SMall Annuli Randomized To Evolut™ or SAPIEN™ Trial (SMART)

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Statistical Analysis Plan: 13Nov2023

Medtronic **Statistical Analysis Plan**	
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1. Version History

Version	Summary of Changes	Author(s)/Title
1.0	• Not Applicable, New Document	[redacted]
2.0	• Changed SAP template to current version C. • Changes made for protocol version 3.0 and 4.0 as follows: ○ Added Evolut™ FX throughout, where applicable ○ Primary endpoint for heart failure rehospitalization updated throughout ○ References to VARC-2 removed throughout ○ Updated units for BMI throughout ○ Section 7.11 Stress Echocardiogram Sub-study: added pre-specified stress echocardiogram parameters for analysis • Additional clarifications to planned analyses: ○ Section 7.1.3.1 Screening Population: corrected "exited prior to the TAVR procedure" to "exited prior to randomization" ○ Section 7.2 General Methodology: clarified that data post-explant will be excluded in analysis of echo data ○ Section 7.3: Center Pooling: Removed requirement for pseudo-sites and added analysis by geographic region ○ Section 7.9.1 Primary Objective #1: Primary Safety Endpoint: Added sensitivity analyses ○ Section 7.9.4 Non-Powered Secondary Objectives: For device success endpoint corrected "discharge" to "30 days" and corrected "large sample confidence interval" to "Exact binomial confidence interval". ○ Section 7.9.3.5 and Section 7.9.4 specified last observation carried forward for BSA and BMI for analysis of PPM outcome. ○ Section 7.10 Safety Evaluation: added summary of serious adverse events by event term and listing of device deficiencies ○ Section 7.12 Changes to Planned Analysis: added justification for change to screening population	[redacted]
3.0	• Changed naming of co-primary endpoints for consistency with terminology in protocol:	[redacted]

Version	Summary of Changes	Author(s)/Title
	○ All occurrences of "Primary Safety Endpoint" updated to say "Clinical Outcome Composite" ○ All occurrences of "Primary Efficacy Endpoint" renamed to say "Valve Function Composite" • Additional clarifications to planned analyses: ○ Section 7.3: edited region poolability analysis to be US/Canada (combined) vs EMEA ○ Section 7.9.2 Primary Objective #2: Valve Function Composite Endpoint – added more details about how composite endpoint will be derived for analysis ○ Section 7.9.2 Primary Objective #2: Valve Function Composite Endpoint – added supportive and sensitivity analyses to examine robustness of the primary result ○ Section 7.9.4 Non-Powered Secondary Objective #1: added clarification that Device Success is analyzed in the AT set only for patients in whom delivery catheter was introduced ○ Section 7.9.4 Non-Powered Secondary Objective #4: added clarification that Clinical Efficacy is analyzed in the Implanted set rather than the AT set ○ Section 7.9.4 Non-Powered Secondary Objectives #4 and #10: added details for visit-driven components in survival analysis ○ Section 7.9.5 Subgroup analyses: added subgroup analyses for the 2 primary endpoints (age<75 vs. ≥75 years, sex, STS risk score (<3, 3-5, 5-8, and >8%), baseline LVEF<50 vs. ≥50%, CKD, atrial fibrillation, prior cerebrovascular accident, and pre-existing LBBB/CHB) • Minor formatting updates throughout	
4.0	• Additional clarifications to planned analyses ○ Section 7.9.2: clarify that HSVD and NSVD events detected up to maximum of 12-month echo date or 395 days are included in primary analysis (ensures counting of any events from unscheduled echos within time window) ○ Section 7.9.2: clarify that patients with no known event will be censored at last echo with fully evaluable data for valve function composite	[redacted]

Version	Summary of Changes	Author(s)/Title
	endpoint rather than latest of all available follow-up ○ Section 7.9.2 added planned supportive analysis excluding 12-month echos that occur after end of 12-month visit window (395 days) ○ Section 7.9.2: clarify that binomial proportion analysis requires patients with no known event to have fully evaluable data for valve function composite endpoint at 12-month echo to be included in denominator as "event free" ○ Section 7.9.4 Non-Powered Secondary Objective #4: clarify that patients will be censored at last time known event free rather than last of all available follow-up ○ Section 7.9.4 Non-Powered Secondary Objective #6: clarify that patients with permanent PPI or ICD prior to study TAVR procedure are excluded from this analysis ○ Section 7.9.4 Non-Powered Secondary Objective #10: clarify additional details regarding handling event timing for longer-term follow-up	
5.0	• Additional clarification to planned analyses ○ Section 7.2 General Methodology: clarification regarding exclusion of echo data after any AV reintervention, not just reinterventions where study valve is no longer functioning ○ Section 7.9.4 Non-Powered Secondary Objectives #12: added clarification that subjects with LVOT obstruction during exercise will be excluded from analysis of mean gradient in stress echo substudy	[redacted]

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
6MWT	6-minute walk test
AE	Adverse event
AF	Atrial fibrillation
ANCOVA	Analysis of Covariance
AT	As-treated
AR	Aortic Regurgitation
BAV	Balloon aortic valvuloplasty
BE	Balloon-expandable transcatheter aortic/heart valve (TAV/THV)
BMI	Body mass index
BVD	Bioprosthetic valve dysfunction
BSA	Body surface area
CEC	Clinical Event Committee
CHB	Complete heart block
CIP	Clinical Investigation Plan
CRF	Case report form
CVA	Cerebrovascular accident
DVI	Doppler velocity index
eCRF	Electronic case report form
EDC	Electronic Data Capture
EMEA	Europe, Middle East and Africa
EOA	Effective orifice area
EOAI	Effective orifice area index
EQ-5D/EQ-5D-5L	EuroQol- 5 Dimension/EuroQol- 5 Dimension-5 Level
HSVD	Hemodynamic structural valve dysfunction
ITT	Intention to treat
KCCQ	Kansas City Cardiomyopathy Questionnaire
LBBB	Left bundle branch block
LVEF	Left ventricular ejection fraction
LVOT	Left ventricular outflow tract
LS-means	Least squares means
MGV	Mean gradient across aortic valve
NSVD	Non-structural valve dysfunction
NYHA	New York Heart Association
PPM	Prosthesis-patient mismatch
PVL	Paravalvular leak
QoL	Quality of Life
SAP	Statistical Analysis Plan
SE	Self-expanding transcatheter aortic/heart valve (TAV/THV)
STS	Society of Thoracic Surgeons

Abbreviation	Definition
SVD	Structural valve dysfunction
TAR	Total aortic regurgitation
TAV	Transcatheter aortic valve
TAVR	Transcatheter aortic valve replacement
TEE	Transesophageal echocardiology
TTE	Transthoracic echocardiogram
VTI	Velocity time integral

3. Introduction

This Statistical Analysis Plan (SAP) has been designed to document, before data are analyzed, the rationale for the study design, and the planned analyses that will be included in study reports for the Small Annuli Randomized To Evolut™ or SAPIEN™ Trial (SMART Trial). This version of the analysis plan was developed under the Clinical Investigation Plan (CIP) version 4.0 and approved Case Report Form (CRF) Requirements.

The purpose of this trial is to generate clinical evidence on valve safety and performance of Self-Expandable (SE) versus Balloon-Expandable (BE) transcatheter aortic valve replacement (TAVR) in subjects with a small aortic annulus and symptomatic severe native aortic stenosis. The Trial is designed to evaluate clinical outcome non-inferiority and hemodynamic superiority of the Evolut PRO/PRO+/FX System when compared to the SAPIEN 3/SAPIEN 3 Ultra System at 12 months post-procedure. In addition, the trial will follow subjects for up to 5 years to evaluate and compare long-term valve function between SE and BE. Due to its focus on small annulus patients, the SMART Trial will likely enroll predominantly women (~80%), which will provide important clinical insights into a currently underrepresented patient population in TAVR literature.

4. Study Objectives

4.1 Primary Objectives

The primary objectives of the trial are to demonstrate clinical non-inferiority and hemodynamic superiority of the Evolut PRO/PRO+/FX System when compared to subjects treated with the SAPIEN 3/SAPIEN 3 Ultra System at 12 months post-procedure.

4.2 Secondary Objectives

The secondary objective of the trial is to generate long-term valve function data for both BE and SE TAVR through 5 years of follow-up.

4.3 Endpoints

The endpoints in this section will be used to evaluate the primary and secondary trial objectives.

4.3.1 Primary Endpoints

The trial will have two powered primary endpoints comparing the Medtronic SE TAVs and Edwards BE TAVs to:

1. A clinical outcome composite endpoint of mortality, disabling stroke or heart failure rehospitalization at 12 months
2. A valve function composite endpoint of bioprosthetic valve dysfunction (BVD) at 12 months including any of the following:
    - Hemodynamic Structural Valve Dysfunction (HSVD): hemodynamic mean gradient ≥ 20mmHg
    - Non-structural Valve Dysfunction (NSVD): severe prosthesis-patient mismatch (PPM), ≥ moderate aortic regurgitation (AR)
    - Thrombosis
    - Endocarditis
    - Aortic valve re-intervention

4.3.2 Powered Secondary Endpoints

The powered secondary endpoints for the trial comparing the SE and BE TAVs are:

1. BVD in female subjects at 12 months
2. HSVD at 12 months
3. Hemodynamic mean gradient as continuous variable at 12 months
4. Effective orifice area (EOA) as continuous variable at 12 months
5. Moderate or severe prosthesis-patient mismatch (PPM) at 30 days

4.3.3 Non-powered Secondary Endpoints

The non-powered secondary endpoints are listed below:

1. Device success at 30 days
2. Incidence of an early safety composite at 30 days defined as:
    - All-cause mortality
    - All stroke (disabling and non-disabling)
    - Life-threatening bleeding
    - Acute kidney injury—Stage 2 or 3 (including renal replacement therapy)
    - Coronary artery obstruction requiring intervention
    - Major vascular complication
    - Valve-related dysfunction requiring repeat procedure (balloon aortic valvuloplasty [BAV], TAVR, or Surgical aortic valve replacement [SAVR])
3. Hospital readmission for any cause at 30 days
4. Incidence of clinical efficacy (after 30 days) at 12 months and annually to 5 years defined as a composite of:
    - All-cause mortality

- All stroke (disabling and non-disabling)
- Requiring hospitalizations for valve-related symptoms or worsening congestive heart failure
- NYHA class III or IV
- Valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 cm^2 and/or Doppler Velocity Index (DVI) <0.35m/s, AND/OR moderate or severe prosthetic valve regurgitation)

5. Components of the co-primary clinical endpoint at 12 months, and annually to 5 years:
   - Mortality
   - Disabling stroke
   - Heart failure rehospitalization
6. New pacemaker implantation rate at 30 days, 12 months, and annually to 5 years
7. Aortic valve re-intervention at 30 days, 12 months, and annually to 5 years
8. 6-minute walk test (6MWT) at 30 days, 12 months, and annually to 5 years
9. Quality of Life (QoL) (Kansas City Cardiomyopathy Questionnaire [KCCQ], EuroQol-5 Dimension [EQ-5D]) at 30 days, 12 months, and annually to 5 years
10. BVD (HSVD, NSVD, thrombosis, endocarditis, and aortic valve re-intervention) at 2 to 5 years annually
11. Echocardiographic measurements (i.e. EOA, mean gradient, PVL, LV mass regression, and DVI (severe <0.25, moderate 0.25-0.5, mild >0.5)) at discharge, 30 days, 12 months and annually to 5 years
12. Mean gradient ≥ 20 mmHg based on stress echocardiogram at 12 months at select sites

5. Investigation Plan

This trial is designed as a prospective, multi-center, international, randomized controlled, post-market trial to generate clinical evidence on valve safety and performance of self-expanding (SE) versus balloon-expandable (BE) transcatheter aortic valve replacement (TAVR) in subjects with small aortic annulus and symptomatic severe native aortic stenosis.

Approximately 700 subjects will be treated in approximately 90 sites located in Canada, Europe, Middle East and Africa region (EMEA), and the United States. Subjects will be randomized on a 1:1 basis to receive either a Medtronic SE or an Edwards BE TAV, and randomization will be stratified by site and sex. As not all subjects randomized will go forward to implantation, the total randomized population is expected to exceed 700 subjects to meet the sample size requirements for the as-treated population. No site will implant more than 140 subjects without prior authorization from Medtronic in order to ensure a widespread distribution of data and minimize trial site bias in trial results.

Subject follow-up visits post-implantation will occur at discharge, 30 days, 12 months, and annually thereafter through 5 years. Subjects who exit from the trial after implantation will not be replaced. The enrollment period is estimated to be approximately 20 months and subjects will be followed for up to five years post TAVR procedure; therefore, the expected trial duration is approximately 6-7 years.

6. Determination of Sample Size

The sample size of 700 as-treated subjects will provide sufficient power to evaluate the pre-specified hypothesis tested endpoints. The study is designed with two hypothesis tested primary endpoints and five hypothesis tested secondary endpoints. The sample size requirements for the trial are driven by the non-inferiority test of the clinical outcome composite endpoint of mortality, disabling stroke, or heart failure rehospitalization at 12 months. Assumptions for sample size requirements are detailed below with all sample size calculations performed using PASS 14 (NCSS, LLC. Kaysville, Utah, USA).

The clinical outcome composite endpoint is designed to evaluate non-inferiority of the Medtronic SE TAV to the Edwards BE TAV. Under the assumption of 16% composite event rate in each arm, non-inferiority margin of 8%, one-sided alpha 0.05, and 1:1 randomization ratio, based on the pooled z-test a minimum evaluable sample size of 520 subjects (260 per arm) would provide 80% power, and 720 subjects (360 per arm) would provide 90% power. Accounting for attrition, the total sample size for the trial is 700 as-treated subjects which will provide at least 85% power for the non-inferiority clinical outcome composite endpoint.

The assumption for the anticipated composite event rate of all-cause mortality, disabling stroke, or heart failure rehospitalization at 12 months post-procedure was based on the literature. It is expected that the trial will enroll predominately women (approximately 80% of the population) due to the recruitment of subjects with small annulus. In prior studies, rates for the composite endpoint by surgical risk were approximately 8%, 20%, and 28% for the low, intermediate, and high surgical risk populations, respectively[(1-5)]. It is anticipated that the recruited native population would be of 20%, 60% and 20% at low, intermediate, and high surgical risk, respectively. Therefore, the estimate rate for the composite endpoint would be around 20%. Given improvement in TAVR technology and operator experience from prior randomized trials, the observed composite endpoint event rate in the present trial is expected to be lower and the anticipated event rate in each arm was therefore assumed to be 16%.

Table 1: TAVR Safety Data from Literature

Literature	Surgical Risk	Valve Type	N	Composite Safety Event Rate at 12 Months
Popma JJ, Deeb GM, Yakubov SJ	Low	SE	725	2.9%[1]
Mack MJ, Leon MB, Thourani VH, et al.	Low	BE	496	8.5%
Leon MB, Smith CR, Mack MJ, et al.	Intermediate	BE	994	27.1%[2]
Szerlip M, Gualano S, Holper E, et al.	Intermediate[3]	BE	1661	22.4% (Female); 20.9% (Male)
Skelding KA, Yakubov SJ, Kleiman NS, et al.	High	SE	183	14.9%[4]

[1]All-cause mortality or disabling stroke.
[2]All-cause mortality, any stroke, or rehospitalization.
[3]Included 583 subjects at high surgical risk.
[4]All-cause mortality or major stroke. In the same cohort, the rate of rehospitalization was 16.3 % at 12 months.[1]

The sample size determined by the clinical outcome composite endpoint will be adequate to provide sufficient power for each of the six remaining hypothesis tested endpoints. For example, 700 subjects

[1] Data on file at Medtronic

would provide >99% power for each of the additional hypothesis tested endpoints. More specifically, the minimum required sample size for the valve function composite endpoint and the five powered secondary endpoints are as follows:

- Primary Objective #2 – Valve Function Composite Endpoint: The valve function composite endpoint is designed to evaluate the superiority of the Medtronic SE TAV to Edwards BE TAV in BVD at 12 months post-procedure. Under the assumptions of 14.0% event rate for Medtronic SE TAV, 36% event rate for Edwards BE TAV, superiority hypothesis, one-sided alpha 0.025, and 1:1 randomization ratio, based on the pooled z-test a minimum evaluable sample size of 120 subjects (60 per arm) would provide 80% power for the endpoint. Assumptions for the valve function composite endpoint were based on historical data from prior randomized trials evaluating the Medtronic SE TAV compared to SAVR in the low, intermediate, and high surgical risk populations[1].

- Powered Secondary Endpoint #1 – BVD in Female Population: Powered secondary endpoint #1 aims to evaluate superiority of the Medtronic SE TAV to Edwards BE TAV in BVD at 12 months post-procedure in the female population. Assumptions for the endpoint are the same as the valve function composite endpoint and therefore the minimum required sample size is 120 subjects (60 per arm). With a total sample size of 700 as-treated subjects of which approximately 80% are expected to be female, the trial sample size will be adequate to power the endpoint within the female population.

- Powered Secondary Endpoint #2 – HSVD: Powered secondary endpoint #2 is designed to evaluate the superiority of the Medtronic SE TAV to Edwards BE TAV in HSVD at 12 months post-procedure. Under the assumptions of 4.0% event rate for the Medtronic SE TAV, 19.0% event rate for the Edwards BE TAV, superiority hypothesis, one-sided alpha 0.025, and 1:1 randomization ratio, based on the pooled z-test a minimum evaluable sample size of 140 subjects (70 per arm) would provide 80% power for the endpoint. Assumptions for the anticipated rate of HSVD were based on historical data from prior randomized trials evaluating the Medtronic SE TAV compared to SAVR in the low, intermediate, and high surgical risk populations[1].

- Powered Secondary Endpoint #3 – Hemodynamic Mean Gradient: Powered secondary endpoint #3 is designed to evaluate the superiority of the Medtronic SE TAV to Edwards BE TAV in mean gradient across aortic valve (MGV) at 12 months post-procedure. Under the assumptions of mean MGV of 9.0±3.3 mmHg and 13.7±5.6 mmHg for Medtronic SE TAV and Edwards BE TAV, respectively, superiority hypothesis, one-sided alpha 0.025, and 1:1 randomization ratio, based on the t-test assuming unequal variance a minimum evaluable sample size of 40 subjects (20 per arm) would provide 80% power for the endpoint. Assumptions for the anticipated mean MGV were based on prior results in the low risk population for the Medtronic SE valve[(1)] and the Edwards BE valve[(3)].

- Powered Secondary Endpoint #4 – Effective Orifice Area: Powered secondary endpoint #4 is designed to evaluate the superiority of the Medtronic SE TAV to Edwards BE TAV in effective orifice area at 12 months post-procedure. Under the assumptions of mean EOA of 2.27 ± 0.65 cm^2 and 1.72 ± 0.37 cm^2 for Medtronic SE TAV and Edwards BE TAV, respectively, superiority hypothesis, one-

sided alpha 0.025, and 1:1 randomization ratio, based on the t-test assuming unequal variance a minimum evaluable sample size of 32 subjects (16 per arm) would provide 80% power for the endpoint. Assumptions for the anticipated mean EOA were based on prior results in the low risk population for the Medtronic SE valve[1] and the Edwards BE valve[3].

- Powered Secondary Endpoint #5 – Moderate or Severe Prosthesis-Patient Mismatch: Powered secondary endpoint #5 is designed to evaluate the superiority of the Medtronic SE TAV to Edwards BE TAV in moderate or severe PPM at 30 days post-procedure. Under the assumptions of 11.0% event rate for the Medtronic SE TAV, 34.0% event rate for the Edwards BE TAV, superiority hypothesis, one-sided alpha 0.025, and 1:1 randomization ratio, based on the pooled z-test a minimum evaluable sample size of 102 subjects (51 per arm) would provide 80% power for the endpoint. Assumptions for the anticipated rate of PPM were based on prior results in the low risk population for the Medtronic SE valve[1] and the Edwards BE valve[3,6].

Based on the above, the trial sample size requirements are driven by the requirements for the non-inferiority clinical outcome composite endpoint and the total trial sample size will be approximately 700 as-treated subjects.

7. Statistical Methods

7.1 Study Subjects

7.1.1 Disposition of Subjects

Subject disposition will be illustrated in a flow diagram. Within each arm, subject visits will be tabulated, compliance to the visit schedule and visit windows will be summarized, and attrition will be identified and summarized. Tabulations will include the number of subjects enrolled, randomized, attempted implant, implanted, died, withdrawn, lost-to-follow-up, and completed the scheduled follow-up visit for each visit. The number of treatment crossover during follow-up, if any, will also be summarized.

7.1.2 Clinical Investigation Plan (CIP) Deviations

Protocol deviations will be reported via Electronic Case Report Form (eCRF) regardless of whether medically justifiable, pre-approved by Medtronic, or taken to protect the subject in an emergency. Study deviations will be reported on the Study Deviation eCRF. Deviations will be summarized by deviation category and visit, separately for each treatment arm. For each category, both event and subject counts will be reported. Percentages will be based on subject counts and the denominator will include all subjects in the analysis population.

7.1.3 Analysis Sets

7.1.3.1 Screening Population

All subjects with a small aortic annulus and severe native aortic stenosis who provide informed consent will be considered screened and enrolled, and all available data will be entered into the Electronic Data

Capture (EDC) system. Data from subjects who were consented, but screen failed and exited prior to randomization will not be analyzed and published.

7.1.3.2 Randomized Population

If the subject signs informed consent, meets all inclusion and none of the exclusion criteria, and the Heart Team determines the subject is suitable for randomization in the trial, then the subject will undergo a Confirmation for Qualification. If the subject is approved, the subject will be randomized and added to the randomized population. Within the randomized population the following analysis sets are distinguished:

- **The intention to treat (ITT) set**: Subjects are reported according to the randomized assignment, either BE or SE TAV, regardless of what, if any, therapy was actually received.
- **The as treated (AT) set**: The AT set consists of all ITT subjects with an attempted implant procedure, defined as when the subject is brought into the procedure room and any of the following have occurred: anesthesia administered, vascular line placed, transesophageal echocardiology (TEE) placed or any monitoring line placed. Subjects will be analyzed according to their first attempted procedure (BE or SE TAV).
- **The implanted set**: The Implanted set consists of all the AT subjects who are actually implanted with either TAV. Subjects will be analyzed according to the last implanted valve (BE or SE TAV) at the index procedure.

The primary analysis for the non-ECHO related objectives will use the AT analysis set. The primary analysis for the ECHO related objectives (such as BVD) will use the Implanted analysis set based on data collected up to the point of reintervention or reoperation. The primary analysis population for each endpoint is detailed in **Section 7.9**. Analysis performed using analysis sets other than the primary would be considered supportive.

7.2 General Methodology

Descriptive statistics of continuous outcomes will be presented by treatment arm and include count, mean, median, standard deviation, first and third quartiles, minimum and maximum. For categorical outcomes, the number and percentage of subjects in each category will be presented by treatment arm.

For time-to-event outcomes using Kaplan-Meier methods, the time points of 30 days, 1 year, 2 years, 3 years, 4 years, and 5 years will correspond to 30, 365, 730, 1095, 1460, and 1825 days post-implant, respectively. For each applicable time point, the event or event-free rate, the number of subjects at risk, the number of subjects with an event, the Greenwood standard error of the estimate, and the log-log transformed 95% confidence interval using the Greenwood standard error will be reported. For subjects with an event, the date of event will be based on the first event occurrence. For subjects without an event, date of censoring will be based on the latest of all follow-up visits, assessments, and events (for non-death events). Methods which account for interval censoring may be considered for survival analysis of events based on echo assessment.

For analyses using echocardiographic data, only echo data corresponding to the implanted study valve will be used; data post-explant or after reintervention will be excluded from analysis.

Subject data listings and tabular and graphical presentations of results will be provided. Unless otherwise specified, a two-sided 0.05 level of significance will be used to declare treatment arms significantly different.

All statistical analyses will be performed using SAS version 9.4 or higher (SAS Institute, Cary, North Carolina, USA) or other widely accepted statistical or graphical software.

7.3 Center Pooling

Investigational sites are to follow a common protocol and data collection. Additionally, the hypothesis tested primary and secondary endpoints will be based on assessments made by the independent Clinical Events Committee (CEC) and/or echocardiographic core lab. Therefore, data are expected to be poolable across sites and analysis will based on data combined across sites. A sensitivity analysis will be performed for the primary endpoints to evaluate poolability by site. For each endpoint, a Cox proportional hazards regression model with treatment arm, site, and treatment-by-site interaction will be fit to understand the treatment effect by site.

An additional analysis will be performed to assess homogeneity of the treatment effect across geographic region (United States/Canada and EMEA). A similar model as used for site will be used with treatment arm, region, and treatment-by-region interaction.

7.4 Handling of Missing, Unused, and Spurious Data and Dropouts

Every effort will be undertaken to minimize missing data. In time-to-event outcomes, dropouts will be censored at the time of discontinuation, consistent with the Kaplan-Meier approach. Unless otherwise specified, no statistical techniques will be used to impute missing data. The number of subjects included in each analysis will be reported so that the reader can assess the potential impact of missing data. To evaluate the potential impact of missing data on study results, sensitivity analyses will be performed for the primary endpoints which will include a tipping point analysis.

In the case of partial dates, if only the month and year are known, the event or assessment will be analyzed as if it occurred on the 15th of that month. If only the year is known, the event or assessment will be analyzed as if it occurred on June 30th of that year. Imputation of partial dates is subject to the restriction that pre-implant events must occur between the date of informed consent and the date of implant and post-implant events must occur after the date of implant and prior to date of study exit.

7.5 Adjustments for Multiple Comparisons

The trial is designed with two hypothesis tested primary endpoints and five hypothesis tested secondary endpoints. The overall type I error will be controlled by serial gatekeeping approach with two families:

1. Set of two primary endpoints
2. Set of five powered secondary endpoints

Hypothesis testing of the two primary endpoints will occur first, with non-inferiority of the clinical outcome composite endpoint evaluated at one-sided alpha 0.05 and superiority of the valve function composite endpoint evaluated at one-sided alpha 0.025. Trial success will be declared if both endpoints are met at the prespecified alpha.

Hypothesis testing of the powered secondary endpoints will only occur when both primary endpoints are met. The family wise type I error rate for the powered secondary endpoints will be controlled using a fixed-sequence testing procedure, in which each endpoint will be tested hierarchically in prespecified order at a one-sided alpha 0.025 until a non-significant result occurs. For a given hypothesis test in the sequence, if the one-sided p-value is ≤0.025, the next endpoint in the sequence will be evaluated. If the one-sided p-value >0.025, hypothesis testing will stop, and subsequent endpoints will not be evaluated for statistical significance.

Secondary endpoints will be tested in the following order:

1. MGV (Powered Secondary Objective #3)
2. EOA (Powered Secondary Objective #4)
3. HSVD (Powered Secondary Objective #2)
4. BVD in the female population (Powered Secondary Objective #1)
5. Moderate or severe PPM at 30 days (Powered Secondary Objective #5)

7.6 Demographic and Other Baseline Characteristics

Baseline demographics and clinical variables will be summarized descriptively by treatment arm for the ITT, AT, and Implanted analysis sets. Data will be summarized by treatment arm with standard descriptive summary statistics, including counts and percentages for categorical variables, and mean, standard deviation, median, first and third quartiles, and minimums and maximums for continuous variables. Continuous variables will be compared between treatment groups using a two-sample t-test or the non-parametric Wilcoxon rank-sum test, as appropriate. Categorical variables will be compared between treatment groups using a Chi-square test or Fisher's exact test, as appropriate. Ordinal variables will be compared using the Cochran-Mantel-Haenszel test with row mean scores.

7.7 Treatment Characteristics

Implant procedure data will be summarized by treatment arm for the AT analysis set as described for Demographic and Other Baseline Characteristics in **Section 7.6**.

7.8 Interim Analyses

No formal interim analyses are planned for the purpose of early stopping or sample size re-estimation.

7.9 Evaluation of Objectives

7.9.1 Primary Objective #1: Clinical Outcome Composite Endpoint

The clinical outcome composite endpoint in this trial is the composite of all-cause mortality, disabling stroke, or heart failure rehospitalization at 12 months post-procedure.

The endpoint is designed to show the Medtronic SE TAV is non-inferior to Edwards BE TAV in the composite event rate of all-cause mortality, disabling stroke or heart failure rehospitalization at 12 months post-procedure with an absolute non-inferiority margin of 8.0%. Formally, the hypothesis is as follows:

$H_o: \pi_{MDT} \geq \pi_{EW} + \delta$

H_A: $\pi_{MDT} < \pi_{EW} + \delta$

In the above expression π_{MDT} and π_{EW} denote the composite event rates of all-cause mortality, disabling stroke, or heart failure rehospitalization at 12 months post-procedure for Medtronic SE TAV and Edwards BE TAV, and δ denotes the non-inferiority margin of 8%.

Non-inferiority of the clinical outcome composite endpoint will be based on the estimated event rate at 365 days for each arm from a Kaplan-Meier survival analysis. Components of the endpoint will be adjudicated by the CEC. Timing of event will be determined from the earliest component event for each subject and only events occurring within 365 days (12 months) will be considered in the analysis. Censoring time will be derived according to **Section 7.2**. The difference in the point estimates at 365 days will be assumed to be asymptotically normal and a two-sided large sample confidence interval for the difference in event rates will be calculated as follows:

$$\left(1 - \hat{S}_{MDT}\right) - \left(1 - \hat{S}_{EW}\right) \pm z_{\alpha/2}\sqrt{\hat{V}\left(\hat{S}_{MDT}\right) + \hat{V}\left(\hat{S}_{EW}\right)},$$

where $\hat{S}_{MDT}$ and $\hat{S}_{EW}$ are the survival point estimates at 365 days from the Kaplan-Meier analysis for the Medtronic SE TAV and Edwards BE TAV, respectively, and $\hat{V}\left(\hat{S}_{MDT}\right)$ and $\hat{V}\left(\hat{S}_{EW}\right)$ are the Greenwood variance estimates corresponding to each survival point estimate. The test statistic for the non-inferiority hypothesis will be calculated as

$$z = \frac{\left(1 - \hat{S}_{MDT}\right) - \left(1 - \hat{S}_{EW}\right) - \delta}{\sqrt{\hat{V}\left(\hat{S}_{MDT}\right) + \hat{V}\left(\hat{S}_{EW}\right)}},$$

where δ is 8%, the non-inferiority margin.

The endpoint will be presented with the Kaplan-Meier estimate of the composite event rate at 365 days (cumulative incidence) within treatment arms along with corresponding Greenwood Standard error, the estimated difference in event rates (SE TAV – BE TAV) at 365 days with associated one-sided 95% upper confidence bound (i.e. upper confidence limit of the two-sided 90% confidence interval), and the p-value from the test statistic for non-inferiority. If the one-sided 95% upper confidence bound is less than the non-inferiority margin of 8%, the endpoint will be considered met at the one-sided alpha 0.05 level. The primary analysis of the clinical outcome composite endpoint will be performed using the AT analysis set. Sensitivity analyses will be conducted using the ITT and Implanted analysis sets. An additional sensitivity analysis will be performed for all subjects with attempted implant with treatment group based on randomized treatment assignment. If this population is the same as the AT analysis set, this additional sensitivity analyses will not be performed.

Components of the composite endpoint will be analyzed descriptively as part of Non-powered Secondary Endpoint 4 (**Section 7.9.4**).

7.9.2 Primary Objective #2: Valve Function Composite Endpoint

The valve function composite endpoint of BVD at 12 months post-procedure includes any of the following:

- HSVD: hemodynamic mean gradient ≥ 20mmHg
- NSVD: severe PPM, or ≥ moderate total aortic regurgitation (AR)

- Thrombosis
- Endocarditis
- Aortic valve re-intervention

The endpoint is designed to show the Medtronic SE TAV is superior to Edwards BE TAV in BVD at 12 months post-procedure. Formally, the hypothesis is as follows:

H_o: $\pi_{MDT} \geq \pi_{EW}$

H_A: $\pi_{MDT} < \pi_{EW}$

In the above expression π_{MDT} and π_{EW} denote the BVD rates at 12 months post-procedure for Medtronic SE TAV and Edwards BE TAV, respectively.

Components of the BVD endpoint will be reported on the echo core lab CRF and the CEC CRF.

Severe patient-prosthesis mismatch (PPM) is defined as follows and will be derived from data reported on the core lab TTE CRF:

- For subjects with BMI < 30 kg/m^2: EOAI ≤ 0.65 cm^2/m^2
- For subjects with BMI ≥ 30 kg/m^2: EOAI ≤ 0.55 cm^2/m^2

where BMI is the body mass index in kg/m^2 and EOAI is the Effective Orifice Area Index in cm^2/m^2.

If BMI and/or BSA are not available at the visit, last observation carried forward method will be used in which the latest available BMI and/or BSA between baseline and follow-up echo will be used to calculate EOAI.

The endpoint will be evaluated using the point estimates at 365 days from a Kaplan-Meier analysis. Components of the valve function composite will be reported on the core lab transthoracic echocardiogram (TTE) CRF and the CEC CRF as follows.

- HSVD and NSVD will be detected on the core lab TTE CRF. Time to event for each will be based on the earliest detected occurrence up to and including the 12-month visit or through 395 days, whichever is later. Events based on the 12-month TTE which occur >365 days will be set to 365 days for the purposes of analysis. This approach allows counting of all HSVD and NSVD events found at the 12-month follow-up, even if the follow-up occurred after 365 days.
- Thrombosis, endocarditis, and aortic valve reintervention will be adjudicated by the CEC and derived based on the first component event. Only events within 365 days will be considered for the primary endpoint analysis.

For subjects that experience more than one component of the composite, the earliest event time will be used for the analysis. For subjects that do not experience any component of the composite within the timeframes described above, the censoring time will be the time of the latest echo known to be free of HSVD and NSVD (requires all evaluable data for all three of: effective orifice area, mean gradient, and aortic regurgitation).

The endpoint will be presented with the Kaplan-Meier estimate of the composite event rate at 365 days (cumulative incidence) within treatment arms along with corresponding Greenwood Standard error, the estimated difference in event rates (SE TAV - BE TAV) at 365 days with corresponding upper limit from the two-sided 95% large sample confidence interval, and the one-sided p-value for the superiority

hypothesis. The two-sided confidence interval and test statistic will be calculated as described for the clinical outcome composite endpoint as

$$\left(1 - \hat{S}_{MDT}\right) - \left(1 - \hat{S}_{EW}\right) \pm z_{\alpha/2}\sqrt{\hat{V}\left(\hat{S}_{MDT}\right) + \hat{V}\left(\hat{S}_{EW}\right)},$$

where $\hat{S}_{MDT}$ and $\hat{S}_{EW}$ are the survival point estimates at 365 days from the Kaplan-Meier analysis for the Medtronic SE TAV and Edwards BE TAV, respectively, and $\hat{V}\left(\hat{S}_{MDT}\right)$ and $\hat{V}\left(\hat{S}_{EW}\right)$ are the Greenwood variance estimates corresponding to each survival point estimate. The test statistic will be calculated as

$$z = \frac{\left(1 - \hat{S}_{MDT}\right) - \left(1 - \hat{S}_{EW}\right)}{\sqrt{\hat{V}\left(\hat{S}_{MDT}\right) + \hat{V}\left(\hat{S}_{EW}\right)}}.$$

If the one-sided p-value is less than or equal to 0.025, the endpoint will be considered met. The components of BVD will be summarized descriptively. The analysis will be performed using the Implanted analysis set.

The following additional supportive analysis for the primary endpoint will be performed using the implanted population:

- Repeat analysis using Kaplan-Meier approach described above, excluding "late" 12-month echos (after end of 12-month visit window: 395 days).
- A tipping point analysis using the Kaplan-Meier estimate at 365 days that will systematically consider each subject with missing outcome at Day 365 as an event or a non-event at 365-days in all combinations.
- Complete case analysis based on the difference in binomial proportions with p-value calculated using a large sample test. This will be run including subjects with events within the timeframes described above for the primary analysis or with evaluable core lab echo (requires evaluable data for all three of: effective orifice area, mean gradient, and aortic regurgitation) free of BVD at 12 months.
- Non-parametric time to first event analysis estimating the cumulative incidence of the valve function composite endpoint while accounting for the competing risk of mortality, with endpoints and event times defined the same way as the primary analysis.
- Non-parametric survival analysis accounting for interval censoring, with the right boundary defined as the earliest event occurrence and the left boundary defined as the last day free of the valve function composite. The event rate estimates corresponding to the interval containing 365 days for each group will be reported, along with the hazard ratio comparing the groups and the p-value for the generalized log-rank test
- Survival analysis accounting for both interval-censoring and competing risk of mortality using the method described by Delord and Génin[7]. As above, the event rate estimates for each group at 365 days will be reported along with a hazard ratio comparing the groups and corresponding significance test.

7.9.3 Powered Secondary Endpoints

There are five hypothesis-tested secondary endpoints defined for the trial. Type I error will be controlled by a serial gatekeeping procedure according to the details in **Section 7.5**. Hypothesis testing of the secondary endpoints will only occur if both the clinical outcome composite and valve function composite endpoints are met.

7.9.3.1 Powered Secondary Objective #1: BVD in Female Population

The first powered secondary endpoint in this trial is the BVD rate at 12 months post-procedure within the female population. The endpoint will be analyzed as described for the Valve Function Composite Endpoint in **Section 7.9.2** in female subjects using the Implanted analysis set. Superiority of the Medtronic SE TAV to Edwards BE TAV in BVD for females will be declared if the one-sided p-value for the difference (SE TAV – BE TAV) is less than or equal to 0.025.

7.9.3.2 Powered Secondary Objective #2: HSVD

The second powered secondary endpoint is the HSVD rate at 12 months post-procedure. HSVD is defined as having mean aortic gradient ≥ 20mmHg and will be reported according to data collected on the core lab TTE CRF at 12 months. The endpoint is designed to evaluate if Medtronic SE TAV is superior to Edwards BE TAV in HSVD at 12 months post-procedure. Formally, the hypothesis is as follows:

H_o: $\pi_{MDT} \geq \pi_{EW}$

H_A: $\pi_{MDT} < \pi_{EW}$

In the above expression π_{MDT} and π_{EW} denote the HSVD rates at 12 months post-procedure for Medtronic SE TAV and Edwards BE TAV, respectively.

The endpoint will be analyzed as described for the Valve Function Composite Endpoint in **Section 7.9.2** using Kaplan-Meier analysis. Superiority of the Medtronic SE TAV to Edwards BE TAV in HSVD will be declared if the one-sided p-value for the difference (SE TAV – BE TAV) is less than or equal to 0.025. The analysis will be performed using the Implanted analysis set.

7.9.3.3 Powered Secondary Objective #3: Hemodynamic Mean Gradient

The third powered secondary endpoint in this trial is the hemodynamic mean gradient as continuous variable at 12 months post-procedure. The endpoint is designed to show the Medtronic SE TAV is superior to Edwards BE TAV in hemodynamic mean gradient at 12 months post-procedure. Formally, the hypothesis is as follows:

H_o: $MGV_{MDT} \geq MGV_{EW}$

H_A: $MGV_{MDT} < MGV_{EW}$

In the above expression MGV_{MDT} and MGV_{EW} denote the hemodynamic mean gradient (MGV) as continuous variable at 12 months post-procedure for Medtronic SE TAV and Edwards BE TAV, respectively.

Within treatment arm, the MGV at 12 months will be summarized descriptively. Superiority of the endpoint will be evaluated using analysis of covariance (ANCOVA) with baseline MGV as a covariate. Along with the descriptive summary statistics of MGV at 12 months within treatment arm, the

difference (SE TAV – BE TAV) in least square means (LS-means) with corresponding upper limit from the two-sided 95% confidence interval, and one-sided p-value from the ANCOVA will be presented. If the one-sided p-value is less than or equal to 0.025, superiority of the Medtronic SE TAV compared to Edwards BE TAV will be met. The analysis will be performed using the Implanted analysis set and will include subjects with available MGV at 12 months from the core lab.

7.9.3.4 Powered Secondary Objective #4: Effective Orifice Area

The fourth powered secondary endpoint in this trial is the effective orifice area as continuous variable at 12 months post-procedure. The endpoint is designed to show the Medtronic SE TAV is superior to Edwards BE TAV in EOA at 12 months post-procedure. Formally, the hypothesis is as follows:

H_o: $EOA_{MDT} \leq EOA_{EW}$

H_A: $EOA_{MDT} > EOA_{EW}$

In the above expression EOA_{MDT} and EOA_{EW} denote the effective orifice area (EOA) as continuous variable at 12 months post-procedure for Medtronic SE TAV and Edwards BE TAV, respectively.

Within treatment arm, the EOA at 12 months will be summarized descriptively. Superiority of the endpoint will be evaluated using ANCOVA with baseline EOA as a covariate. Along with the descriptive summary statistics of EOA at 12 months within treatment arm, the difference (SE TAV – BE TAV) in LS-means with corresponding lower limit from the two-sided 95% confidence interval, and one-sided p-value from the ANCOVA will be presented. If the one-sided p-value is less than or equal to 0.025, superiority of the Medtronic SE TAV compared to Edwards BE TAV will be met. The analysis will be performed using the Implanted analysis set and will include subjects with available EOA at 12 months from the core lab.

7.9.3.5 Powered Secondary Objective #5: Moderate or Severe Prosthesis-Patient Mismatch

The fifth powered secondary endpoint is the rate of moderate or severe PPM at 30 days post-procedure. PPM is defined for the valve function composite endpoint in **Section 7.9.2** and will be reported according to data collected on the core lab TTE CRF at 30 days. The endpoint is designed to evaluate if Medtronic SE TAV is superior to Edwards BE TAV in moderate or severe PPM at 30 days post-procedure. Formally, the hypothesis is as follows:

H_o: $\pi_{MDT} \geq \pi_{EW}$

H_A: $\pi_{MDT} < \pi_{EW}$

In the above expression π_{MDT} and π_{EW} denote the rate of moderate or severe PPM at 30 days post-procedure for Medtronic SE TAV and Edwards BE TAV, respectively.

Moderate or severe PPM will be defined as follows:

For subjects with BMI < 30 kg/m^2

- **Moderate PPM:** EOAI = 0.85 – 0.65 cm^2/m^2
- **Severe PPM:** EOAI = ≤ 0.65 cm^2/m^2

For subjects with BMI ≥ 30 kg/m^2

- **Moderate PPM:** EOAI = 0.70 – 0.55 cm^2/m^2
- **Severe PPM:** EOAI = ≤ 0.55 cm^2/m^2

where EOAI = EOA / BSA (body surface area).

Superiority of the endpoint will be evaluated using the absolute risk difference (SE TAV – BE TAV) in the rate of moderate or severe PPM at 30 days. The endpoint will be reported with the PPM rate within treatment arm, the absolute risk difference in the rate of moderate or severe PPM (SE TAV – BE TAV) with corresponding upper limit from the two-sided 95% Wald confidence interval, and the one-sided p-value for the superiority hypothesis. If the one-sided p-value is less than or equal to 0.025, the endpoint will be considered met. Within each arm, the numerator will include the number of subjects with moderate or severe PPM based on the core lab at 30 days and the denominator will include all subjects evaluable for PPM (i.e., have evaluable BMI and EOAI at 30 days to be defined as a known success or failure). If BSA and BMI are missing at the 30-day echo, last observation carried forward method will be used in which the latest available BSA or BMI between baseline and the 30-day echo will be used. The analysis will be performed using the Implanted analysis set.

7.9.4 Non-Powered Secondary Objectives

Additional outcome measures are defined for the trial without pre-specified hypothesis testing planned and all analyses will be descriptive and will reported by treatment arm.

1. **Device success at 30 days**

   Device Success is defined as meeting all of the following:

   - Freedom from mortality AND
   - Correct positioning of a single prosthetic heart valve into the proper anatomical location AND
   - Intended performance of the prosthetic heart valve (no prosthesis-patient mismatch (PPM) and mean aortic valve gradient <20 mmHg or peak velocity <3 m/s) AND No moderate or severe prosthetic valve regurgitation)

   Components of device success will be reported on the procedure CRF, the echo core lab CRF at 30 days (or discharge when the 30-day echo is not available), and CEC CRF:

   - Mortality will be defined as any death occurring within 30 days of implant or prior to hospital discharge.
   - Correct positioning of the single prosthetic heart valve into the proper anatomical location will be reported by the investigator on the procedure CRF.
   - Absence of PPM will be derived from the echo core lab data at 30 days. If the 30-day echo is not available, the discharge echo will be used. If BSA and BMI are missing at the visit, last observation carried forward method will be used in which the latest available BSA or BMI between baseline and the echo used for device success will be used. PPM is

defined in **Section 7.9.3.5**. Subjects with available BMI and EOAI will have known PPM and be included in the analysis of the component.

- Mean aortic valve gradient < 20 mmHg (or peak velocity < 3 m/sec) will be derived from the echo core lab CRF at 30 days or discharge when the 30-day echo is unavailable.
- Absence of moderate or severe prosthetic valve regurgitation will be derived from the echo core lab CRF at 30 days or discharge when the 30-day echo is unavailable.

The endpoint will be reported within treatment arm as the count and percentage of subjects achieving device success with two-sided 95% exact binomial confidence interval. Subjects will be defined as success if all components are met. Subjects will be defined as failure if any one component with available data is not met, regardless of if data are available for all components. Subjects missing data for any components and not meeting criteria for failure will be considered to have a missing outcome. The numerator will include the number of subjects with device success and the denominator will include subjects evaluable for device success (known status of success or failure). The components of device success will also be summarized descriptively. The endpoint will be analyzed using the AT analysis set for all subjects where the delivery catheter was introduced.

2. **Incidence of an early safety composite at 30 days defined as:**
    - All-cause mortality
    - All stroke (disabling and non-disabling)
    - Life-threatening bleeding
    - Acute kidney injury—Stage 2 or 3 (including renal replacement therapy)
    - Coronary artery obstruction requiring intervention
    - Major vascular complication
    - Valve-related dysfunction requiring repeat procedure (BAV, TAVR, or SAVR)

    Components of the early safety composite will be adjudicated by the CEC and analysis will be based on the data collected on the CEC adjudication form. The overall composite will be based on occurrence of the earliest component event and only events within 30 days will be considered for the analysis. The rate at 30 days will be estimated by Kaplan-Meier survival analysis. The rate at 30 days for each component will also be reported. Analysis of the endpoint will use the AT analysis set.

3. **Hospital readmission for any cause at 30 days**

    Hospital readmission will be based on data collected on the site-reported rehospitalization form. The rate at 30 days will be estimated by Kaplan-Meier survival analysis. Analysis of the endpoint will use the AT analysis set.

4. **Incidence of clinical efficacy (after 30 days) at 12 months and annually to 5 years defined as a composite of:**
    - All-cause mortality
    - All stroke (disabling and non-disabling)
    - Requiring hospitalizations for valve-related symptoms or worsening congestive heart failure

- NYHA class III or IV
- Valve-related dysfunction (mean aortic valve gradient ≥20 mmHg, EOA ≤0.9-1.1 cm^2 and/or DVI <0.35m/s, AND/OR moderate or severe prosthetic valve regurgitation)

Note that the EOA threshold of 0.9 applies for subjects with BSA <1.6 m^2 and EOA threshold of 1.1 applies for subjects with BSA ≥1.6 m^2. The endpoint will be evaluated at each time point using the point estimates from a Kaplan-Meier analysis. Components of the endpoint will be reported on the echo core lab CRF, the follow-up visit CRF, and the CEC CRF. Events occurring within 12 months and annually to 5 years, will be counted towards the event rate at each time point. Time to event for the overall composite will be based on the earliest component event; components of the event (NYHA class, valve-related dysfunction) that are detected on scheduled follow-up visits (e.g., 12 months) will be the minimum of the assessment date or the visit target date (e.g., 365 days). Censoring time will be the last available time where subjects are known to be fully event free. Subjects with an event within 30 days will be excluded from the analysis. Analysis of the endpoint will use the Implanted analysis set.

5. **Components of the primary clinical endpoint at 12 months and annually to 5 years:**
    - Mortality
    - Disabling stroke
    - Heart failure rehospitalization

    Mortality, disabling stroke, and heart failure rehospitalization will be adjudicated by the CEC and analysis will be based on data collected on the CEC adjudication form. Each component will be analyzed with Kaplan-Meier survival analysis according to **Section 7.2** for each time point. Analysis of the endpoint will use the AT analysis set.

6. **New pacemaker implantation rate at 30 days, 12 months and annually to 5 years**

    New pacemaker implantation will be reported according to data reported by the investigator on the Permanent Pacemaker Implant CRF. The endpoint will be analyzed with Kaplan-Meier survival analysis according to **Section 7.2** for each time point. Analysis of the endpoint will use the AT analysis set, excluding patients with PPI or ICD prior to the study TAVR procedure.

7. **Aortic valve re-intervention at 30 days, 12 months and annually to 5 years**

    Aortic valve re-intervention will be adjudicated by the CEC and analysis will be based on data collected on the CEC adjudication form. The endpoint will be analyzed with Kaplan-Meier survival analysis according to **Section 7.2** for each time point. Analysis of the endpoint will use the AT analysis set.

8. **6MWT at 30 days, 12 months and annually to 5 years**

    The six-minute walk test (6MWT) measures the distance walked in meters (m). Distance walked at each time point will be summarized as a continuous outcome within treatment arm. The number of subjects unable to perform the test will also be tabulated by reason at each visit. Within each arm, change from baseline will be summarized descriptively. Analysis will be performed using the AT analysis set for all subjects able to complete the assessment at the follow-up visit.

9. **QoL (KCCQ, EQ-5D) at 30 days, 12 months and annually to 5 years**

The Kansas City Cardiomyopathy Questionnaire (KCCQ) is a 23-item self-administered instrument and responses will be collected in the CRF. The domain and summary scores include: Physical Limitation, Symptom Stability, Symptom Frequency, Symptom Burden, Total Symptom Score, Self-efficacy, Quality of Life, Social Limitation, Overall Summary Score, and Clinical Summary Score. At each follow-up time point, the overall summary score and clinical summary score will be summarized descriptively as continuous data within treatment arm. For each treatment arm, change from baseline will be summarized. Analysis will be performed using the AT analysis set.

The EQ-5D Index will be summarized as continuous data within treatment arm at each follow-up timepoint. Additionally, for each treatment arm, change from baseline will be summarized descriptively. Analysis will be performed using the AT analysis set.

10. **BVD (HSVD, NSVD, thrombosis, endocarditis, and aortic valve re-intervention) at 2 to 5 years annually**

    The endpoint will be derived following the same principles as described for the valve function composite co-primary endpoint in **Section 7.9.2**, with same method used for the primary analysis at 12 months. Cutoff days for point estimates are 730, 1095, 1465, and 1825 for analysis time points of 2 years, 3 years, 4 years, and 5 years, respectively. Time to event for events detected on scheduled follow-up echos at 2 years, 3 years, 4 years, and 5 years will be the minimum of the echo date or the visit target date (e.g., 365 days). As in the primary endpoint analysis, HSVD and NSVD events detected through the maximum of the annual visit echo date or the end of the corresponding visit window will be counted to ensure inclusion of events detected on unscheduled echos. Thrombosis, endocarditis, and aortic valve re-intervention events detected through the visit target date (730, 1095, 1465, and 1825 days respectively) will be counted. Components of the endpoint will also be reported at each time point. Analysis will use the Implanted analysis set.

    Given the increasing impact of mortality on availability of the BVD endpoint at later time points, a survival analysis for interval-censored outcome data in the presence of competing risks will be performed as a supportive analysis, as described in the list of supportive analyses at the end of **Section 7.9.2**.

11. **Echocardiographic measurements (i.e., EOA, mean gradient, PVL, LV mass regression, and DVI (severe <0.25, moderate 0.25-0.5, mild >0.5)) at discharge, 30 days, 12 months and annually to 5 years**

    Echocardiographic measurements will be summarized descriptively based on core lab reported data at each time point within arm. Analysis will be performed using the Implanted analysis set.

    EOA and mean gradient will be analyzed as continuous data. Change from baseline in EOA and mean gradient will be summarized descriptively within each arm. Paravalvular leak (PVL) and DVI (severe <0.25, moderate 0.25-0.5, mild >0.5) will be analyzed descriptively as categorical data.

12. **Mean gradient ≥ 20 mmHg based on stress echocardiogram at 12 months at select sites**

    Mean gradient ≥ 20 mmHg based on stress echocardiogram at 12 months will be summarized descriptively as categorical data for each treatment arm. Stress echocardiogram will only be

performed within a subset of select sites in the trial and analysis will be based on available mean gradient on stress echocardiogram at 12 months. Analysis will use the Implanted analysis set for subjects enrolled in the stress echo sub-study, excluding subjects with LVOT obstruction during exercise.

7.9.5 Subgroup Analysis

The following subgroup analyses will be performed for the clinical outcome composite endpoint and for the valve function composite endpoint at 12 months:

1. Age (<75, ≥ 75 years)
2. Sex (female, male)
3. STS-PROM (<3, 3-5, 5-8, >8%)
4. Baseline left ventricular ejection fraction (LVEF) (< 50%, ≥ 50%)
5. Renal dysfunction (on dialysis) vs. not on dialysis at time of screening
6. History of atrial fibrillation (AF)
7. Prior cerebrovascular accident (CVA)
8. Pre-existing left bundle branch block (LBBB) / complete heart block (CHB)

For each subgroup, the incidence of the composite endpoint will be presented with the Kaplan-Meier estimate of the composite event rate at 365 days (cumulative incidence) within treatment arm along with the estimated difference in event rates (SE TAV - BE TAV) at 365 days and corresponding two-sided 95% large sample confidence interval. Additionally, p-values testing for interaction between treatment and subgroup will be computed using a Cox proportional-hazards model. The same approach will be used for the clinical outcome composite endpoint and valve function composite endpoint.

Additionally, analyses by sex will be performed for the powered secondary endpoint.

7.10 Safety Evaluation

CEC adjudicated adverse events will be summarized at 30 days, 1 year, and annually through 5 years. The number of events, number of subjects with event, and the Kaplan-Meier event rate (cumulative incidence) will be reported for each category and time point by treatment arm.

Additionally, a summary of procedure related adverse events, and device related adverse events will be reported by MedDRA system organ class and preferred term by treatment arm. Device deficiencies including deficiencies which could have led to a serious adverse device effect and listing of subject deaths will also be reported.

7.11 Stress Echocardiogram Sub-study

A subset of subjects will undergo a stress echocardiogram at selected sites. Demographic, baseline, and treatment characteristics will be summarized descriptively by arm for this cohort. In additional to non-powered secondary endpoint #12, additional parameters collected from the stress echocardiogram may be summarized descriptively including PPM, LV diastolic function, severity of MR, and LVOT obstruction during exercise.

7.12 Changes/Clarification to Planned Analysis

This analysis plan is consistent with the CIP for which the plan was developed with the following clarifications:

7.1.3.1 Screening Population. The CIP states that subjects consented who exit prior to the TAVR procedure will not be analyzed or reported. However, the screening population was revised in the SAP to state that subjects who are consented and exited prior to randomization will not be reported as analyses of the ITT population are planned, which will include all randomized subjects including those who exit the study between randomization and the TAVR procedure.

7.9.4 Non-Powered Secondary Objective #1 (Device Success). The CIP states that Device Success will be analyzed on the AT analysis set. The SAP has clarified that this endpoint will be analyzed for patients in the AT analysis set in which the delivery catheter was introduced, since the intended performance component cannot be assessed otherwise.

7.9.4 Non-Powered Secondary Objective #4 (Clinical Efficacy). The CIP states that Clinical Efficacy will be analyzed on the AT analysis set. This has been revised in the SAP to clarify that this endpoint will be analyzed in the Implanted analysis set, since the valve dysfunction component contains echo-derived components which are analyzed using the Implanted analysis set.

Any other deviations from the planned analysis in the CIP will be documented in an amended statistical analysis plan, when possible, and/or will be described with justification and rationale in the study report.

8. Validation Requirements

Level 1 validation (independent validation) will be used for the analysis datasets and for all hypothesis tested endpoints (co-primary endpoints and five powered secondary endpoints). Level 2 validation (peer review), at minimum, will be used for additional analyses, data summaries, and listings.

9. References

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