Statistical Analysis Plan

Repositionable Percutaneous Replacement of Stenotic Aortic Valve through Implantation of Lotus™ Valve System – Evaluation of Safety and Performance

REPRISE III

Protocol Number: S2282

CONFIDENTIAL

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1 PROTOCOL SUMMARY

Objective(s)	To evaluate the safety and effectiveness of the Lotus™ Valve System for transcatheter aortic valve replacement (TAVR) in symptomatic subjects with calcific, severe native aortic stenosis who are considered at extreme or high risk for surgical valve replacement.
Intended Use	The Lotus Valve System is intended to improve aortic valve function for symptomatic subjects with calcific, severe native aortic stenosis who are at extreme or high risk for standard surgical valve replacement.
Test Device and Sizes	The Lotus Valve System consisting of two main components: - a bioprosthetic bovine pericardial aortic valve, and - a delivery system. Devices sizes include 23 mm, 25 mm, and 27 mm diameter.
Control Device and Sizes	Commercially available self-expanding CoreValve® Transcatheter Aortic Valve Replacement System (CoreValve) that is introduced percutaneously via the femoral artery using conventional catheterization techniques (Medtronic, Inc., Minneapolis, MN, USA). Devices sizes include 26 mm, 29 mm, and 31 mm diameter. ***Note 1:*** Every subject must be deemed treatable with an available size of both the test (Lotus) and the control (CoreValve) device. The CoreValve device in the planned size must be approved for use and commercially available at the investigational center where the implant procedure is being performed. ***Note 2:*** A center may use the CoreValve® Evolut™ R Recapturable TAVR System with the aforementioned size matrix if it is approved and commercially available, but only if the center no longer has access to CoreValve.
Study Design	REPRISE III is a prospective, multicenter, 2:1 randomized (Lotus Valve System versus a commercially available CoreValve Transcatheter Aortic Valve Replacement System), controlled trial designed to evaluate the safety and effectiveness of the Lotus Valve System for TAVR in symptomatic subjects who have calcific, severe native aortic stenosis and who are at high or extreme risk for surgical aortic valve replacement (SAVR). There will be a non-randomized roll-in phase with only the test device for centers that do not have previous experience implanting the Lotus Valve; each of these centers will perform at least 2 roll-in cases before commencing randomization. Data from roll-in subjects will be summarized separately

	from the randomized population. Roll-in subjects will not be included in the endpoint analyses. The REPRISE III study will be conducted in accordance with the relevant parts of the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practices (GCP) or the International Standard ISO 14155: 2011; ethical principles that have their origins in the Declaration of Helsinki; and pertinent individual country/state/local laws and regulations.
Planned Subjects/ Centers/ Countries	Subjects will be enrolled at up to 60 centers in the United States, Canada, Western Europe, and Australia. There will be up to 1032 subjects in REPRISE III. Up to 120 subjects will be enrolled and included in a roll-in phase (test device only) among centers that do not have previous experience implanting the Lotus Valve (a minimum of 2 roll-in subjects per center) before randomization begins. There will be 912 subjects enrolled and randomized.
Primary Endpoints	Primary Safety Endpoint: Composite of all-cause mortality, stroke, life-threatening and major bleeding events, stage 2 or 3 acute kidney injury, or major vascular complications at 30 days Primary Effectiveness Endpoint: Composite of all-cause mortality, disabling stroke, or moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year
Secondary Endpoint	Moderate or greater paravalvular aortic regurgitation (based on core lab assessment) at 1 year
Additional Measurements	Additional measurements based on the VARC[a,b] endpoints and definitions (see **Note 1** below) will be collected peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, and 1, 2, 3, 4, and 5 years post index procedure, unless otherwise specified below. • Safety endpoints adjudicated by an independent Clinical Events Committee (CEC): o Mortality: all-cause, cardiovascular, and non-cardiovascular o Stroke: disabling and non-disabling o Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure) o Bleeding: life-threatening (or disabling) and major o Acute kidney injury (≤7 days post index procedure): based on the AKIN System Stage 3 (including renal replacement therapy) or Stage 2 o Major vascular complication

	○ Repeat procedure for valve-related dysfunction (surgical or interventional therapy) ○ Hospitalization for valve-related symptoms or worsening congestive heart failure (NYHA class III or IV) ○ New permanent pacemaker implantation resulting from new or worsened conduction disturbances ○ New onset of atrial fibrillation or atrial flutter ○ Coronary obstruction: periprocedural (≤72 hours post index procedure) ○ Ventricular septal perforation: periprocedural (≤72 hours post index procedure) ○ Mitral apparatus damage: periprocedural (≤72 hours post index procedure) ○ Cardiac tamponade: periprocedural (≤72 hours post index procedure) ○ Prosthetic aortic valve malpositioning, including valve migration, valve embolization, or ectopic valve deployment ○ Transcatheter aortic valve (TAV)-in-TAV deployment ○ Prosthetic aortic valve thrombosis ○ Prosthetic aortic valve endocarditis • Device Performance endpoints peri- and post-procedure: ○ Successful vascular access, delivery and deployment of the study valve, and successful retrieval of the delivery system ○ Successful retrieval of the study valve if retrieval is attempted ○ Successful repositioning of the study valve if repositioning is attempted (see **Note** 2 below) ○ Grade of aortic valve regurgitation: paravalvular, central, and combined • Clinical procedural success (30 days), defined as implantation of the study device in the absence of death, disabling stroke, major vascular complications, and life-threatening or major bleeding • Procedural success, defined as absence of procedural mortality, correct positioning of a single transcatheter valve into the proper anatomical location , intended performance of the study device (effective orifice area [EOA] >0.9 cm^2 for BSA <1.6 m^2 and EOA >1.1 cm^2 for BSA ≥1.6 m^2 plus either a mean aortic valve gradient <20 mm Hg or a peak velocity <3m/sec, and no moderate or severe prosthetic valve aortic regurgitation) plus no serious adverse events at 30 days • Additional indications of prosthetic aortic valve performance as measured by transthoracic echocardiography (TTE; see **Note 3** below) and assessed

	by an independent core laboratory, including effective orifice area, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation • Modified device success (30 days), reported for subjects randomized and implanted with an assigned study device and defined as follows: absence of mortality with the originally implanted transcatheter valve in the proper anatomical location, no additional aortic valve procedures, and with the intended performance of the prosthetic valve (either a mean aortic valve gradient <20 mm Hg or a peak velocity <3m/sec with no moderate or severe prosthetic valve aortic regurgitation) • For subjects who received a permanent pacemaker related to the index procedure, results of pacemaker interrogation at 30 days and 1 year • Functional status as evaluated by the following: o 5-m gait speed test (at 1 year compared to baseline) o New York Heart Association (NYHA) classification • Neurological status (see **Note 4** below) as determined by the following: o Neurological physical exam at discharge and 1 year (conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner) o National Institutes of Health Stroke Scale (NIHSS) at discharge and 1 year o Modified Rankin Scale (mRS) at all time points • Health status as evaluated by Kansas City Cardiomyopathy and SF-12 Quality of Life questionnaires at baseline; 1 and 6 months; and 1, 3, and 5 years ***Note 1:*** The most current VARC definitions and endpoints available at the beginning of the trial were used. ***Note 2:*** For the Lotus Valve (test), repositioning may be achieved with partial or full resheathing of the valve. ***Note 3:*** At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis. ***Note 4:*** For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam (conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner), NIHSS assessment, and mRS must be performed after the event; mRS must also be administered 90±14 days post-neurological event. a: Kappetein AP, *et al*. *J Am Coll Cardiol*. 2012;60:1438

	b: Leon M, *et al. J Am Coll Cardiol.* 2011;57:253
Follow-up Schedule	All subjects implanted with a test or control device will be assessed at baseline, peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, 1 year, and then annually for up to 5 years post-procedure. Subjects who are enrolled but not implanted with a test or control device at the time of the procedure will be followed for safety through 1 year.
Study Duration	Subjects implanted with a test or control device will be followed for 5 years after the procedure.

2 INTRODUCTION

This statistical plan addresses the planned analyses for the REPRISE III Trial based on the protocol with PDM # 90899936. Specified analyses may be used for scientific presentations and/or manuscripts and may not all be provided to Regulatory Authorities.

3 ENDPOINT ANALYSIS

Testing of endpoints will be carried out in a hierarchal manner in order to ensure the experiment-wise type I error rate is controlled. Testing will be done in three steps with each step needing to reject the null hypothesis in order to proceed to the next step:

1. Test the primary safety endpoint (Section 3.1) and the primary hypothesis of the primary effectiveness endpoint (Section 3.2.1.1). If the null hypothesis for both endpoints is rejected to show non-inferiority of the Lotus group to the CoreValve group, then proceed to step 2.
2. Test the secondary endpoint (Section 3.3); if the null hypothesis is rejected to show superiority of the Lotus group over the CoreValve group, then proceed to step 3.
3. Test the secondary hypothesis of the primary effectiveness endpoint (Section 3.2.1.2).

3.1 Primary Safety Endpoint

3.1.1 Hypotheses

The primary safety endpoint is the composite of all-cause mortality, all stroke, life-threatening and major bleeding events, acute kidney injury (stage 2 or 3), or major vascular complications evaluated at 30 days after the implant procedure. The primary analysis for the primary safety endpoint will be based on the implanted analysis set.

The null and alternative hypotheses for the primary safety endpoint are as follows:

H_0: $P_{S\_Lotus} - P_{S\_Control} \geq \Delta$ (Inferior)

H_1: $P_{S\_Lotus} - P_{S\_Control} < \Delta$ (Non-inferior)

where P_{S_Lotus} and $P_{S\_Control}$ are the rate of primary safety endpoint at 30 days for the Lotus Valve (test) group and the CoreValve group, respectively, and Δ (delta) is the non-inferiority margin.

A Farrington-Manning standardized test will be used to test the one-sided hypothesis of non-inferiority in the difference between the rates of the two treatment groups. If the *P* value from the Farrington-Manning standardized test is <0.025, the primary safety endpoint rate at 30 days for the Lotus Valve will be concluded to be non-inferior to that of the CoreValve rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference in observed rates between treatment groups (Lotus Valve minus CoreValve) in the primary safety endpoint rate at 30 days being less than the non-inferiority margin.

3.1.2 Sample Size

The sample size calculation for the primary safety endpoint at 30 days is based on the following assumptions:

- Expected Lotus Valve (test) rate = 40%
- Expected CoreValve (control) rate = 40%
- Non-inferiority margin (Δ) = 10.5%
- Test significance level (α) = 0.025 (1-sided)
- Test : Control ratio = 2:1
- Expected rate of attrition = 5%

Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 5% attrition, there is approximately 85% power to show non-inferiority with the expected rates

3.2 Primary Effectiveness Endpoint

3.2.1 Hypothesis

3.2.1.1 Primary Hypothesis

The primary hypothesis is that the rate of the primary effectiveness endpoint (composite of all-cause mortality, disabling stroke, and moderate or greater paravalvular aortic regurgitation* [based on core lab assessment] evaluated at 1 year [365 days]) for the Lotus Valve group is non-inferior to that for the CoreValve group. The primary analysis for the primary hypothesis of the primary effectiveness endpoint will be based on the implanted analysis set.

The null and alternative hypotheses for the primary hypothesis of the primary effectiveness endpoint are as follows:

H_0: $P_{E\_Lotus} - P_{E\_Control} \geq \Delta$ (Inferior)

H_1: $P_{E\_Lotus} - P_{E\_Control} < \Delta$ (Non-inferior)

where P_{E_Lotus} and $P_{E\_Control}$ are the primary effectiveness endpoint rates at 1 year for the Lotus Valve (test) group and the CoreValve group, respectively, and Δ (delta) is the non-inferiority margin.

A Farrington-Manning standardized test will be used to test the one-sided hypothesis of non-inferiority in the difference between the rates of the two treatment groups. If the *P* value from the Farrington-Manning standardized test is <0.025, the primary effectiveness endpoint rate at 1 year for the Lotus Valve will be concluded to be non-inferior to that of the CoreValve rate. This corresponds to the one-sided upper 97.5% confidence bound on the difference in observed rates between treatment groups (Lotus Valve minus CoreValve) in the primary effectiveness endpoint rate at 1 year being less than the non-inferiority margin.

***Note:** Moderate or greater indicates a regurgitation grade of moderate or severe.

3.2.1.2 Secondary Hypothesis

The secondary statistical hypothesis is that the rate of the primary effectiveness endpoint for the Lotus Valve group is superior to that for the CoreValve group. This test will be carried out only if the null hypothesis from the statistical hypothesis is rejected for all of the primary safety endpoint (Section 3.1), primary hypothesis of the primary effectiveness endpoint (Section 3.2.1.1), and the secondary endpoint (Section 3.3) and the rate for the primary effectiveness endpoint for the Lotus group is less than that of the CoreValve group. The primary analysis for

the secondary hypothesis of the primary effectiveness endpoint will be based on the ITT analysis set.

The null and alternative hypotheses for the secondary hypothesis of the primary effectiveness endpoint are as follows:

H_0: $P_{E\_Lotus} = P_{E\_Control}$

H_1: $P_{E\_Lotus} \neq P_{E\_Control}$

where P_{E_Lotus} and $P_{E\_Control}$ correspond to the rates of the primary effectiveness endpoint for the Lotus Valve group (test) and the CoreValve group (control), respectively.

A chi-square test will be used to test the two-sided hypothesis of superiority between the rates of the two treatment groups. If the *P* value from the chi-square test is <0.05 and the rate of the Lotus group is less than the rate of the CoreValve group, the rate of the primary effectiveness endpoint for the Lotus Valve will be concluded to be superior to the CoreValve. This corresponds to the two-sided upper 95% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the primary effectiveness endpoint being less than zero.

3.2.2 Sample Size

3.2.2.1 Primary Hypothesis

The sample size calculation for the primary hypothesis of the primary effectiveness endpoint at 1 year is based on the following assumptions:

- Expected Lotus Valve (test) rate = 32%
- Expected CoreValve rate = 32%
- Non-inferiority margin (Δ) = 9.5%
- Test significance level (α) = 0.025 (1-sided)
- Test : Control ratio = 2:1
- Power ($1-\beta$) = 80%
- Total number of evaluable subjects = 819
- Expected rate of attrition = 10%

Given the above assumptions, the planned enrollment is 912 subjects (608 Lotus Valve, 304 CoreValve).

3.2.2.2 Secondary Hypothesis

The sample size calculation for the secondary hypothesis of the primary effectiveness endpoint at 1 year is based on the following assumptions:

- Expected Lotus Valve (test) rate = 22%
- Expected CoreValve rate = 32%
- Test significance level (α) = 0.05 (2-sided)

- Test : Control ratio = 2:1
- Expected rate of attrition = 10%

Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 10% attrition, there is approximately 86% power to show superiority with the given expected rates.

3.3 Secondary Endpoint

3.3.1 Hypothesis

The statistical hypothesis is that the secondary endpoint of moderate or greater* paravalvular aortic regurgitation (AR) rate at 1 year (based on review by an independent core lab) for the Lotus Valve is superior to that for the CoreValve group. The primary analysis for the secondary endpoint will be based on the ITT analysis set.

To control for experiment-wise type I error, testing for the secondary endpoint will be conducted only if the null hypotheses for the primary safety endpoint and the primary analysis of the primary effectiveness endpoint are rejected. That is, non-inferiority must be shown for the primary safety endpoint and the primary effectiveness endpoint for testing to be conducted for the secondary endpoint.

The null and alternative hypotheses for the secondary endpoint are as follows:

H_0: $P_{AR\_Lotus} = P_{AR\_Control}$

H_1: $P_{AR\_Lotus} \neq P_{AR\_Control}$

where P_{AR_Lotus} and $P_{AR\_Control}$ correspond to the moderate or greater paravalvular aortic regurgitation rates at 1 year for the Lotus Valve group (test) and the CoreValve group (control), respectively.

A chi-square test will be used to test the two-sided hypothesis of superiority between the rates of the two treatment groups. If the *P* value from the chi-square test is <0.05 and the rate of the Lotus group is less than the rate of the CoreValve group, the rate of the secondary endpoint for the Lotus Valve will be concluded to be superior to the CoreValve rate. This corresponds to the two-sided upper 95% confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) for the observed rate of the secondary endpoint being less than zero.

***Note:** Moderate or greater indicates a regurgitation grade of moderate or severe.

3.3.2 Sample Size

The sample size calculation for the secondary endpoint (moderate or greater paravalvular aortic regurgitation rate at 1 year) is based on the following assumptions.

- Expected Lotus Valve (test) rate P_{AR_Lotus} = 1.1%
- Expected CoreValve (control) rate $P_{AR\_Control}$ = 5.3%
- Test significance level (α) = 0.05 (2-sided)
- Test : Control ratio = 2:1
- Expected rate of attrition = 25%

Given enrollment of 912 subjects (608 Lotus Valve, 304 CoreValve) and 25% attrition, there is approximately 86% power to show superiority with the given expected rates.

3.4 Statistical Methods for the Primary Effectiveness, Primary Safety, and Secondary Endpoints

3.4.1 Non-Inferiority Testing

The following methodology will be used for the non-inferiority testing of the primary safety endpoint and the primary hypothesis of the primary effectiveness endpoint.

All subjects who are enrolled will be eligible for evaluation. The primary safety and effectiveness endpoints will be analyzed for patients in the ITT, as-treated, and implanted analysis sets.

If the *P* value from the one-sided Farrington-Manning test comparing the treatment groups is <0.025, the Lotus group will be concluded to be non-inferior to the CoreValve group. This corresponds to the one-sided upper 97.5% confidence bound for the difference in rates (Lotus – CoreValve) being less than the non-inferiority margin (Δ). That is,

$$(p_{Lotus}\text{-}p_{Control}) + Z_{0.025}\tilde{\sigma}_{MLE} < \Delta$$

where

$$\tilde{\sigma}^2_{MLE} = \frac{\tilde{p}_{Lotus}(1\text{-}\tilde{p}_{Lotus})}{n_{Lotus}} + \frac{\tilde{p}_{Control}(1\text{-}\tilde{p}_{Control})}{n_{Control}}$$

$$\tilde{p}_{Lotus} = 2u\cos(w)\text{-}b/3a$$

$$\tilde{p}_{Control} = \tilde{p}_{Lotus}\text{-}\Delta$$

$$w = \frac{\pi + cos^{-1}(v/u^3)}{3}$$

$$v = \frac{b^3}{27a^3}\text{-}\frac{bc}{6a^2} + \frac{d}{2a}$$

$$u = sign(v)\sqrt{\frac{b^2}{9a^2}\text{-}\frac{c}{3a}}$$

$$a = 1 + R$$

$$b = \text{-}(1 + R + p_{Lotus} + Rp_{Control} + R\Delta + 2\Delta)$$

$$c = \Delta^2 + \Delta(2p_{Lotus} + R + 1) + p_{Lotus} + Rp_{Control}$$

$$d = \text{-}p_{Lotus}\Delta(1 + \Delta)$$

$$R = n_{Control}/n_{Lotus}$$

and p_{Lotus} is the observed rate of primary safety endpoint at 30 days (primary effectiveness endpoint at 30 days) for Lotus patients,

$p_{Control}$ is the observed rate of primary safety endpoint at 30 days (primary effectiveness endpoint at 1 year) for CoreValve patients,

n_{Lotus} is the number of Lotus patients evaluated for primary effectiveness endpoint at 30 days (primary safety endpoint at 1 year),

$n_{Control}$ is the number of CoreValve patients evaluated for primary effectiveness endpoint at 30 days (primary safety endpoint at 1 year), and

$Z_{0.025}$ is upper 2.5th percentile of the standard normal distribution.

The test statistic for the Farrington-Manning test is

$$Z = \frac{(p_{Lotus} - p_{Control}) - \Delta}{\tilde{\sigma}_{MLE}}.$$

A sensitivity analysis (e.g. tipping-point analysis) will be performed to assess the impact of subjects not evaluable for the primary safety and effectiveness endpoints and to assess the robustness of the conclusion of the primary analysis. Assuming no loss to follow-up and given the observed number of patients with primary safety endpoint/primary effectiveness endpoint evaluable for both treatment groups, for all combinations of success/failure for patients with missing data, the endpoints will be evaluated until the point at which the conclusion of the study changes. For each endpoint, a plot with the number of patients with missing values for the Lotus group on the x-axis and the number of patients with missing values for the CoreValve group on y-axis will be provided. There will be shaded regions on the plot which represent the cases where the p-value from the test of non-inferiority is <0.025 and ≥0.025 to demonstrate which combinations of successes and failures among the patients missing data change the conclusion of the study.

3.4.2 Superiority Testing

The following methodology will be used for the superiority testing of the secondary hypothesis of the primary effectiveness endpoint and the secondary endpoint.

All subjects who are enrolled will be eligible for evaluation. The primary effectiveness and secondary endpoints will be analyzed for patients in the ITT, as-treated, and implanted analysis sets.

If the *P* value from the chi-square test comparing the treatment groups is <0.05 and the Lotus group has lower rate than the CoreValve group, the Lotus group will be concluded to be superior to the CoreValve group. This corresponds to the two-sided upper 95% confidence bound for the difference in rates (Lotus – CoreValve) being less than zero. That is,

$$(p_{Lotus} - p_{Control}) + z_{0.025}\sigma_{MLE} < 0$$

where

$$\sigma^2_{MLE} = \frac{p_{Lotus}(1-p_{Lotus})}{n_{Lotus}} + \frac{p_{Control}(1-p_{Control})}{n_{Control}}$$

and p_{Lotus} is the observed rate for Lotus patients,

$p_{Control}$ is the observed rate for CoreValve patients,

n_{Lotus} is the number of Lotus patients evaluated for the endpoint,

$n_{Control}$ is the number of CoreValve patients evaluated the endpoint,

σ^2_{MLE} is the variance from the Pearson chi-square test, and

$z_{0.025}$ is upper 2.5th percentile of the standard normal distribution.

A sensitivity analysis (e.g. tipping-point analysis) will be performed to assess the impact of subjects not evaluable for the primary effectiveness and secondary endpoints and to assess the robustness of the conclusion of the primary analysis. Assuming no loss to follow-up and given the observed number of patients with primary effectiveness endpoint/secondary evaluable for both treatment groups, for all combinations of success/failure for patients with missing data, the endpoints will be evaluated until the point at which the conclusion of the study changes. For each endpoint, a plot with the number of patients with missing values for the Lotus group on the x-axis and the number of patients with missing values for the CoreValve group on y-axis will be provided. There will be shaded regions on the plot which represent the cases where the p-value from the test of non-inferiority is <0.025 and ≥ 0.025 to demonstrate which combinations of successes and failures among the patients missing data change the conclusion of the study.

4 GENERAL STATISTICAL METHODS

4.1 Description of Statistical Methods

Descriptive statistics will be presented on the trial results by treatment group for randomized patients and separately for roll-in patients. For continuous variables, summaries will include the sample size (N), mean, standard deviation, minimum, and maximum. Frequency tables will be used to summarize discrete variables. Treatment groups will be compared for randomized patients using the chi-square test or Fisher's exact test for binary variables and Student's t-test for continuous variables. Alpha-adjustments for multiple comparisons on the additional measures will not be used. The Kaplan-Meier product-limit method will be used to determine rates for time-to-event endpoints. Adverse event and SAE rates will be reported.

4.2 Analysis Sets

The primary safety endpoint, primary effectiveness endpoint, and all additional endpoints up to 1 year will be analyzed on an intent-to-treat (ITT), as-treated, and implanted basis. After 1-year, all analyses will be based on the safety analysis set.

For the ITT analysis set, all subjects who sign the written ICF and are enrolled in the study will be included in the analysis sample, regardless of whether or not the study device was implanted. The primary analysis for the superiority testing of the second hypothesis of the primary effectiveness endpoint and the secondary endpoint will be based on the ITT analysis set.

For the as-treated analysis set, all ITT subjects who received a study device will be included in this analysis sample and analyzed based on the treatment actually received. For example, if a subject is assigned to receive a test device but instead receives a control device, that subject will be considered a control subject for the as-treated analyses of implant subgroups. Note that if a subject receives 2 valves, the subject is assigned to the group corresponding to the first valve received.

For the implanted analysis set, all ITT subjects who have the assigned study device implanted will be included in the analysis sample. The primary analysis for the primary safety endpoint and primary effectiveness endpoint will be based on the implanted analysis set.

For the safety analysis set, all ITT subjects who have a study device implanted regardless of the device and treatment assignment will be included in the analysis sample, which is identical to the as-treated analysis set.

For the intent-to-treat analysis set, events starting from the randomization date will be included in the analysis.

For the as-treated, safety and implanted analysis sets, events starting from the procedure date will be included in the analysis.

4.3 Eligibility of Subjects, Exclusions, and Missing Data

All subjects who are enrolled will be eligible for evaluation. Handling of dropouts and missing data will depend on their frequency and the nature of the outcome measure. The distribution of prognostic factors between subjects with and without data will be examined. Methods to eliminate or minimize bias will be implemented and are described in Section 4.4. Statistical models that account for censored data will be employed in appropriate circumstances (e.g., for time-to-event outcomes). Sensitivity analyses for the primary safety, primary effectiveness, and secondary endpoints, described in Section 3.4, will be conducted to assess the impact of different assumptions on interpretation of the results. Outlier values will be evaluated for their validity. Suspected invalid data will be queried and corrected in the database prior to statistical analysis.

When calculating rates of adverse events, missing and partial dates will be handled as shown below:

Partial Date Description	**Action Taken**
Entire onset date is missing	The procedure date will be used for the onset date.
The month and the day of the month are missing but the year is available	January 1 will be used for the month and day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

Partial Date Description	Action Taken
Day is missing, but the month and year are available	The 1st will be used as the day of the onset date. However, if the imputed date falls before the procedure date, then the procedure date will be used for the onset date.

4.4 Control of Systematic Error/Bias

All subjects who have met the inclusion/exclusion criteria (including a positive recommendation from the Case Review Committee) and have signed the ICF will be eligible for enrollment in the study. The center heart team's assessment of transthoracic echocardiography (TTE) measurements before device placement will then determine subject eligibility for the study.

To control for inter-observer variability, an Echocardiography Core Laboratory will independently analyze echocardiography images collected for each subject during the study. Echocardiographic data obtained from the core laboratory will be used for analyses.

An independent Core Laboratory will centrally assess all CT's and rotational X-ray data for all patients to reduce variability. These analyses will minimize bias and inconsistencies by providing an independent interpretation of all measurements using standard techniques. Angiographic data obtained from the core laboratory will be used for analyses.

Similarly, an Electrocardiography Core Laboratory will independently analyze protocol-required 12-lead ECGs performed for each subject. Data obtained from the ECG core laboratory will be used for analyses.

5 ADDITIONAL DATA ANALYSES

5.1 Other Endpoints/Measurements

5.1.1 Additional Measures

Additional measurements based on the VARC (Leon M, *et al. J Am Coll Cardiol*. 2011;57:253 and Kappetein AP, *et al*. *J Am Coll Cardiol*. 2012;60:1438) endpoints and definitions (definitions in Table 26.2-1 of the protocol; see **Note 1** below) will be collected peri- and post-procedure, at discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, and 1, 2, 3, 4, and 5 years post index procedure, unless otherwise specified below.

- Safety endpoints (see **Note 2** below) adjudicated by an independent Clinical Events Committee (CEC; Section 7.7):
  - Mortality: all-cause, cardiovascular, and non-cardiovascular
  - Stroke: disabling and non-disabling
  - Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure)
  - Bleeding: life-threatening (or disabling) and major
  - Acute kidney injury (≤7 days post index procedure): based on the AKIN System Stage 3 (including renal replacement therapy) or Stage 2

- Major vascular complication
- Repeat procedure for valve-related dysfunction (surgical or interventional therapy)
- Hospitalization for valve-related symptoms or worsening CHF (NYHA class III or IV)
- New permanent pacemaker implantation resulting from new or worsened conduction disturbances (definitions in Table 26.2-1 of the protocol; see **Note 3** below)
- New onset of atrial fibrillation or atrial flutter
- Coronary obstruction: periprocedural (≤72 hours post index procedure)
- Ventricular septal perforation: periprocedural (≤72 hours post index procedure)
- Mitral apparatus damage: periprocedural (≤72 hours post index procedure)
- Cardiac tamponade: periprocedural (≤72 hours post index procedure)
- Prosthetic aortic valve malpositioning, including valve migration, valve embolization, or ectopic valve deployment
- Transcatheter aortic valve (TAV)-in-TAV deployment
- Prosthetic aortic valve thrombosis
- Prosthetic aortic valve endocarditis

- Device performance endpoints peri- and post-procedure:
  - Successful vascular access, delivery and deployment of the study valve and successful retrieval of the delivery system
  - Successful retrieval of the study valve if retrieval is attempted
  - Successful repositioning of the study valve if repositioning is attempted (see **Note 4** below)
  - Grade of aortic valve regurgitation: paravalvular, central and combined; the overall distribution of paravalvular aortic regurgitation (none, trace/trivial, mild, moderate, severe) will be determined as well as the percentage of subjects who have moderate or severe paravalvular regurgitation and the percentage of subjects who have mild, moderate or severe paravalvular regurgitation
- Clinical procedural success (30 days), defined as implantation of the study device in the absence of death, disabling stroke, major vascular complications, and life-threatening or major bleeding
- Procedural success (30 days), defined as absence of procedural mortality, correct positioning of a single transcatheter valve into the proper anatomical location , intended performance of the study device (effective orifice area [EOA] >0.9 cm^2 for BSA <1.6 m^2 and EOA >1.1 cm^2 for BSA ≥1.6 m^2 plus either a mean aortic valve gradient <20 mm Hg or a peak velocity <3m/sec, and no moderate or severe prosthetic valve aortic regurgitation) plus no serious adverse events at 30 days
- Additional indications of prosthetic aortic valve performance as measured by transthoracic echocardiography (TTE; see **Note 5** below) and assessed by an independent core laboratory, including effective orifice area, mean and peak aortic gradients, peak aortic velocity, and grade of aortic regurgitation (see **Note 6** below).
- Modified device success (30 days), reported for subjects randomized and implanted with an assigned study device and defined as follows: absence of mortality with the originally implanted transcatheter valve in the proper anatomical location, no additional aortic valve procedures, and with the intended performance of the prosthetic valve (either a mean aortic valve gradient <20 mm Hg or a peak velocity <3m/sec with no moderate or severe prosthetic valve aortic regurgitation)

- Functional status as evaluated by the following:
  - 5-m gait speed test (at 1 year compared to baseline)
  - New York Heart Association (NYHA) classification
- Neurological status (see **Note 7** below) as determined by the following:
  - Neurological physical exam by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner at discharge and 1 year
  - National Institutes of Health Stroke Scale (NIHSS) at discharge and 1 year
  - Modified Rankin Scale (mRS) at all time points
- Health status as evaluated by Kansas City Cardiomyopathy and SF-12 Quality of Life (QOL) questionnaires at baseline; 1 and 6 months; and 1, 3, and 5 years
- Resource utilization associated with the procedure and/or follow-up.

Note 1: The most current VARC definitions and endpoints available at the beginning of the trial were used.

Note 2: The VARC-2 safety composite at 30 days includes all-cause mortality, all stroke (disabling and non-disabling), life-threatening bleeding, acute kidney injury (Stage 2 or 3), coronary artery obstruction requiring intervention, major vascular complication, and repeat procedure for valve-related dysfunction. The VARC-2 time-related valve safety composite includes structural valve deterioration (valve-related dysfunction requiring repeat procedure [TAVR or SAVR]), prosthetic valve endocarditis, prosthetic valve thrombosis, thromboembolic events (e.g., stroke), and VARC bleeding (unless clearly unrelated to valve therapy based on investigator assessment)

Note 3: Clinical indications for permanent pacemaker implantation are outlined in the ACCF/AHA/HRS Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities (Epstein AE, *et al. J Am Coll Cardiol* 2013;61:e6). Permanent pacemaker implantation should generally be performed only for accepted Class I indications.

Note 4: For the Lotus Valve System, repositioning may be achieved with partial or full resheathing of the valve; the proportion of subjects with partial valve resheathing and full valve resheathing will be determined.

Note 5: At least 1 echocardiogram must be obtained before discharge or 7 days (whichever comes first); if multiple echocardiographic studies are performed prior to discharge and within 7 days of the procedure, the latest study performed will be used for analysis.

Note 6: The VARC-2 clinical efficacy composite (after 30 days) includes all-cause mortality, all stroke, required hospitalization for valve-related symptoms or worsening CHF (NYHA class III or IV), and prosthetic heart valve dysfunction (mean aortic valve gradient ≥20 mmHg, effective orifice area ≤0.9-1.1 cm and/or Doppler velocity index [DVI] <0.35, AND/OR moderate or severe prosthetic valve aortic regurgitation [per VARC definition]). The need for hospitalization associated with valve-related symptoms or worsening CHF serves as a basis for calculation of a "days alive outside the hospital" endpoint. This includes heart failure, angina, or syncope due to aortic valve disease requiring intervention or intensified medical management; clinical symptoms

of CHF with objective signs including pulmonary edema, hypoperfusion, or documented volume overload AND administration of intravenous diuresis or inotropic therapy, performance of aortic valvuloplasty, institution of mechanical support (intra-aortic balloon pump or ventilation for pulmonary edema), or hemodialysis for volume overload; clear documentation of anginal symptoms AND no clinical evidence that angina was related to coronary artery disease or acute coronary syndrome; documented loss of consciousness not related to seizure or tachyarrhythmia.

Note 7: For subjects diagnosed with a neurological event (e.g., stroke, transient ischemic attack), a neurological physical exam (conducted by a neurologist, neurology fellow, neurology physician assistant, or neurology nurse practitioner), NIHSS assessment, and mRS must be performed after the event. Additionally, mRS must be administered at 90±14 days post-neurological event (see Table 11.1-1 of the protocol). If a subject who has not received a study device (investigational or control) experiences a neurological event within the first 1 year after the index procedure, mRS must be performed on that subject after the event and at 90±14 days post-neurological event and the results must be reported to the Sponsor.

Data will be summarized as described in Section 4.1.

5.2 Interim Analyses

5.2.1 Analysis for Trial Discontinuation

There are no planned interim analyses for stopping the trial early for effectiveness or futility.

5.2.2 Administrative Analysis

An administrative analysis based on 30-day data for the implanted patients in the first 300 randomized (ITT) patients will be performed for review as required by designated regulatory agencies after these 300 patients have completed their 30-day follow-up visits. This analysis will be conducted by an independent statistician from a contract research organization (CRO; Quintiles) and will only be distributed to designated regulatory agencies and limited internal Boston Scientific personnel preparing for the submission. The study team executing the trial will remain blinded to the results from this analysis, which will not be disclosed publicly.

This administrative analysis will not include any analyses of the primary and secondary endpoints and thus will not affect the type I error of the analyses of those endpoints.

5.2.2.1 Administrative Analysis **Hypothesis testing**

Hypothesis: Moderate or greater aortic regurgitation rate (includes central plus paravalvular regurgitation) as assessed by the echocardiograph core lab at 30 days for the Lotus Valve group is non-inferior to that for the CoreValve group for implanted patients in the first 300 randomized patients.

If non-inferiority of the Lotus Valve group compared to the CoreValve group is demonstrated, then the superiority testing of the Lotus Valve group compared to the CoreValve group will be carried out.

Non-inferiority Testing:

The null and alternative hypotheses for the 30-day aortic regurgitation rate are as follows:

H_0: $P_{30Day\ All\ AR\_Lotus} - P_{30Day\ All\ AR\_Control} \geq \Delta$ (Inferior)

H_1: $P_{30Day\ All\ AR\_Lotus} - P_{30Day\ All\ AR\_Control} < \Delta$ (Non-inferior)

where $P_{30Day\ All\ AR\_Lotus}$ and $P_{30Day\ All\ AR\_Control}$ correspond to the rates of moderate or greater aortic regurgitation (includes central plus paravalvular) at 30 days for the Lotus Valve group (test) and the CoreValve group (control), respectively, and Δ (delta) is the non-inferiority margin.

Sample Size Parameters for this 30-day aortic regurgitation (includes central plus paravalvular) **rate non-inferiority testing:**

- Expected Lotus Valve (test) rate $P_{30Day\ All\ AR\_Lotus} = 1.2\%$
- Expected CoreValve (control) rate $P_{30Day\ All\ AR\_Control} = 12\%$ (average from CoreValve IDE High Risk [HR] and Extreme Risk [ER] study data)
- Non-inferiority margin (Δ) = 2%
- Test significance level (α) = 0.05 (1-sided)
- Test : Control ratio = 2 : 1
- Power ($1-\beta$) $\geq$ 0.98 using Farrington-Manning test
- Number of evaluable subjects = 240 (160 test and 80 control)
- Expected rate of attrition = 20%
- Number of subjects randomized = 300

A Farrington-Manning standardized test will be used to test the one-sided hypothesis of non-inferiority in the difference between the rates of the two treatment groups. If the *P* value from the Farrington-Manning standardized test is <0.05, the moderate or greater aortic regurgitation (central plus paravalvular) rate at 30 days for the Lotus Valve will be concluded to be non-inferior to the CoreValve rate. This corresponds to the one-sided 95% upper confidence bound on the difference between treatment groups (Lotus Valve minus CoreValve) in the moderate or greater aortic regurgitation at 30 days being less than the non-inferiority margin.
***Note:** Moderate or greater indicates a regurgitation grade of moderate or severe.

Superiority Testing:
The null and alternative hypotheses for the 30-day aortic regurgitation rate are as follows:

H_0: $P_{30Day\ All\ AR\_Lotus} = P_{30Day\ AR\_Control}$

H_1: $P_{30Day\ All\ AR\_Lotus} \neq P_{30Day\ AR\_Control}$

where $P_{30Day\ All\ AR\_Lotus}$ and $P_{30Day\ AR\_Control}$ correspond to the rates of moderate or greater aortic regurgitation (includes central plus paravalvular) at 30 days for the Lotus Valve group (test) and the CoreValve group (control), respectively.

Sample Size Parameters for this 30-day moderate or greater aortic regurgitation (includes central plus paravalvular) rate analysis:

- Expected Lotus Valve (test) rate $P_{30Day\ All\ AR\_Lotus}$ = 1.2%
- Expected CoreValve (control) rate $P_{30Day\ All\ AR\_Control}$ = 12.0% (average from CoreValve IDE HR and ER study data)
- Test significance level (α) = 0.05 (2-sided)
- Test : Control ratio = 2 : 1
- Power (1-β) = 0.91
- Number of evaluable subjects = 240 (160 test and 80 control)
- Expected rate of attrition = 20%
- Number of subjects randomized = 300

If the *P* value from the chi-square test is <0.05, and the aortic regurgitation rate at 30 days for the Lotus Valve group is less than the rate of the CoreValve group, the aortic regurgitation (includes central plus paravalvular) rate at 30 days for the Lotus Valve group will be concluded to be superior to that of the CoreValve group.

Other analyses

Descriptive statistics will be used to summarize the following 30-day endpoints for the Lotus and CoreValve groups for the first 300 randomized (ITT) patients: all-cause mortality, disabling stroke, major bleeding events, and major vascular complications.

5.3 Subgroup Analyses

Subgroup analyses will be performed in the following subgroups:

- gender (male, female)
- surgical risk (high, extreme)
- region (North America, outside North America)

No adjustments for multiple comparisons will be made. Additional analyses may be performed as appropriate.

5.4 Justification of Pooling

The analyses will be presented using data pooled across regions, surgical risk (high or extreme) as well as by center for the primary safety, primary effectiveness, and secondary endpoints. An assessment of the poolability of subjects across centers, regions, and surgical risk group will be made using logistic regression to determine if there is a relationship between each factor and the primary safety, primary effectiveness, and secondary endpoints.

Main effects for the factor (site, region, surgical risk group) and treatment and the interaction of the factor by treatment will be included in separate logistic regression models with primary safety, /primary effectiveness, and secondary endpoints as the outcome. If the p-value for the

coefficient for the factor by treatment interaction is ≥0.15, it can be concluded that the treatment effect is not significantly different across the different levels of the factor, and the data can be pooled across that factor.

In the analysis to justify pooling across centers, the centers with fewer than 6 subjects enrolled in the study will be combined into "virtual centers" based on geographic region so that "virtual centers" have ≥6 subjects in the study but no more than the largest enrolling center.

5.5 Multivariable Analyses

Univariate and multivariate analyses will be performed to assess the effect of potential predictors on the primary safety, primary effectiveness, and secondary endpoints.

Univariate and multivariate analyses will be performed to assess possible predictors of the primary safety, primary effectiveness, and secondary endpoints. Possible predictors (see below) will be modeled univariately; factors from the univariate models with p≤0.20 will also be modeled multivariately using a stepwise procedure in a logistic regression model. The significance level thresholds for entry and exit of independent variables into the multivariate model will be set at 0.1.

From the final models, predictors will be listed in ascending order of p-value. Univariate analyses will be performed overall as well as separately for each treatment group for randomized patients.

The following variables will be analyzed as possible predictors of primary safety, primary effectiveness, and secondary endpoints:

Category	**Possible Predictors**
Treatment	Group (CoreValve=0, Lotus=1)
Demographics	Sex, age, race (Caucasian)
Baseline Characteristics	STS score, EuroSCORE, CHF, previous TIA or CVA, history of renal disease, medically-treated diabetes, hyperlipidemia, hypertension, current smoking at baseline, history of COPD, history of CAD, history of MI, history of CHF, prior balloon aortic valvuloplasty, history of atrial fibrillation, 5‑meter walk >6 seconds, Katz ADL score of 3/6 or less, body mass index <21, wheelchair bound, unable to live independently
Baseline Echocardiographic Characteristics (Core Lab)	LVEF, aortic valve area, mean pressure gradient, , Doppler velocity index
Baseline Computed Tomography (CT) (Core Lab)	Annulus area, LVOT area, annular calcification, LVOT calcification

Category	Possible Predictors
Peri-Procedural Variables	Ratio of pre-dilation balloon diameter to annulus diameter (derived from area), post-dilation performed, repositioning performed, retrieval performed

5.6 Other Analyses

5.6.1 Baseline Characteristics

Baseline data will be summarized to assess subject demographics, clinical history, risk factors, and pre-procedure characteristics. Data will be summarized as described in Section 4.1.

5.6.2 Post-Procedure Endpoints

Post-procedure information will be collected at regularly scheduled follow-up examinations as detailed in the clinical trial schedule in the protocol. Data will be summarized as described in Section 4.1.

5.6.3 Subject Disposition

Subject disposition (e.g., number completing the study, number lost-to-follow-up) will be summarized with frequency tables.

5.6.4 Time-to-Event Methods

The Kaplan-Meier product-limit method will be used to estimate event rates for time-to-event endpoints. Kaplan-Meier plots of time-to-event endpoints will be constructed.

5.7 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the analyses will be documented in an amended statistical analysis plan approved before performing the analyses. Changes from the planned statistical methods after performing the analyses will be documented in the clinical study report along with a reason for the deviation.

6 Validation

All clinical data reports generated per this plan will follow the Global WI: Clinical Data Reporting Validation (PDM 90702587).

7 Programming Considerations

7.1 Statistical Software

Statistical data review will be performed by the sponsor. Statistical analyses will be performed using SAS System software, version 9.2 or later (Copyright © 2000 SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513, USA. All rights reserved).

7.2 Format of Output

Results of analysis will be output programmatically to Word documents from SAS with no manual intervention. All output for the final statistical report will be in the form of a Word document containing tables, figures, graphs, and listings, as appropriate.

7.3 Rules and Definitions for Calculated Variables

7.3.1 Transthoracic Echocardiographic (TTE) Variables

Transthoracic echocardiograms will be assessed at each of the following visits: screening, 1 day post-procedure, discharge or 7 days post-procedure (whichever comes first), 30 days, 6 months, and then annually for up to 5 years post-procedure.

One transthoracic echocardiographic study will be performed for each visit. If multiple transthoracic echocardiographic studies are performed for the same visit, the latest study performed for each visit will be used for analysis.

7.3.1.1 Body Mass Index (BMI)

Valid Data Sources

- Assessment Form (Weight, Weight unit, Height, Height unit)
- Diss_FU_Assessment Form (Weight, Weight unit, Height, Height unit)

Valid Data Points

- Weight
- Weight unit
- Height
- Height unit

Analysis approach: Body Mass Index is calculated for each visit.

Weight (Kg) = Weight (lbs) / 2.20462262.
Height (cm) = Height (in) / 0.393700787

$$BMI = \frac{Weight\,(Kg) \times 10000}{\left(Height\,(cm)\right)^2}$$

7.3.1.2 Body Surface Area (BSA)

Valid Data Sources

- Assessment Form (Weight, Weight unit, Height, Height unit)

- Diss_FU_Assessment Form (Weight, Weight unit, Height, Height unit)

Valid Data Points

- Weight
- Weight unit
- Height
- Height unit

Analysis approach: Body Surface Area (BSA) is calculated using the following formula:

$$BSA(m^2) = \sqrt{(Height(cm) x Weight(Kg))/3600}$$

7.3.1.3 Indexed Aortic Valve Area (iAVA) or Indexed Effective Orifice Area (iEOA).

Effective Orifice Area (EOA) is synonymous with Aortic Valve Area (AVA). Both terms will be used in this SAP to easily follow either the protocol or the CRFs as reference documents.

Valid Data Sources

- Assessment Form (Weight, Weight unit, Height, Height unit)
- Diss_FU_Assessment Form (Weight, Weight unit, Height, Height unit)
- Echo Core Lab Form (AVA [TVI])

Valid Data Points

- Weight, Weight unit, Height, Height unit
- AVA (TVI)

Analysis approach:

Indexed Aortic Valve Area (iAVA) or Indexed Effective Orifice Area (iEOA) is calculated for each visit.

iAVA(cm2/m2) = iEOA(cm^2/m2) = AVA (TVI) (cm^2) / BSA (m^2),

where AVA (TVI) is the aortic valve area for a specific visit and BSA is the body surface area (calculated in Section 7.3.1.2) for the same specific visit under analysis.

7.3.2 ECG Variables

The following algorithm will be used to determine the ECG diagnosis codes for each time-point and subject.

If baseline ECG, then is ECG interpretable?

If No, then:

Rhythm/AV Conduction Abnormalities = Uninterpretable
IV Conduction Abnormalities = Uninterpretable
New Major ST-T Abnormalities = Uninterpretable

If Yes, then:

Rhythm/AV Conduction Abnormalities = 1.1, 1.2, 1.3, 1.4
IV Conduction Abnormalities = 2.1, 2.2, 2.3, 2.4
New Major ST-T Abnormalities = 4.1, 4.2, 4.3, 4.4

If not baseline ECG, then is ECG interpretable?

If No, then:

Rhythm/AV Conduction Abnormalities = Uninterpretable
IV Conduction Abnormalities = Uninterpretable
New Major ST-T Abnormalities = Uninterpretable

If Yes, then:

If No change is checked, then
Rhythm, IV Conduction, Major ST-T = their values from the most recent interpretable ECG

If No change is not checked, then

- Is a New Rhythm/AV Conduction Abnormality?
  - If Yes, then Rhythm = 1.1, 1.2, 1.3, 1.4
  - If No, then Rhythm = their values from the most recent interpretable ECG
- Is a New IV Conduction Abnormality?
  - If Yes, then IV Conduction = 2.1, 2.2, 2.3, 2.4
  - If No, then IV Conduction = their values from the most recent interpretable ECG
- Is a New Major ST-T Abnormality?
  - If Yes, then Major ST-T = 4.1, 4.2, 4.3, 4.4
  - If No, then IV Conduction = their values from the most recent interpretable ECG.

7.3.3 Days to Last Follow-up

Valid Data Sources

- Adverse Event Form
- Hospitalization Form
- Procedure Form

- Date of Visit Form
- CEC data.

Valid Data Points

- Adverse event date is “Onset date” from the Adverse Event Form.
- Admission and Discharge dates are “Admission date” and “Discharge date” from the Hospitalization Form.
- Index procedure date is “Date of Procedure” from the Procedure Form.
- Randomization date is “Date of Randomization” from the Randomization Form
- Follow-up visit date is “Date of Visit” from the Date of Visit Form at each of the visits (discharge or 7 days post-procedure, 30 days, 6 months, and 1 to 5 years post index procedure).
- CEC event date – date of event as adjudicated by the CEC.

Last follow-up date will be the latest of the following dates for each subject:

adverse event onset date,
admission and discharge dates from hospitalization,
index procedure date,
randomization date
discharge or follow-up visit date, and
CEC event date.

Follow-up days will be calculated for as-treated and implanted analysis sets

Day 0 is the index procedure date.Days to last follow-up = last follow-up date - index procedure date. Days to (event or last known status) = (event or status) date – index procedure date.

Follow-up days will be calculated for intent-to-treat analysis set

Day 0 is the randomization date.

Days to last follow-up = last follow-up date - randomization date.

Days to (event or last known status) = (event or status) date - randomization date.

7.3.4 Variable “Days alive outside the hospital”

Valid Data Sources

- Adverse Event Form.
- Hospitalization Form.
- Procedure Form.
- Randomization Form

- Date of Visit Form
- End of Study Form.

Analysis approach: Days alive outside the hospital is calculated for each visit.

$$Days\ alive\ within\ the\ hospital = \sum_{\substack{All\ Hospitalizations\ through \\ the\ visit\ under\ study}} (Dischage\ date - Admission\ date),$$

$$Days\ alive\ outside\ the\ hospital = Days\ to\ last\ \ follow up - Days\ alive\ within\ the\ hospital,$$

where *Days to last follow-up* is calculated as described in Section 7.3.3 at each visit under study.

7.3.5 Event Rates

7.3.5.1 Time-to-event Endpoints

This section describes the calculation of events for the safety endpoints adjudicated by the CEC as described in Section 7.7. Time-to-event safety endpoints are events that can occur at any time during the course of the study, for example all-cause mortality. For time-to-endpoints, the date of the event is expected to be known and the days from the index procedure can be calculated. In some cases, the exact date of the event will not be known however partial information should be available, e.g. missing date of month. Binary endpoints measured at pre-specified intervals during the study do not count as time-to-events endpoints. Examples of non-time-to-event binary endpoints are NYHA Class II at 30 days and aortic regurgitation at 12 months.

For the calculation of event rates for the primary safety, primary effectiveness, and secondary endpoints, see Sections 7.4, 7.5, and 7.6, respectively.

Binary event rates will be calculated only up to 1 year. After 1 year, events rates for time-to-event endpoints will be calculated using the Kaplan-Meier product-limit method.

The calculation of binary rates to 1 year will be the same for any endpoint and time point in regards to the appropriate numbers of days as indicated below in Table 1.1 for as-treated and implanted analysis sets and Table 1.2 for ITT analysis set, respectively. As an example, for 30 days binary endpoint in the as-treated and implanted analysis sets, the event must have occurred within 30 days of procedure (maximum days to event from procedure) and the subject must have ≥ 23 days of follow-up (days for adequate follow-up from procedure as shown in Table 1.1).

Table 1.1 Days Post-procedure to Event and for Adequate Follow-up for As-Treated and Implanted Analysis Sets.

Follow-up Visit	Maximum Days to Event from Procedure*	Days for Adequate Follow-up from Procedure**
30 Days	30	23
6 Months	180	150
12 Months	365	335
2 Years	730	NA

Follow-up Visit	Maximum Days to Event from Procedure*	Days for Adequate Follow-up from Procedure**
3 Years	1095	NA
4 Years	1460	NA
5 Years	1825	NA

* Target date for the follow-up visit.
** Start of the follow-up visit window. Not used after the 12-month follow-up

Table 1.2 Days Post-randomization to Event and for Adequate Follow-up for ITT Analysis Set.

Follow-up Visit	Maximum Days to Event from Randomization*	Days for Adequate Follow-up from Randomization**
30 Days	30	23
6 Months	180	150
12 Months	365	335
2 Years	730	NA
3 Years	1095	NA
4 Years	1460	NA
5 Years	1825	NA

* Target date for the follow-up visit.
** Start of the follow-up visit window. Not used after the 12-month follow-up

Rates in this section are described for all analysis sets. If the variable is calculated based on the ITT analysis set, "all subjects" refers to all subjects enrolled/randomized. If the variable is calculated based on the as-treated, implanted or safety analysis set, "all subjects" refers to all subjects within the respective analysis set.

Binary event rates (proportions) are calculated on a per subject basis.

All events through discharge or 7 days post-procedure (whichever comes first) are considered in-hospital. Event rates through discharge or 7 days post-procedure (whichever comes first) are calculated as the proportion of subjects who experience the specified event from index procedure or randomization through day of discharge or 7 days post-procedure (whichever comes first) out of all subjects in the as-treated and implanted analysis sets or ITT analysis set, respectively.

Event rates through a follow-up visit through 1 year are calculated using the following for inclusion in the denominator and numerator:

- Denominator:

  Subjects in the specific analysis set count in the denominator with one of the following:

  - ***Subject experiences any CEC adjudicated event from Section 7.7 ≤ maximum number of days as specified in Table 1.1 and Table 1.2, as appropriate or***
  - ***date of last follow-up ≥ days for adequate follow-up post-procedure from Table 1.1 and Table 1.2, as appropriate:***

- Numerator:

Subjects in the specific analysis set count in the numerator if the subject experiences specified event ≤ maximum number of days as specified in Table 1.1 and Table 1.2, as appropriate.

Event rates from a previous visit to a current follow-up visit date are calculated as the proportion of "subjects in the analysis set who experience the specified event after the maximum number of days in the previous visit and through the maximum number of days of the current follow-up visit as specified in Table 1.1 and 1.2, as appropriate" out of "all subjects in the analysis set who have adequate follow-up as specified in Table 1.1 and 1.2, as appropriate or have experienced the specified event in the time interval".

7.3.5.2 Other Binomial Endpoints

Binomial endpoints that are not time based will be presented as binary rates. Such endpoints include any binary measures that collected at baseline or at pre-specified intervals during the study such, for example medically-treated diabetes at baseline and NYHA Class II at 30 days.

For categorical variables, "unknown" and "not evaluated" responses and missing values will not be counted in rate denominators.

7.4 Calculation of Primary Safety Endpoint Rate

The Primary Safety Endpoint of all-cause mortality, all stroke, acute kidney injury (stage 2 or 3), life-threatening and major bleeding, and major vascular complications at 30 days is calculated on an ITT, as-treated, and implanted basis.

Valid Data Sources

- Procedure Form (Procedure date)
- Randomization Form
- CEC Adjudication Forms at 30 days (death, stroke, kidney injury stage 2 or 3, life-threatening or major bleeding, major vascular complication)
- Case report forms (CRFs) used in determining length of follow-up (see Section 7.3.3).

Valid Data Points

- Date of procedure.
- Date of randomization
- Date of death.
- Date of any stroke
- Date of acute kidney injury (stage 2 or 3)
- Date of life-threatening or major bleeding
- Date of major vascular complication
- Date of last follow-up (Section 7.3.3).

Analysis approach

- Denominator for as-treated and implanted analysis sets:

  Subjects in the analysis set count in the denominator with one of the following:

- date of death ≤ 30 days post-procedure.
- date of any stroke ≤ 30 post-procedure.
- date of acute kidney injury (stage 2 or 3) ≤ 30 post-procedure.
- date of life-threatening or major bleeding ≤ 30 post-procedure.
- date of major vascular complications ≤ 30 post-procedure.
- date of last follow-up ≥ 23 days post-procedure.

- Numerator for as-treated and implanted analysis sets

  Subjects in the analysis set count in the numerator with <u>one</u> of the following:

  - Subject experiences death ≤ 30 days post-procedure.
  - Subject experiences any stroke ≤ 30 post-procedure.
  - Subject experiences acute kidney injury (stage 2 or 3) ≤ 30 post-procedure.
  - Subject experiences life-threatening or major bleeding ≤ 30 post-procedure.
  - Subject experiences major vascular complication ≤ 30 post-procedure.

- Denominator for ITT analysis set:

  Subjects in the analysis set count in the denominator with one of the following:

  - date of death ≤ 30 days post-randomization,
  - date of any stroke ≤ 30 post-randomization,
  - date of acute kidney injury (stage 2 or 3) ≤ 30 post-randomization,
  - date of life-threatening or major bleeding ≤ 30 post-randomization,
  - date of major vascular complications ≤ 30 post-randomization.
  - date of last follow-up ≥ 23 days post-randomization.

- Numerator for ITT analysis set

  Subjects in the analysis set count in the numerator with <u>one</u> of the following:

  - Subject experiences death ≤ 30 days post randomization,
  - Subject experiences any stroke ≤ 30 days post randomization,
  - Subject experiences acute kidney injury (stage 2 or 3) ≤ 30 days post randomization,
  - Subject experiences life-threatening or major bleeding ≤ 30 days post randomization,
  - Subject experiences major vascular complication ≤ 30 days post randomization.

Note that events occurring >30 days within the visit window of 30+7 days will not be included in the 30-day endpoint analysis.

7.5 Calculation of Primary Effectiveness Endpoint Rate

The Primary Effectiveness Endpoint of all-cause mortality, disabling stroke, and moderate or severe paravalvular aortic regurgitation (core lab assessment) at 12 months is calculated on an ITT, as-treated, and implanted basis.

Valid Data Sources

- Procedure Form (Procedure date)
- Randomization Form (Randomization date)
- CEC Adjudication Forms at 1 year (Death, Disabling Stroke)
- Echocardiography Forms at 6 months and 1 year (Aortic Regurgitation)
- Case report forms (CRFs) used in determining length of follow-up (see Section 7.3.3).

Valid Data Points

- Date of procedure.
- Date of randomization
- Date of death.
- Date of disabling stroke
- Moderate or greater paravalvular aortic regurgitation present or not from the 12-month echocardiography form (use 6-month echocardiography form if aortic regurgitation is missing at 12 months or there is no 12 month echocardiography form and the patient has not died ≤365 days post-procedure).
- Date of last follow-up (Section 7.3.3).

Analysis approach

- Denominator for as-treated and implanted analysis sets:

  Subjects in the analysis set count in the denominator with <u>both</u> of the following:

  - *Yes or No for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes or No for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-procedure), and*
  - one of the following:
    - *date of death ≤365 days post-procedure.*
    - *date of disabling stroke ≤365 days post-procedure.*
    - *date of last follow-up ≥335 days post-procedure.*

- Numerator for as-treated and implanted analysis sets:

  Subjects in the analysis set count in the numerator with <u>one</u> of the following:

- *Subject experiences death ≤365 days post-procedure.*
- *Subject experiences disabling stroke ≤365 post-procedure.*
- *Subject has Yes for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-procedure)*

- Denominator for ITT analysis sets:

  Subjects in the analysis set count in the denominator with <u>both</u> of the following:

  - *Yes or No for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes or No for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-radomization), and*
  - one of the following:
    - *date of death ≤365 days post-randomization.*
    - *date of disabling stroke ≤365 days post-randomization.*
    - *date of last follow-up ≥335 days post-randomization.*

- Numerator for ITT analysis sets:

  Subjects in the analysis set count in the numerator with <u>one</u> of the following:

  - *Subject experiences death ≤365 days post-randomization.*
  - *Subject experiences disabling stroke ≤365 post-randomization*
  - *Subject has Yes for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-randomization)*

Note that deaths or disabling strokes occurring >365 days within the visit window of 365+45 days will not be included in the endpoint analysis.

7.6 Calculation of Secondary Endpoint Rate

The Secondary Endpoint of moderate or greater paravalvular aortic regurgitation (core lab assessment) at 12 months is calculated on an ITT, as-treated, and implanted basis.

Valid Data Sources

- Echocardiography Forms at 6 months and 1 year (Aortic Regurgitation).

Valid Data Points

- Moderate or greater paravalvular aortic regurgitation present or not from the 12-month echocardiography form (use 6-month echocardiography form if aortic regurgitation is missing at 12 months or there is no 12 month echocardiography form and the patient has not died ≤365 days post-procedure).

Analysis approach

- Denominator:

  Subjects in the analysis set count in the denominator with the following:

  - *Yes or No for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes or No for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-procedure).*

- Numerator

  Subjects in the analysis set count in the numerator with the following:

  - *Subject has Yes for moderate or greater paravalvular aortic regurgitation on the 12-month echocardiography form (or Yes for moderate or greater paravalvular aortic regurgitation on the 6-month echocardiography form when paravalvular aortic regurgitation is missing on the 12-month echocardiography form or the 12-month echocardiography is missing and the patient has not died ≤365 days post-procedure)*

7.7 Clinical Events Committee (CEC)

A CEC will be used in this study. A CEC is an independent group of individuals with pertinent expertise that reviews and adjudicates important endpoints and relevant adverse events reported by study Investigators.

CEC events (definitions in Table 26.2-1 of the protocol) to be reported are:

- Mortality: all-cause, cardiovascular, and non-cardiovascular
- Stroke: disabling and non-disabling
- Myocardial infarction (MI): periprocedural (≤72 hours post index procedure) and spontaneous (>72 hours post index procedure)
- Bleeding: life-threatening (or disabling) and major
- Acute kidney injury (≤7 days post index procedure): based on the AKIN System Stage 3 (including renal replacement therapy) or Stage 2
- Major vascular complication
- Repeat procedure for valve-related dysfunction (surgical or interventional therapy)
- Hospitalization for valve-related symptoms or worsening CHF (NYHA class III or IV)

- New permanent pacemaker implantation resulting from new or worsened conduction disturbances (definitions in Table 26.2-1 of the protocol)
- New onset of atrial fibrillation or atrial flutter
- Coronary obstruction: periprocedural (≤72 hours post index procedure)
- Ventricular septal perforation: periprocedural (≤72 hours post index procedure)
- Mitral apparatus damage: periprocedural (≤72 hours post index procedure)
- Cardiac tamponade: periprocedural (≤72 hours post index procedure)
- Prosthetic aortic valve malpositioning, including valve migration, valve embolization, or ectopic valve deployment
- Transcatheter aortic valve (TAV)-in-TAV deployment
- Prosthetic aortic valve thrombosis
- Prosthetic aortic valve endocarditis

CEC periprocedural events are events that occur ≤72 hours after index procedure. The CEC will make the final adjudication and classification of all events mentioned above per the CEC charter, and the CEC determinations will supersede the site-reported data in all analyses of the events mentioned above.

7.8 Analysis of Site-Reported Serious and Non-Serious Adverse Events

Subject-based event rates will be calculated at various time points based on all events reported by the site regardless of whether or not they are ultimately adjudicated by the CEC. Rates will be calculated on an ITT basis through 1 year and on a safety basis from 2 years through the 5-year follow-up.

Non-Serious Adverse Events will be reported from the time of enrollment through 1-year follow-up.

Serious Adverse Events will be reported from the time of enrollment through termination of the study.

8 Revision History

Revision Number	Section	Change	Reason for Change
AA	All	Original version	
AB	4.2, 5.2,7.3.3, 7.3.4, 7.4 and 7.5	Add the following details about the administrative analysis: • Updated neurological status and control device in section 1 for Protocol summary • who will receive the analysis • state that the analysis will not affect the type I error for the primary and secondary endpoints • state that descriptive statistics will be used to summarize endpoints for treatment groups. • Events collecting date for ITT analysis set • the randomization date as valid date if a subject wasn't implanted in section 7.3.3, 7.3.4, 7.4 and 7.5	Addressing comments from the FDA