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

[redacted]

Statistical Analysis Plan (SAP)

[redacted]
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NCT02000115

[redacted]

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

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. [redacted], 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:
   - Absence of procedural mortality AND
   - Correct positioning of a single prosthetic heart valve into the proper anatomical location AND
   - 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
   - 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
    - All-cause mortality at 30 days, 6 months, one year and two years
    - 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

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. [redacted]

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.

[redacted]

[redacted]

In the FlexNav cohort, the analysis population included all subjects in whom an Portico valve implant was attempted [redacted]

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).

[redacted]

[redacted]

[redacted]

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.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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 [redacted]

[redacted]

[redacted]

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.

[redacted]

2.5 Interim Analysis

No formal interim analyses are planned for this study. [redacted]

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 [redacted]

[redacted]

[redacted]

[redacted]

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.

[redacted]

2.12 Adjustments for Covariates

[redacted]

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 OHER CONSIDERATIONS

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

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
AR	Aortic regurgitation
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
CMS	Centers for Medicare and Medicaid Services
CRF	case report form
ITT	Intention-to-treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
PMA	Premarket Approval
PVL	Paravalvular Leak
SAE	serious adverse event
SAP	statically analysis plan
SAVR	surgical aortic valve replacement
TAVR	Transcatheter aortic valve replacement
TIA	Transient Ischemic Attack
QOL	Quality of Life

6.0 REFERENCES

[redacted]

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