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Portico NG Approval Study

Evaluation of the Portico™ NG Transcatheter Aortic Valve in High and Extreme Risk Patients with Symptomatic Severe Aortic Stenosis

Statistical Analysis Plan (SAP)

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Statistical Analysis Plan

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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 NG clinical investigation plans (CIP)[redacted]. This plan is based on [redacted] the CIP.

1.2 Clinical Investigation Objectives

The primary objective of this clinical study is to evaluate the acute safety and effectiveness of the Navitor Transcatheter Aortic Heart Valve as assessed by the rate of all-cause mortality at 30 days and the rate of moderate or greater paravalvular leak at 30 days. The results for the primary safety endpoint will be descriptively compared to published data on FDA approved TAVR devices, and the results for the primary effectiveness endpoint will be compared to a performance goal derived from published results of FDA approved TAVR devices studied in the same patient population (e.g., high and extreme surgical risk).

1.3 Clinical Investigation Design

The Portico NG Approval study is a prospective, multi-center, international, single-arm investigational study designed in accordance with ISO standards 14155:2011 and 5840-3:2013. To be eligible for study participation, a patient must have symptomatic, severe native aortic stenosis and be considered high or extreme risk for surgical valve replacement. Implanting physicians must either have prior Portico TAVI system experience or must complete roll-in cases. Upon provision of informed consent and approval by the subject selection committee, subjects will undergo Navitor Valve implantation via a transfemoral or alternative access approach according to the site's anesthesia protocol for TAVR procedures.

To ensure sufficient number of subjects for primary endpoint analysis (described in detail in section 2.4), a total of [redacted] subjects may undergo a Navitor implant attempt in the PMA cohort for the 23-29mm Navitor sizes (Portico NG cohort).

A separate cohort of 60 subjects (Titan cohort) will undergo an implant attempt with the Navitor Titan valve. Data from the Titan cohort will be analyzed separately to support submissions for regulatory approval. Prospective data from Titan subjects enrolled under a separate, regional OUS protocol may be combined with US subjects to meet the minimum required sample size for the PMA submission. Importantly, both protocols enroll high and extreme surgical risk subjects with severe symptomatic AS who undergo Navitor Titan valve implantation with the FlexNav Delivery System in a premarket setting and are aligned in terms of inclusion/exclusion criteria, devices being studied, training requirements and Instructions for Use, follow-up requirements and data collection. Furthermore, subjects enrolled in the Titan cohort will undergo the same screening, baseline, procedure and follow-up assessments as the Portico NG cohort.

In addition, up to a total of 20 roll-in subjects may be enrolled and undergo a Navitor implant attempt.

Subjects participating in the clinical study will be followed for a total of 5 years with data collected at screening, baseline, procedure, prior to hospital discharge, and follow-up at 30 days, 12 months and annually thereafter up to 5 years. The expected duration of enrollment is 12 months, and the total duration of the clinical study is expected to be 6.5 years. Global regulatory submissions for the Navitor Titan valve will be completed when 60 subjects have 30-day follow-up data. Follow-up data through 5 years will be submitted as part of a final report to respective regulatory agencies.

1.4 Endpoints

This clinical study has two (2) co-primary endpoints. The same primary endpoints will be evaluated in both the Portico NG and Titan cohorts and analyzed independently for each cohort.

1.4.1 Primary Safety Endpoint

The primary safety endpoint is all-cause mortality at 30 days.

1.4.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is moderate or greater paravalvular leak at 30 days.

1.4.3 Secondary Endpoint

This clinical study has one secondary endpoint, a non-hierarchical composite of all-cause mortality, disabling stroke, life threatening bleeding, acute kidney injury (stage 3), or major vascular complications at 30 days. The secondary endpoint is the same for the Titan cohort as the Portico NG cohort and will be analyzed independently for each cohort.

1.4.4 Descriptive Endpoints

The following key outcomes (relevant to characterizing the safety profile and outcomes based on the design modifications) will be assessed as descriptive endpoints for the study (for both the Portico NG and Titan cohorts, but analyzed independently for each cohort):

- Technical device success defined as successful vascular access, delivery and deployment of the Portico NG Valve; retrieval with the delivery system and correct positioning of a single valve in the proper anatomical location and the absence of procedural mortality
- All-cause mortality at 12 months from the index procedure
- Cardiovascular-related mortality at 30 days and 12 months from the index procedure
- Disabling stroke at 30 days and 12 months from the index procedure
- Life threatening and major bleeding at 30 days from the index procedure
- Acute kidney injury at 30 days from the index procedure
- Major and minor vascular complications at 30 days from the index procedure
- Permanent pacemaker insertion at 30 days and 12 months from the index procedure
- Changes in functional status from baseline to follow-up assessments at 30 days and 12 months (e.g., NYHA classification, six-minute walk test, quality of life measures)
- Paravalvular leak at discharge, 30 days and 12 months from the index procedure
- Changes in echocardiographic parameters from baseline to follow-up at 30 days and 12 months (e.g., mean effective orifice area, mean transvalvular gradient, mean peak velocity)
- Symptomatic valve thrombosis at 30 days and 12 months from the index procedure

Additional outcomes to be collected and assessed during the study:

- Myocardial infarction at 30 days and 12 months from the index procedure
- New-onset atrial fibrillation at 30 days and 12 months from the index procedure
- Coronary obstruction requiring intervention at 30 days from the index procedure
- Valve embolization during procedure, and at 30 days and 12 months from the index procedure
- Reintervention to treat valve-related dysfunction at 30 days and 12 months from the index procedure
- Total aortic valve regurgitation (transvalvular plus paravalvular leak) at discharge, 30 days and 12 months from the index procedure

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Attempted Population

The attempted population will include all subjects in whom a Navitor implant is attempted, excluding roll-in cases. A Navitor implant attempt is defined as insertion of the FlexNav™ Delivery System (loaded with a Navitor valve) into the subject's vasculature.

2.1.2 Implanted Population

The implanted population will include all subjects in the attempted population excluding any subject with competitor valve implanted or subject without a valve implanted.

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 and secondary endpoints set forth in assessing the trial success and labeling claims. In alignment with the guidance document "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 (Portico NG cohort)

The primary safety endpoint for the Portico NG cohort is all-cause mortality at 30 days post index procedure.

The proportion of Portico NG subjects experiencing a primary safety endpoint will be estimated from the binomial model. COVID-19 relatedness of mortality will be adjudicated by the Clinical Events Committee (CEC), and any 30-day death that is adjudicated as COVID-19 related will be excluded from the primary analysis (i.e., from both numerator and denominator). The 95% confidence intervals will be calculated using the exact Clopper-Pearson method. The estimated primary safety endpoint rate at 30 days will be descriptively compared with the all-cause mortality rates (and 95% confidence intervals) of FDA approved TAVR devices studied in the same patient population (e.g., high and extreme risk), and additional published data on high and extreme surgical risk subjects available at the time of PMA submission, as described in the CIP.

The analysis population will include subjects who undergo a Navitor implant attempt 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 Safety Endpoint (Titan cohort)

The primary safety endpoint for the Titan cohort is all-cause mortality at 30 days post index procedure.

The proportion of Titan subjects experiencing a primary safety endpoint will be estimated from the binomial model. COVID-19 relatedness of mortality will be adjudicated by the Clinical Events Committee (CEC), and any 30-day death that is adjudicated as COVID-19 related will be excluded from the primary analysis (i.e., from both numerator and denominator). The 95% confidence intervals will be calculated using the exact Clopper-Pearson method. The estimated primary safety endpoint rate at 30 days will be descriptively compared with the all-cause mortality rates (and 95% confidence intervals) of FDA approved large valve TAVR devices studied in the same patient population (e.g., high and extreme risk) as well as results from the Portico NG cohort.

The analysis population will include subjects who undergo a Navitor Titan implant attempt that is described in Section 2.1.1, including subjects who withdraw or are lost to follow-up prior to 30-day visit.

2.3.1.3 Primary Effectiveness Endpoint (Portico NG cohort)

The primary effectiveness endpoint for the Portico NG cohort is moderate or greater paravalvular leak at 30 days.

Let π be the proportion of Portico NG subjects who experience a primary effectiveness endpoint event at 30 days. The following hypothesis will be tested:

H_0: $\pi \geq 8.5\%$
H_a: $\pi < 8.5\%$

π will be estimated as a binomial proportion. The hypothesis will be tested at the 0.05 significance level and the null hypothesis will be rejected if the 95% upper confidence bound (UCB) for the proportion, π, is less than the performance goal of 8.5%. The results for the primary effectiveness endpoint will be considered successful if the null hypothesis is rejected. If a subject was unable to have an echocardiogram performed during the 30-day visit window (+21 days) due to the COVID-19 pandemic, sites were instructed to perform the echocardiographic imaging as soon as possible after this visit window and submit a protocol deviation. For the purpose of primary effectiveness endpoint analysis, all echocardiographic imaging submitted for the 30-day time point (including the out of window exams) will be used for analysis.

The analysis will include both the attempted population and the implanted population that are described in Section 2.1 and who have 30-day paravalvular leak status as determined by the echocardiography core laboratory, with the analysis on the implanted population as the primary analysis.

2.3.1.4 Primary Effectiveness Endpoint (Titan cohort)

The primary effectiveness endpoint for the Titan cohort is moderate or greater PVL at 30 days post index procedure.

The proportion of Titan subjects experiencing a primary effectiveness endpoint will be estimated from the binomial model. The 95% confidence intervals will be calculated using the exact Clopper-Pearson method. The estimated primary effectiveness endpoint rate at 30 days will be descriptively compared with 30-day moderate or greater PVL rates (and 95% confidence intervals) of FDA approved large valve TAVR devices studied in the same patient population (e.g., high and extreme risk) as well as results from the Portico NG cohort.

The analysis will include both the attempted population and the implanted population that are described in Section 2.1 and who have 30-day paravalvular leak status as determined by the echocardiography core laboratory.

2.3.2 Secondary Endpoint

The secondary endpoint is a non-hierarchical composite of all-cause mortality, disabling stroke, life threatening bleeding, acute kidney injury (stage 3), or major vascular complications at 30 days. This endpoint will be analyzed for both the Portico NG and Titan cohorts separately.

The proportion of subjects experiencing a secondary endpoint will be estimated from the binomial model. COVID-19 relatedness of secondary endpoint events will be adjudicated by the CEC, and any 30-day secondary endpoint event that is adjudicated as COVID-19 related will be excluded from the primary analysis (i.e., from both numerator and denominator). The 95% confidence intervals will be calculated

using the exact Clopper-Pearson method. As described in the CIP, the estimated secondary endpoint rate at 30 days will be descriptively compared with rates observed with FDA approved TAVR devices studied in the same patient population (e.g., high and extreme risk), including the observed rates and 95% confidence intervals from published sources and data from FDA approved devices available at the time of PMA submission.

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

2.3.3 Descriptive Endpoints

Hemodynamic outcomes such as mean gradient, effective orifice area (EOA), paravalvular leak, etc. will be analyzed in the Implanted population described in Section 2.1.2, other descriptive endpoints will be analyzed in the Attempted population described in Section 2.1.1. All analyses will be performed on available data.

2.4 Sample Size Calculations

The total sample size required for the Portico NG cohort (to ensure adequate number of subjects for analysis of the primary endpoints) is [redacted] subjects.

Up to a total of [redacted] subjects will undergo a Navitor implant attempt to allow for analysis of the primary effectiveness endpoint.

For the Titan cohort, a total of [redacted] analysis provides an adequate sample size to descriptively compare to results from competitor studies of a larger valve size (e.g., Evolut R 34mm) and the Portico NG cohort.

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 analysis for the PMA submission will be conducted on a dataset locked after a minimum of [redacted] analysis subjects in the Portico NG cohort have had a 30-day study visit and have PVL data assessed by the echocardiography core laboratory. As stated in section 1.3, an analysis of the first [redacted] subjects (with a Navitor implant attempt) with 30-day follow-up data will be provided to support the CE Mark submission.

Data from the Titan cohort will be analyzed independently from the Portico NG cohort. The analysis for the Titan cohort will be conducted on a dataset locked after 60 analysis subjects have had a 30-day study visit and have PVL data assessed by the echocardiography core laboratory, excluding any subjects who die or are lost to follow-up within 30 days.

2.7 Study/Trial Success

Study success will be determined independently for the Portico NG and Titan cohorts. The Portico NG cohort will be considered successful if the rate for the primary safety endpoint (all-cause mortality within 30 days) is within expected ranges as compared to previous commercially approved devices studied in

the same patient population (e.g., high and extreme surgical risk) and the null hypothesis is rejected for the primary effectiveness endpoint (moderate or greater PVL at 30 days).

The Titan cohort will be considered successful if [redacted] deaths occur within 30 days of the index procedure in [redacted] analysis subjects.

2.8 Subgroups for Analysis

Subgroup analyses may be performed to examine the consistency of the primary endpoints across baseline risk categories, valve sizes implanted, region (US vs OUS), and sex (male vs female). KM estimates on the primary endpoints event will be reported along with 95% confidence intervals.

2.9 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.

2.10 Poolability

To assess poolability of the primary safety and effectiveness endpoints across sites, Fisher's exact test will be used to test the rate of a subject with a primary endpoint event within each site. If the primary endpoint by site is significant at the 0.15 significance level, the clinical relevance will be considered, additional analyses will be performed to determine if differences in the distributions of baseline factors account for site differences, and primary endpoints be presented at the site level. In the pooling analysis, investigational sites that have less than five (5) subjects enrolled will be grouped as one 'small' center 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. Poolability analysis will be performed for both the Portico NG and Titan cohorts independently.

2.11 Multiplicity

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

2.12 Adjustments for Covariates

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

2.13 Sensitivity Analysis

For the primary safety endpoint, a sensitivity analysis will be conducted including all CEC adjudicated death events regardless relationship to COVID-19 to assess the impact of the pandemic. Sensitivity analysis will also be conducted including all CEC adjudicated VARC-2 events regardless to COVID-19 to assess the impact of the pandemic. Sensitivity analysis on the primary endpoint and the VARC-2 event rate will be performed for both the Portico NG and Titan cohorts independently.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized separately for the subjects enrolled in both the Portico NG and Titan cohorts: gender, age, ethnicity, race, surgical risk, medical co-morbidities, arrhythmia history, previous pacemaker implant, history of smoking, implant procedural characteristics, etc.

3.2 Adverse Events

All adverse events, serious adverse events (SAEs), unanticipated serious adverse device effects (USADEs) will be summarized for all subjects in the attempted population 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. AE summaries will be presented for both the Portico NG and Titan cohorts independently.

3.3 Subject Early Termination

Subject early termination reasons including deaths, withdrawals, lost-to-follow-up, etc. will be summarized at all scheduled visits for both the Portico NG and Titan cohorts independently.

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. Protocol deviations summaries will be presented for both the Portico NG and Titan cohorts independently.

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
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
EOA	Effective Orifice Area
PG	Performance Goal
PMA	Premarket Approval

Statistical Analysis Plan

Acronym or Abbreviation	Complete Phrase or Definition
PVL	Paravalvular Leak
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TAVR	Transcatheter Aortic Valve Replacement
USADE	Unanticipated serious adverse device effect