Portico™ Re-sheathable Transcatheter Aortic Valve System
US IDE Trial (PORTICO)

Statistical Analysis Plan (SAP)

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NCT02000115
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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 Clinical Investigation Plan (CIP) CL06799, the Portico™ Re-sheathable Transcatheter Aortic Valve System US IDE clinical investigation.

1.2 Clinical Investigation Objectives

The objective of this clinical trial is to evaluate the safety and effectiveness of the SJM Portico Transcatheter Heart Valve and Delivery Systems (Portico) via transfemoral and alternative delivery methods. The Portico™ Transcatheter Heart Valve is indicated for patients with symptomatic severe native aortic stenosis, who are considered high or extreme surgical risk. An additional study arm ("FlexNav study" or "FlexNav cohort") has been added to the pivotal IDE trial. The objective of the FlexNav study is to characterize the safety of the second-generation Portico Delivery System ("FlexNav™ Delivery System").

1.3 Clinical Investigation Design

The pivotal IDE trial is a prospective, multi-center, randomized, controlled clinical trial, designed to evaluate the safety and effectiveness of the SJM Portico Transcatheter Heart Valve and Delivery Systems (Portico) via transfemoral and alternative delivery methods. The pivotal IDE trial includes a randomized cohort of 750 patients that will be used to support a Premarket Approval (PMA) application for the Portico™ Transcatheter Aortic Heart Valve in the United States. This trial includes both high-risk and extreme-risk patients. Prior to randomization, patients will be classified as high or extreme risk and stratified by vascular access within each risk group. At the time of the primary analysis, the risk cohorts will be combined.

The FlexNav study will be conducted as a prospective, multicenter, investigational study arm of the pivotal IDE trial. Thirty-day outcomes data from the 100 subjects in FlexNav study will be used to support the PMA application for the Portico™ Transcatheter Aortic Heart Valve and the FlexNav™ Delivery System.

1.4 Endpoints

1.4.1 Pivotal IDE Endpoints (Randomized cohort)

Primary Safety Endpoint

Non-hierarchical composite of all-cause mortality, disabling stroke, life threatening bleeding requiring blood transfusion, acute kidney injury requiring dialysis, or major vascular complications at 30 days.

Primary Effectiveness Endpoint

A composite of all-cause mortality or disabling stroke at one year.
Secondary Endpoints

1. Severe aortic regurgitation (AR) at one year
2. Kansas City Cardiomyopathy Questionnaire (KCCQ) at one year
3. Moderate or severe aortic regurgitation at one year
4. Six-minute walk at one year

Descriptive Endpoints

1. Acute device success defined as:
   a. Absence of procedural mortality AND
   b. Correct positioning of a single prosthetic heart valve into the proper anatomical location AND
   c. Intended performance of the prosthetic heart valve (mean aortic valve gradient <20 mmHg or peak velocity <3 m/s, no moderate or severe prosthetic valve regurgitation) AND
   d. Successful access was obtained as intended by group assignment
2. Kansas City Cardiomyopathy Questionnaire (KCCQ) at one year for Centers for Medicare and Medicaid Services (CMS) National Coverage Decision primary quality of life endpoint
3. Major vascular complications at 30 days from the index procedure
4. NYHA functional classification at 30 days, 6 months, and one year
5. Six-minute walk test at 30 days, 6 months, and one year
6. Paravalvular Leak (PVL) at 30 days, 6 months, and one year
7. Aortic insufficiency greater than trace at 30 days, 6 months, one year, and two years
8. Reintervention to treat aortic insufficiency at 1 year and 2 years
9. Permanent pacemaker insertion at 30 days from the index procedure
10. Major bleeding at 30 days from the index procedure
11. Acute kidney injury at 30 days from the index procedure
12. Individual components of the primary effectiveness endpoint
   a. All-cause mortality at 30 days, 6 months, one year and two years
   b. Disabling stroke at 30 days, 6 months, one year and two years
13. Non-disabling Stroke and Transient Ischemic Attack (TIA) at 30 days, 6 months, one year, and two years
14. Atrial fibrillation at one year and two years
15. Quality of Life (QOL) from baseline to 30 days, 6 months and one year

1.4.2 FlexNav Study Endpoints

Primary Safety Endpoint:
VARC II defined major vascular complication rate at 30 days.

Descriptive Endpoints:

1. Non-hierarchical composite of all-cause mortality, disabling stroke, life threatening bleeding requiring blood transfusion, acute kidney injury requiring dialysis, or major vascular complications at 30 days from the index procedure
2. All-cause mortality at 30 days and one year from the index procedure
3. Disabling stroke at 30 days and one year from the index procedure
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4. Non-disabling stroke at 30 days from the index procedure
5. Life threatening bleeding requiring blood transfusion at 30 days from the index procedure
6. Major bleeding at 30 days from the index procedure
7. Acute kidney injury at 30 days from the index procedure
8. Minor vascular complication rates at 30 days from the index procedure
9. Permanent pacemaker insertion at 30 days from the index procedure
10. Paravalvular Leak (PVL) at 30 days from the index procedure
11. NYHA functional classification at 30 days from the index procedure
12. KCCQ Quality of Life score from baseline to 30 days from the index procedure
13. Technical device success defined as successful vascular access, delivery and deployment of the Portico Valve; retrieval with the delivery system and correct positioning of a single valve in the proper anatomical location
14. Composite of all-cause mortality or disabling stroke at one year from the index procedure

1.5 Randomization (Randomized cohort)

Subjects will be randomized per 1:1 ratio to test (Portico) vs. commercially available valve (CAV). group according to a computer-generated randomization scheme.

1.6 Blinding

Subjects were not blinded to their assigned treatment. Packaging and design of the Portico and CAVs are different, and thus, implanters were not blinded to the assigned treatment. There was no randomization or blinding of treatment in the FlexNav cohort.

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

The primary analysis for the randomized cohort will be based on the intention-to-treat (ITT) population. In addition, results were summarized for the As Treated and Per Protocol populations. The definitions of these analysis populations are defined below.
In the FlexNav cohort, the analysis population included all subjects in whom an Portico valve implant was attempted.

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables
For continuous variables, results will be summarized with the numbers 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, results will be reported as frequencies with percentages and were compared using chi-square tests or two-tailed Fisher’s exact test.

2.2.3 Descriptive Statistics for Time-to-event Variables
Time-to-event analyses will be performed using the Kaplan-Meier method and all comparisons were made using the log-rank test.

2.3 Endpoint Analysis

2.3.1 Primary Endpoints (Randomized Cohort)
Primary Effectiveness Endpoint
The primary effectiveness endpoint is the composite endpoint of all-cause mortality or disabling stroke at one year. This endpoint will be evaluated by a non-inferiority test comparing the Portico test group to the control (CAV) group, and the primary analysis will be conducted on the ITT population. The primary analysis will be performed based on combined high and extreme risk cohort with pooled access data.

The primary analysis will be conducted on a dataset locked after all enrolled subjects have had their one-year study visit (except those withdrawn or lost-to-follow-up before one year).
**Primary Safety Endpoint**

The primary safety endpoint is the non-hierarchical composite endpoint of all-cause mortality, disabling stroke, life-threatening bleeding requiring blood transfusion, acute kidney injury requiring dialysis, or major vascular complications at 30 days. This endpoint will be evaluated by a non-inferiority test comparing Portico test group to the control group, and the primary analysis will be conducted on the ITT population. The primary analysis will be performed based on combined high and extreme risk cohort with pooled access data.
Statistical Analysis Plan

The study hypotheses are:

Null hypothesis: The probability of a subject experiencing a primary safety endpoint event at 30 days for the test group is inferior to the probability in the control group.

$$\text{H}_0: \mu_{\text{test}} > \mu_{\text{control}} + \Delta p_2$$

Alternative hypothesis: The probability of a subject experiencing a primary safety endpoint event at 30 days for the test group is not inferior to the probability in the control group by more than $$\Delta p_2$$.

$$\text{H}_a: \mu_{\text{test}} < \mu_{\text{control}} + \Delta p_2$$

where $$\mu_{\text{test}}$$ is the probability of a subject experiencing a primary safety endpoint event by 30 days in the Portico test group, $$\mu_{\text{control}}$$ is the probability of a subject experiencing a primary safety endpoint event in the control group, and $$\Delta p_2$$, the non-inferiority margin for the primary safety endpoint, is set at 8.5%. The event rates, $$\mu_{\text{test}}$$ and $$\mu_{\text{control}}$$, will be estimated as 30-day Kaplan-Meier event rates. The hypothesis will be tested at the one-sided 5% level of significance, i.e., the upper bound of the one-sided 95% confidence interval for $$\mu_{\text{test}} - \mu_{\text{control}}$$ must be entirely less than $$\Delta p_2$$.

Non-inferiority margin

The selection of the non-inferiority margin is based upon clinically acceptable outcomes. It has been demonstrated that inoperable subjects with severe aortic stenosis had a 1-year mortality rate of 50%. Based on the data from the PARTNER trial for subjects who cannot undergo SAVR, the TAVR treated subjects have 31% mortality rate, therefore choosing a Delta ($$\Delta$$) that is 30% of this rate will preserve more than half of 19% treatment effect. On the other hand, a non-inferiority margin of 7.5% was used for PARTNER A (high risk subjects), which is 31% of the one-year mortality rate 24.2% for the High risk cohort for TAVR group. A conservative value of 30% of the rate in the control group is chosen for the non-inferiority margin in each of the high risk and extreme risk groups:

The expected $$\mu_{\text{control}}$$ rate for the high-risk group is 27.59%, therefore $$\Delta p_2 = 0.083 (0.2759 \times 0.30)$$. The expected $$\mu_{\text{control}}$$ rate for the extreme risk group is 43.69%, therefore $$\Delta p_2 = 0.131 (0.4369 \times 0.30)$$. The expected $$\mu_{\text{control}}$$ rate for combined high-risk and extreme-risk group by enrolling 80% high-risk subjects and 20% extreme-risk subjects is 30.81%, therefore $$\Delta p_2 = 0.092 (0.3081 \times 0.30)$$. Therefore, a conservative value of 8.5% is chosen as the non-inferiority margin for the primary safety endpoint for the combined high and extreme risk cohort.

Hypothesis Test

The hypothesis test will be performed by calculating a 95% one-sided upper confidence limit for the difference of $$(\mu_{\text{test}} - \mu_{\text{control}})$$, using the Kaplan-Meier estimates for the event rates and standard errors. This analysis is performed on all patients, combing data from the high risk cohort and extreme risk cohort. If the upper confidence limit for the difference is less than 0.085, the Portico test group will be determined to be non-inferior to the control group. The standard error of the test statistic $$L_{\text{test}} - L_{\text{control}}$$ is defined as

$$\text{SE} = \sqrt{\text{SE}(L_{\text{test}})^2 + \text{SE}(L_{\text{control}})^2},$$

where $$\text{SE}(L_{\text{test}})$$ and $$\text{SE}(L_{\text{control}})$$ are Greenwood standard errors for the Kaplan-Meier estimates.

If non-inferiority is demonstrated, a reflex test for superiority will be performed to determine if the Portico test group is superior to the control group. If the upper bound of the two-sided 95% CI for $$(\mu_{\text{test}} - \mu_{\text{control}})$$ is entirely < 0, superiority will be claimed.

The hypotheses of superiority test are:

$$\text{H}_0: \mu_{\text{test}} - \mu_{\text{control}} \geq 0$$
Secondary Endpoints

All secondary endpoints are defined in section 1.4.1. Among these, 4 have hypotheses to be tested:

1. Severe aortic regurgitation (AR) at one year
2. Kansas City Cardiomyopathy Questionnaire (KCCQ) at one year
3. Moderate or severe aortic regurgitation at one year
4. 6-minute walk at one year

Non-inferiority tests will be performed for each endpoint. The first and third endpoints will use tests of proportions, and the second and fourth endpoints will use a test of means.

Specifically, null and alternative hypotheses for each endpoint are:

- **Severe aortic regurgitation at one year (higher proportion is worse)**
  
  Ho: \( \theta_{test,1} \geq \theta_{control,1} + 0.04 \)
  
  Ha: \( \theta_{test,1} < \theta_{control,1} + 0.04 \)
  
  Where \( \theta_{test,1} \) and \( \theta_{control,1} \) are the proportions of subjects with severe aortic regurgitation at 1 year in the Portico test and control groups, respectively. The test statistic is based on the Farrington-Manning method of testing non-inferiority of proportions.

- **KCCQ at one year (higher mean better)**
  
  Ho: \( \theta_{test,2} \leq \theta_{control,2} - 10 \)
  
  Ha: \( \theta_{test,2} > \theta_{control,2} - 10 \)
  
  Where \( \theta_{test,2} \) and \( \theta_{control,2} \) are the KCCQ scores at 1 year in the Portico test and control groups, respectively. The test statistic is based on a two-sample t-test.

- **Moderate or severe aortic regurgitation at one year (higher proportion is worse)**
  
  Ho: \( \theta_{test,3} \geq \theta_{control,3} + 0.06 \)
  
  Ha: \( \theta_{test,3} < \theta_{control,3} + 0.06 \)
  
  Where \( \theta_{test,3} \) and \( \theta_{control,3} \) are the proportions of patients with moderate or severe aortic regurgitation at 1 year in the Portico test and control groups, respectively. The test statistic is based on the Farrington-Manning method of testing non-inferiority of proportions.

- **6-minute walk distance at one year (higher mean better)**
  
  Ho: \( \theta_{test,4} \leq \theta_{control,4} - 36 \)
  
  Ha: \( \theta_{test,4} > \theta_{control,4} - 36 \)
  
  Where \( \theta_{test,4} \) and \( \theta_{control,4} \) are the mean 6-minute walk distance at 1 year in the Portico test and control groups, respectively. The test statistic is based on a two-sample t-test.
2.3.2 Primary Endpoint (FlexNav cohort)

Acceptable safety of the FlexNav™ Delivery System will be determined from a predefined precision estimate for VARC II-defined major vascular complications at 30 days. Results will be summarized and descriptively compared in context of results for the first-generation Delivery System in the randomized cohort (Portico arm) of the pivotal IDE trial.

2.4 Sample Size Calculations (Randomized cohort)

The sample sizes of pivotal IDE trial randomized cohort are estimated based on the primary effectiveness and safety endpoints and tests. The study is powered on combined high and extreme risk cohort. The sample size is calculated to achieve at least 80% power for both primary effectiveness and safety endpoints assuming 80% of subjects are high risk and 20% of subjects are extreme risk based on recent publication from the TVT registry.

2.4.1 Sample Size for the Primary Effectiveness Endpoint

The operating characteristics of the statistical test for the primary effectiveness endpoint are calculated by simulating 10,000 trials for a given sample size using custom-written software in the R software package. The expected proportion of subjects with a primary effectiveness endpoint event in the control and Portico test groups are 22.9% for high risk group and 29.6% for extreme risk group. The expected proportion of subjects with primary effectiveness endpoint event in control and Portico test group for the combined cohort of 80% high risk subjects and 20% extreme risk subjects are each 24.24%. This event rate assumption is consistent with data reported on commercially available TAVR within the TVT registry.

As TAVR is currently indicated in the United States for extreme risk or high risk, the TVT registry is representative of patients to be studied in the PORTICO pivotal IDE trial. More than half of patients within the TVT registry have undergone transfemoral access and overall the rate of death or disabling stroke at 1 year is reported to be 26%, with transfemoral access providing safer outcomes. Therefore, the event rate of the primary effectiveness endpoint at one year is assumed to be 25% for both control and Portico test groups. Using the above estimated event rates and an 8% non-inferiority margin, a sample size of 750 will provide 80% power at the 5% significance level to demonstrate non-inferiority of the Portico test group to the control group for the primary effectiveness endpoint. All power calculations assume 7.5% loss-to-follow-up per year. Subjects who are lost-to-follow-up without experiencing an endpoint event will be censored in the Kaplan-Meier analysis for the primary effectiveness endpoint.

2.4.2 Sample Size for the Primary Safety Endpoint

The operating characteristics of primary safety endpoint are calculated by simulating 10,000 trials per scenario using custom-written software in the R software package. All power calculations assume 5% loss-to-follow-up at 30 days. Subjects who are lost-to-follow-up without experiencing an endpoint event will be censored in the Kaplan-Meier analysis for primary safety endpoint.

The expected rates of subjects with primary safety endpoint event in control and Portico test group are both 27.59% for high-risk group and 43.69% for extreme-risk group. The expected rates of subjects with primary safety endpoint event in control and Portico test group for combined cohort by enrolling 80% high risk subjects and 20% extreme risk subjects are both 30.8%. Using the above estimated event rates and an 8.5% non-inferiority margin a sample size of 750 will provide 80% power at the 5% significance level.
2.4.3 **Total Sample Size**

The total sample size required for evaluating the primary effectiveness and safety endpoints is 750 and 750 subjects respectively. Thus, the total sample size is 750 for the pivotal IDE trial randomized cohort.

2.5 **Interim Analysis**

No formal interim analyses are planned for this study.

2.6 **Trial Success**

Success will be declared when all the primary endpoints are met.

2.7 **Subgroups for Analysis (Randomized cohort)**

For the primary safety and effectiveness endpoints and secondary endpoints (aortic regurgitation, KCCQ score at one year, 6-minute walk at one year) in the randomized cohort tests will be performed...
2.11 Multiplicity Issues

Multiplicity adjustment will apply to hypothesis testing for the superiority tests of primary endpoints and four non-inferiority tests of secondary endpoints (severe AR, KCCQ, moderate or severe AR, and 6-minute walk) in pivotal IDE trial.

2.12 Adjustments for Covariates

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized for the subjects enrolled: gender, age, ethnicity, race, cardiac disease history, arrhythmia history, history of smoking, implant procedural characteristics, etc.
3.2 **Adverse Events**

All of the adverse device effects, serious adverse device effects will be summarized for all subjects who enrolled in this trial in terms the number of events, the percentage of subjects with events and event per AE term. All CEC adjudicated adverse events will also be summarized for all subjects who enrolled in the trial by treatment arms in terms the number of events, the percentage of subjects with events.

4.0 **DOCUMENTATION AND OTHER CONSIDERATIONS**

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

5.0 **ACRONYMS AND ABBREVIATIONS**

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<th>Acronym or Abbreviation</th>
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6.0 **REFERENCES**

