 Sample Size Calculations

It is anticipated that up to [redacted] subjects may be enrolled in the primary analysis population. Additional subjects that have undergone an attempted Portico ViV implant may be analyzed. The exploratory registry arm will have no limit on the number of enrolled subjects.

2.5 Interim Analysis

No formal statistical rule for early termination of the trial is defined. Interim study reports may be produced for regulatory or reimbursement purposes.

2.6 Timing of Analysis

The primary endpoints analyses will be conducted on datasets locked after approximately [redacted] subjects completed their 1-year follow-up excepting deaths, withdrawals and loss to follow-up before 1-year or crossed the 1-year visit window without a visit (missed visit).

2.7 Subgroups for Analysis

Subjects that were treated with adjunctive therapies during the ViV procedure (eg. snorkel, basilica, or chimney techniques), will be analyzed for study primary endpoints.

2.8 Handling of Missing Data

All analyses will be performed on available data and additional considerations due to the COVID-19 pandemic are detailed in Section 2.2.4 and in the primary and secondary endpoint sections.
This is a retrospective study collecting data that is available per the site standard of care (SOC) and the majority of subjects will be followed for at least 1 year. Therefore, there is no plan to impute missing data.

2.9 Poolability Issue

To assess poolability of the primary safety endpoint across sites, Fisher's exact test will be used to test the rate of a subject with a primary endpoint event within each site. To assess poolability of the primary performance endpoint across sites, Cox regression model will be constructed that model the rate of a subject with a primary endpoint event as a function of site. If the primary endpoint by site is significant at the 0.15 significance level, the clinical relevance may be considered, additional analyses may be performed to determine if differences in the distributions of baseline factors account for site differences. In the pooling analysis, investigational sites that have less than five (5) subjects enrolled will be grouped as one "small" site for the purpose of this analysis. If the number of subjects in this 'small' center exceeds the total number of subjects enrolled in the "biggest" site, then multiple small sites will be created based on geographic region as appropriate.

2.10 Multiplicity Issues

The clinical study has two (2) co-primary endpoints with no prespecified hypothesis testing for the primary endpoints. Therefore, there is no multiplicity adjustment planned in this clinical study.

2.11 Adjustments for Covariates

Unless otherwise specified, no adjustments for covariates will be made for any of the variables in the analyses.

2.12 Sensitivity Analysis

For the primary safety endpoint and performance endpoint, a sensitivity analysis will be conducted including all CEC adjudicated component events regardless of relationship to COVID-19 to assess the impact of the pandemic. Sensitivity analysis will also be conducted including all CEC adjudicated VARC-2 events and VARC-3 events regardless to COVID-19 to assess the impact of the pandemic.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized (when available) for enrolled subjects: gender, age, ethnicity, race, surgical risk, medical co-morbidities, arrhythmia history, previous pacemaker implant, history of smoking, implant procedural characteristics, device details, etc.

3.2 Adverse Events

All adverse events, serious adverse events (SAEs), unanticipated serious adverse device effects (USADEs) will be summarized for all subjects who enrolled in this trial in terms the number of events and the number of subjects, as well as the percentage of subjects with events per AE term if relevant for the specific analysis. All CEC adjudicated adverse events will also be summarized for all subjects who underwent an implant attempt in terms the number of events, the percentage of subjects with events. Moreover, COVID-19 related AEs will be summarized in terms of number of events and the number of subjects, as well as the percentage of subjects with events per AE term if relevant for the specific analysis.

3.3 Subject Early Termination

Subject early termination reasons including deaths, withdrawals, lost-to-follow-up, etc. will be summarized at all scheduled visits.

3.4 Protocol Deviation

For subjects in whom a protocol deviation was reported, protocol deviations will be summarized in terms of number of deviations and number of subjects with deviations by type of deviation. COVID-19 related protocol deviations will also be reported.

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

All analyses will be performed using SAS® for Windows, version 9.4 or higher.

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
AKI	Acute Kidney Injury
AVA	Aortic Valve Area
BMI	Body Mass Index
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
DVI	Doppler Velocity Index
EOA	Effective Orifice Area
HVD	Hemodynamic Valve Deterioration
iEOA	Indexed Effective Orifice Area
PPM	Prosthetic Patient Mismatch
PVL	Paravalvular Leak
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SVD	Structural Valve Deterioration
TAVI	Transcatheter Aortic Valve Implantation
USADE	Unanticipated serious adverse device effect
ViV	Valve-in-Valve

6.0 APPENDICES

APPENDIX A: STATISTICAL ANALYSIS PLAN REVISIONS

Ver	Details	Rationale
A	Not Applicable	First release of SAP