Statistical Analysis Plan

The **CONFIDENCE** Registry

CONtrolled delivery **F**or **I**mprove**D** outcom**E**s with cli**N**i**C**al **E**vidence

[redacted]

Statistical Analysis Plan (SAP)

[redacted]

Date: 23 June-2021

[redacted]

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1 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 Clinical Investigation Plan [redacted] the CONFIDENCE clinical investigation. [redacted]

1.2 Clinical Investigation Objectives

The objective of this registry is to characterize the procedural safety and device performance of the Portico™ valve from experienced TAVI centers that commercially use the Portico™ valve, delivery system and loading system to treat patients with severe aortic stenosis.

1.3 Clinical Investigation Design

The CONFIDENCE Registry is a prospective, non-randomized, observational, single-arm, multicenter registry of patients clinically indicated for implantation of a Portico™ transcatheter aortic heart valve. The registry has broad inclusion criteria (symptomatic degenerative aortic stenosis) and minimal exclusion criteria to ensure the results are generalizable to the broadest TAVI population. Approximately 1000 subjects from up to 50 centers will undergo transcatheter aortic valve replacement (independent of valve size) using a commercially available Portico™ valve and transfemoral delivery system. No center may enroll more than 10% of total subjects (100) and maximum 50 subjects in each half of the study.

In order to evaluate the current generation product to the next generation, the total enrollment in the CONFIDENCE Registry will consist of approximately 500 subjects treated with the first generation Portico delivery system (Models PRT-DS-TF-18F/19F) and 500 with the next generation FlexNav delivery System (Models FN-DS-SM/LG).

Subjects will undergo prospective enrollment with baseline data collection prior to receiving their Portico Valve (up to a maximum of 180 days prior to the Portico valve implant procedure). The implant procedure will be conducted per standard protocol established at each center. After the procedure, subjects will undergo a pre-discharge visit at the time of hospital discharge or within seven days of the index procedure, whichever occurs first. Subjects will return to the participating institution for a 30-day follow-up visit followed by a 12-month vital status/survival status check. The 12-month vital status/survival status check may be conducted via a phone call if an in-office visit is not feasible. [redacted]

An independent Clinical Events Committee (CEC) will be utilized to adjudicate key adverse events pertinent to the study's descriptive endpoints.

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1.4 Endpoints

The following descriptive endpoints will be reported using summary statistics and no hypothesis tests will be performed.

1. Evaluation of the VARC-2 event rates at 30 days from the index procedure
   - Cardiovascular Mortality
   - Myocardial Infarction
   - Stroke (including disabling and non-disabling)
   - Bleeding (life-threatening, major, minor)
   - Acute kidney injury
   - Vascular access site and access-related complications (major and minor)
   - Annular rupture
   - Conversion to open surgery
   - Coronary obstruction
   - Valve embolization
   - Transcatheter valve-in-valve deployment
   - Permanent pacemaker insertion

   Additional analysis of predictors of VARC-2 events (e.g. PVL or new permanent pacemaker) may be conducted.

2. Delivery profile characteristics such as access vessel diameter, sheath utilization and sheath size

3. Implant success defined as:
   - Absence of procedural mortality
   - Correct positioning of a single Portico prosthetic heart valve into the proper anatomical location

4. Echocardiographic assessment of hemodynamic valve performance at 30 days compared to baseline for the subjects with Portico valve implanted.
   - Mean gradient
   - Effective orifice area
   - Paravalvular leak (PVL)

   (Core Lab adjudicated echocardiographic measures will be utilized for evaluating valve hemodynamic performance at 30 days)

5. Clinical improvement from baseline to 30 days for the subjects with Portico valve implanted assessed by:
   - New York Heart Association (NYHA) functional class
   - Quality of Life (QoL) questionnaire (EQ5D-3L)

6. All-cause mortality at 30 days and 12-months

2 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

[redacted]

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, etc.), results will be summarized with the numbers of observations, means, and standard deviations, with median and range for the means.

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.

2.2.3 Survival Analysis

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. Survival curves will be constructed using Kaplan-Meier (KM) estimates.

2.2.4 Analyses in Response to COVID-19 Impact

As the coronavirus disease of 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 endpoints set forth in final report. In alignment with the guidance document EU "Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic" updated 28-April-2020, additional consideration will be given to the impact of the COVID-19 pandemic on the 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.

2.3 Endpoint Analysis

All endpoints are descriptive and will be summarized as described below. No hypotheses tests will be performed. All analyses will be performed on available data and all applicable summary.

2.3.1 Evaluation of the VARC-2 event rates at 30 days from the index procedure.

For each VARC-2 adverse event reported within 30 days of index procedure (i.e. 0 ≤ Number of days since index procedure ≤ 30), number of events, number of subjects with event and event rate will be provided.

[redacted]

Evaluation of all-cause Mortality is discussed in section 2.3.6.

2.3.2 Delivery system profile characteristics.

Delivery system characteristics such as access vessel diameter, sheath utilization, sheath size, etc. will be presented as follows:
Continuous characteristics will be summarized using descriptive statistics including mean, standard deviation, median, and range. Categorical characteristics will be summarized using frequencies and percentages. For the estimation of percentages, all subjects in AP with available data will be evaluated.

2.3.3 Implant success.

Implant success is defined as:

1. Absence of procedural mortality
2. Correct positioning of a single Portico prosthetic heart valve into the proper anatomical location

Each component of implant success will be summarized using frequencies and percentages.

[redacted]

2.3.4 Hemodynamic valve performance at 30 days compared to baseline.

- Mean gradient
- Effective orifice area

[redacted]

- Paravalvular leak (PVL)

(Core Lab adjudicated echocardiographic measures will be utilized for evaluating valve hemodynamic performance at 30 days)

Paired and unpaired analyses will be implemented. Only available data will be used in the summary.

[redacted]

2.3.5 Clinical improvement from baseline to 30 days by assessment of:

- **New York Heart Association functional class**

NYHA Class will be summarized at Baseline and 30 days using frequencies and percentages. Additionally, paired analysis will be used to evaluate NYHA Class Improvement from Baseline to 30 days for all enrolled subjects in AP who have completed NYHA assessments at **both** Baseline and the 30-day follow-up.

- **Quality of Life (QoL) questionnaire (EQ5D-3L)**

All five dimensions captured on the EQ5D-3L questionnaire and Visual analogue score will be summarized at Baseline and 30 days using descriptive statistics including mean, standard deviation, median, and range. In addition, paired analysis will be used to evaluate QoL improvement from Baseline to 30 days for all enrolled subjects in AP.

2.3.6 All-cause mortality at 30 Days and 12 Months

To understand the impact of COVID-19 pandemic on all-cause mortality, sensitivity analysis will be performed. All analyses will be performed on subjects in the AP.
All-cause Mortality at 30 days will be analyzed as follows:
Number of deaths reported at 30 days post index procedure (i.e. 0≤Number of days since index procedure≤ 30) will be summarized with subject count and rates; rates will be estimated as proportion of subjects who died within 30-Day post procedure.

[redacted]

Kaplan–Meier (KM) method will be used to estimate the mortality rate at 12-months.

[redacted]

2.4 Sample Size Calculations

[redacted]

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[redacted]

2.5 Interim Analysis

No formal interim analysis is planned for this trial. As such, no formal statistical rule for early termination of the trial is defined. Interim study reports with descriptive analysis may be provided for Investigator meetings, Ethics committee review or reimbursement purposes.

2.6 Timing of Analysis

Final analysis will be conducted after all enrolled subjects (First generation and Next generation Portico delivery system have either been terminated or completed the 12-month follow-up.

2.7 Subgroups for Analysis

Subgroup analyses will be performed to evaluate endpoints across study cohorts (first generation delivery system vs. FlexNav delivery system).
Baseline Characteristics (refer to section 3.1) and study endpoints (refer to section 2.3) will be descriptively summarized for each subgroup; no hypotheses tests will be performed.
Results for both subgroups will be presented within the same output table.

2.8 Handling of Missing Data

There is no plan for imputing missing data for this clinical investigation. All analyses will be performed on available data and additional considerations due to the COVID-19 pandemic are detailed where applicable.

2.9 Poolability Analysis

No poolability analysis is planned for this registry.

2.10 Multiplicity Adjustments

There are no multiplicity adjustments planned for this registry.

2.11 Adjustments for Covariates

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

3 ADDITIONAL DATA

All additional data are descriptive and will be summarized as described below.

3.1 Baseline, Demographic Characteristics

Baseline and medical characteristics such as age, gender, Euroscore, STS mortality risk score, cardiovascular history, neurovascular history, etc. will be summarized using appropriate summary statistics.

3.2 Adverse Events

All adverse events (AEs) reported will be summarized by seriousness (serious AE vs. nonserious AE), primary relationship (device, procedure, and unrelated).
The follow definitions will apply:

- AE: Adverse Events (Non-serious and non-device or procedure related)
- ADE: Adverse Device Effects (Non-serious and device or procedure related)
- SAE: Serious Adverse Events (Serious and non-device or procedure related)
- SADE: Serious Adverse Device Effects (Serious and device or procedure related)

The number of events and number of subjects who experienced one or more incidents of the adverse event category of interest will be presented for each category. Categories will be non-overlapping.
All events adjudicated as related or possibly related to COVID-19 will also be summarized as above.

Evaluation of all-cause Mortality at 30 days is discussed in section 2.3.6

3.3 Subject Early Termination

Reasons for early termination including deaths, withdrawals, lost to follow-up, unsuccessful implant, etc. will be summarized.

3.4 Protocol Deviation

Protocol deviations will be summarized by follow-up visit and by deviation category (Inclusion/Exclusion criteria not met, Informed consent, visit not done etc.) using number of events.

[redacted]

3.5 30-Day Follow-up

[redacted] For the purpose of the valve hemodynamic performance evaluation, all echocardiographic data submitted for the 30-day time point [redacted] will be used for analysis.

4 DOCUMENTATION AND OTHER CONSIDERATIONS

All analyses will be performed using SAS® for Windows, version 9.3 or higher.

5 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
AE	Adverse Event
AP	Attempted Procedure
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CRF	Case Report Form
IP	Implanted Population
KM	Kaplan-Meier
NYHA	New York Heart Association
SAP	Statistical Analysis Plan
SD	Standard Deviation