Abbott

Statistical Analysis Plan

[redacted]

VANTAGE Clinical Trial [redacted]

Evaluation of TAVI Using the NAVITOR Valve in a Global Investigation

Statistical Analysis Plan (SAP)

Version C

August 01, 2024

[redacted]

Statistical Analysis Plan

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Statistical Analysis Plan

1.0 SYNOPSIS OF STUDY DESIGN

1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) provides a detailed and comprehensive description of the planned methodology and analysis to be used for Clinical Investigation Plan ABT-CIP-10342, the VANTAGE clinical investigation. This plan is based on the Version C Clinical Investigation Plan (CIP).

1.2 Clinical Investigation Objectives

The objective of the proposed clinical trial is to evaluate the safety and effectiveness of the Navitor™ Transcatheter Aortic Valve Implantation (TAVI) System in patients with severe, symptomatic native aortic stenosis who are at intermediate or low risk of surgical mortality. This trial will also evaluate the safety and effectiveness of the Navitor TAVI System in a valve-in-valve application in patients with symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve across all surgical risk categories.

1.3 Clinical Investigation Design

The VANTAGE trial is a prospective, single-arm, multi-center, international, pre-market clinical investigation designed to evaluate the safety and effectiveness of the Navitor TAVI System in accordance with ISO standard 14155:2020. The trial will register subjects in three cohorts: (1) primary analysis cohort (up to 450 subjects), (2) roll-in cohort (up to 40 subjects), and (3) valve-in-valve (ViV) cohort (up to 100 subjects). To be eligible for participating in the primary analysis and roll-in cohorts, a patient must have symptomatic, severe native aortic stenosis and have intermediate or low risk for surgical valve replacement. To be eligible for participating in the ViV cohort, a patient must have symptomatic heart disease due to failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve, and the patient can be in any risk category.[1]

Subjects will be enrolled and treated with the Navitor Valve at up to 40 experienced TAVI implant centers across Australia, Europe, and Israel. All sites must either have prior Portico or Navitor TAVI system experience or must complete roll-in cases. Upon providing informed consent and approval by the Screening Committee (SC), subjects will undergo Navitor Valve implantation via a transfemoral or alternative access (subclavian or axillary) approach using the site's anesthesia protocol for TAVI procedures. In the trial, the point of enrollment is defined as informed consent signing, whereas the point of registration is defined as the insertion of the FlexNav Delivery System (loaded with a Navitor Valve) into the subject's vasculature (the subject is considered attempted with Navitor Valve implantation at this point). Only registered subjects will be included in the analysis.

There are two co-primary endpoints for the primary analysis cohort, each of which will be tested against a literature-derived performance goal. The primary safety endpoint is a composite of all-cause mortality or fatal stroke/stroke with disability at 12 months post index Navitor implantation procedure. The primary effectiveness endpoint is moderate or greater paravalvular leak (PVL) at 30 days post index Navitor implantation procedure. The number of subjects required to be registered in the primary analysis cohort is 434. In addition, per ISO 5840-3:2021, the standard for heart valve substitutes implanted by transcatheter techniques, 400 patient-years of follow-up are required to assess late adverse events.

[1] In Germany, only subjects at high or extreme surgical risk can be included in the ViV cohort. Sites in Switzerland will not participate in the ViV enrollment.

[redacted]

Roll-in and ViV cohorts will be summarized separately and will not contribute to the required sample sizes for hypothesis testing or the 400 patient-year requirement.

Subjects participating in the clinical trial will be followed for a total of 10 years with data collected at screening, baseline, procedure, prior to hospital discharge, and follow-up at 30 days, 12 months and annually thereafter up to 10 years.[2] Key assessments required at each visit are described in Section 6.0 in the CIP. The expected duration of enrollment in the primary analysis cohort is [redacted] months, and the total duration of the clinical study including final data cleaning, reporting, and site close-out is expected to be approximately [redacted] years. Follow-up data through 10 years will be submitted as part of a final report to respective regulatory agencies.

1.4 Endpoints

1.4.1 Primary Endpoints

The trial has two (2) co-primary endpoints in the primary analysis cohort.

1.4.1.1 Primary Safety Endpoint

The primary safety endpoint is a composite of all-cause mortality or fatal stroke/stroke with disability at 12 months post index Navitor implantation procedure per the Valve Academic Research Consortium (VARC) 3 event definitions[3].

1.4.1.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is moderate or greater paravalvular leak at 30 days post index Navitor implantation procedure, assessed by the echocardiographic core laboratory.

1.4.2 Secondary Endpoints

The trial has three (3) secondary endpoints in the primary analysis cohort.

1. Mean change in mean transvalvular gradient between baseline and 12 months
2. Mean change in effective orifice area between baseline and 12 months
3. Mean change in Kansas City Cardiomyopathy Questionnaire (KCCQ) quality of life score between baseline and 12 months

[2] Subjects in the high or extreme risk category in the ViV cohort will be followed up to 5 years.
[3] Varc-3 Writing, C. *et al.* Valve Academic Research Consortium 3: Updated Endpoint Definitions for Aortic Valve Clinical Research. *J Am Coll Cardiol* **77**, 2717-2746, doi:10.1016/j.jacc.2021.02.038 (2021).

1.4.3 Descriptive Endpoints[4]

The rate of the following outcomes will be assessed as descriptive endpoints for the trial in the primary analysis cohort as well as the roll-in and ViV cohorts:

1. Major adverse events (non-hierarchical composite of all-cause mortality, fatal stroke/stroke with disability, type 3/type 4 bleeding, stage 3/stage 4 acute kidney injury, major vascular complications, or major access-related non-vascular complications) at 30 days
2. Non-hierarchical composite of all-cause mortality or all stroke at 12 months
3. Procedural success defined as successful vascular access, delivery and deployment of the Navitor Valve; retrieval of the delivery system and correct positioning of a single Navitor Valve in the proper anatomical location and the absence of procedural mortality
4. Mortality (all-cause, cardiovascular, and valve-related) at 30 days and 12 months
5. Stroke (All stroke, fatal stroke, stroke with disability, and stroke without disability) at 30 days and 12 months
6. Transient ischemic attack (TIA) at 30 days and 12 months
7. Bleeding (type 4, type 3, and type 2) at 30 days
8. Major vascular complications at 30 days
9. Major access-related non-vascular complications at 30 days
10. Major cardiac structural complications at 30 days
11. Acute kidney injury (stage 4, stage 3, and stage 2) at 30 days
12. Permanent pacemaker insertion at 30 days and 12 months
13. Myocardial infarction at 30 days and 12 months
14. Coronary obstruction requiring intervention at 30 days and 12 months
15. Changes in functional status from baseline to follow-up assessments at 30 days and 12 months (e.g., New York Heart Association (NYHA) functional classification, six-minute walk test, quality of life measure: Kansas City Cardiomyopathy Questionnaire (KCCQ))
16. Rehospitalization (procedure-related or valve-related hospitalization, and other cardiovascular hospitalization) at 30 days and 12 months
17. Paravalvular leak (none/trace, mild, moderate or severe) at discharge, 30 days, 12 months and annually (when collected) through 10 years
18. Changes in echocardiographic parameters from baseline to follow-up at 30 days, 12 months and annually (when collected) through 10 years (e.g., mean effective orifice area, mean transvalvular gradient)
19. Aortic valve reintervention at 30 days, 12 months, and annually through 10 years
20. Prosthetic valve endocarditis at 12 months and annually through 10 years
21. Structural valve deterioration at 12 months and annually through 10 years

[4] Event definitions for descriptive endpoints #1, 2, 4, 5, 6, 7, 8, 9, 10, 11, 13, 16, 20, 21, 22, and 24 are based on the VARC-3 definitions.

[redacted]

22. Non-structural valve dysfunction at 12 months and annually through 10 years
23. Successful coronary access as needed at 12 months and annually through 10 years
24. Clinically significant prosthetic valve thrombosis at 12 months and annually through 10 years

All endpoints will be assessed from the index procedure unless otherwise noted.

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Attempted Population

The attempted population (AP) will include all registered subjects (subjects attempted with Navitor Valve implantation, defined as the insertion of the FlexNav Delivery System (loaded with a Navitor Valve) into the subject's vasculature).

2.1.2 Implanted Population

The implanted population (IP) will include all registered subjects successfully implanted with the Navitor Valves at the end of the index procedure.

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age, BMI, etc.), results will be summarized with the numbers of observations, means, and standard deviations, with quartiles, minimums, maximums, and 95% confidence intervals for the means when specified.

2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables (e.g., gender, diabetic status, etc.), results will be summarized with subject counts and percentages/rates, and where specified in the table mockups, with exact 95% Clopper-Pearson confidence intervals.

2.2.3 Survival Analyses

Survival analysis will be conducted to analyze time-to-event variables. Subjects without events will be censored at their last known event-free time point. Survival curves will be constructed using Kaplan-Meier (KM) estimates.

2.2.4 Analysis in Response to COVID-19 Impact

As the Coronavirus Disease 2019 (COVID-19) pandemic has spread around the globe, the following analysis mechanism will be implemented to minimize the potential confounding effect from this emerging infectious disease for the trial primary safety endpoint set forth in assessing the trial success and labeling claims. In alignment with the EU guidance document "Guidance on the Management of Clinical Trials during the COVID-19 (Coronavirus) Pandemic" updated on 28-April-2020, additional consideration was given to the impact of the COVID-19 pandemic on the primary safety endpoint analyses for this study. As such, prespecified methods are included in the sections that follow to indicate the handling of any

outcomes impacted by COVID-19 as well as efforts to minimize missing endpoint data during the COVID-19 pandemic. Specific analyses to address COVID-19 impacts are included in relevant subsections in Section 2.3.

2.3 Endpoint Analysis

This section describes the statistical methods for the primary analysis cohort (subjects with stenosis of the native aortic valve) unless otherwise specified. Data on roll-in and ViV cohorts will be descriptively summarized. The ViV cohort will be summarized relative to data from studies in which patients with a failed surgical bioprosthetic aortic valve were treated with TAVI for the valve-in-valve application.[5,6]

2.3.1 Primary Endpoints Analysis

2.3.1.1 Primary Safety Endpoint

The primary safety endpoint is a composite of all-cause mortality or fatal stroke/stroke with disability at 12 months post index Navitor implantation procedure as adjudicated by the CEC per the VARC-3 event definitions.[7] COVID-19 relatedness of mortality and fatal stroke/stroke with disability will be adjudicated by the CEC, and any 12-month death or fatal stroke/stroke with disability that is adjudicated as COVID-19 related will be excluded and subjects' follow-up will be censored at the first COVID-19 related event from the primary analysis.

The hypothesis testing of the primary safety endpoint will be performed for the mixed-risk (mixed intermediate and low risk) group based on the attempted population described in Section 2.1.1. If the primary safety endpoint is met, the trial will have demonstrated that the Navitor TAVI System is safe in the intermediate and low risk populations.

Specifically, the following hypotheses will be tested:

H_{10}: $p_{Mixed} \geq PG_{Mixed}$

H_{1a}: $p_{Mixed} < PG_{Mixed}$

where p_{Mixed} is the primary safety endpoint event rate in the mixed intermediate and low risk group at 12 months and PG_{Mixed} is the performance goal for a mixed intermediate and low risk group. This hypothesis will be tested at a one-sided significance level of 0.025 and the null hypothesis will be rejected if the one-sided 97.5% upper confidence bound (UCB) for the event rate, p_{Mixed}, is less than the performance goal, PG_{Mixed}. The 12-month event rate will be estimated using the KM method, and the standard error of KM estimate will be calculated using Greenwood method.

The performance goal for the mixed-risk group (PG_{Mixed}) is determined by the proportion of the study population registered in the trial that is intermediate risk ($prop_{Int}$) or low risk ($prop_{Low}$). The performance goals in the intermediate risk and low risk groups are PG_{Int} and PG_{Low}, respectively. The mixed-risk group performance goal is determined by:

[5] Edwards SAPIEN 3 Transcatheter Heart Valve System. Summary of Safety and Effectiveness Data. https://www.accessdata.fda.gov/cdrh_docs/pdf14/P140031S028b.pdf. (2017).
[6] Medtronic CoreValve System: Summary of Safety and Effectiveness Data. https://www.accessdata.fda.gov/cdrh_docs/pdf13/P130021S010B.pdf. (2015).
[7] A composite of all-cause mortality or fatal stroke/stroke with disability per VARC-3 is equivalent to a composite of all-cause mortality or disabling stroke per VARC-2.

[redacted]

$$PG_{Mixed} = (prop_{Int} * PG_{Int}) + (prop_{Low} * PG_{Low})$$

The 12-month primary safety endpoint event rates for the Navitor TAVI System in intermediate and low risk groups are assumed to be [redacted], respectively, based on published data from other TAVI pivotal trials [redacted]. Per the recommendation of ISO 5840-3:2021, [redacted] the performance goals in the intermediate risk group (PG_{Int}) and low risk group (PG_{Low}) are set to be 16.6% and 5.4%, respectively. Assuming a 1:1 ratio between intermediate and low risk groups, with 262 registered subjects, there is 85% power at a one-sided 2.5% significance level [redacted] with the performance goal set at 11%, and an attrition rate of 10% at 12 months (due to withdrawal or loss to follow-up prior to 365 days). [redacted] A ratio of 1:1 is used for the assumed mix based on the minimum proportion of the intermediate risk group in the range (50%) that is required in the trial. The sample size of 262 subjects provides at least 85% power for all scenarios within the range of proportions of intermediate risk group between 50% and 70%. [redacted]

The first 262 consecutively registered subjects will be used to test this hypothesis.

2.3.1.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint is moderate or greater PVL at 30 days post index Navitor implantation procedure, as assessed by the echocardiographic core laboratory.

The hypothesis testing of the primary effectiveness endpoint will be performed based on the implanted population (described in Section 2.1.2) in whom a functional Navitor Valve remains implanted at 30 days. If the primary effectiveness endpoint is met, the trial will have demonstrated that the Navitor TAVI System is effective in the intermediate and low risk populations. Given TAVI devices have the same anatomical considerations regardless of a subject's surgical risk category, the expected event rate and performance goal for the primary effectiveness endpoint do not need to be adjusted according to the subject's risk classification. Based on published data from other TAVI pivotal trials [redacted], the [redacted] performance goal, [redacted] is set to 6.6%.

Specifically, the following hypothesis will be tested:

H_{20}: $\pi \geq 6.6\%$
H_{2a}: $\pi < 6.6\%$

where π is the proportion of subjects who have moderate or greater PVL at 30 days. π will be estimated as a binomial proportion. The hypothesis will be tested at a one-sided significance level of 0.025, and the null hypothesis will be rejected if the 97.5% upper confidence bound (UCB) for the proportion, π, is less than the performance goal of 6.6%. The 97.5% UCB will be calculated by the Clopper-Pearson method for exact confidence intervals for binomial proportion.

With 390 subjects, there is approximately 85% power at a one-sided 2.5% significance level [redacted]. With an approximately 10% attrition rate at 30 days (due to death or withdrawal

[redacted]

[redacted]

prior to the 30-day visit, missing echo images, or inability of echo core lab to assess PVL on echo image), the sample size needed is 434 subjects. [redacted]

All registered subjects with available 30-day PVL data will be used to test this hypothesis.

2.3.2 Secondary Endpoints

There are three secondary endpoints described below.

1. Mean change in mean transvalvular gradient between baseline and 12 months

   The null and alternative hypotheses are stated as:

   H_{30}: $\Delta\mu_{3,12\text{ months - Baseline}} \geq -10$ mmHg

   H_{3a}: $\Delta\mu_{3,12\text{ months - Baseline}} < -10$ mmHg

   where $\Delta\mu_{3,12\text{ months - Baseline}}$ is the mean paired difference in mean transvalvular gradient from baseline to 12 months.

   This secondary endpoint will be assessed in the implanted population in whom a functional Navitor Valve remains implanted at 12 months.

2. Mean change in effective orifice area between baseline and 12 months

   The null and alternative hypotheses are stated as:

   H_{40}: $\Delta\mu_{4,12\text{ months - Baseline}} \leq 0.4$ cm^2

   H_{4a}: $\Delta\mu_{4,12\text{ months - Baseline}} > 0.4$ cm^2

   where $\Delta\mu_{4,12\text{ months - Baseline}}$ is the mean paired difference in effective orifice area from baseline to 12 months.

   This secondary endpoint will be assessed in the implanted population in whom a functional Navitor Valve remains implanted at 12 months.

3. Mean change in KCCQ quality of life score between baseline and 12 months

   The null and alternative hypotheses are stated as:

   H_{50}: $\Delta\mu_{5,12\text{ months - Baseline}} \leq 5$

   H_{5a}: $\Delta\mu_{5,12\text{ months - Baseline}} > 5$

   where $\Delta\mu_{5,12\text{ months - Baseline}}$ is the mean paired difference in KCCQ quality of life score from baseline to 12 months.

   This secondary endpoint will be assessed in the attempted population.

All secondary endpoint hypothesis tests will be performed with one-sample *t*-test at one-sided significance level of 0.025. The first 262 consecutively registered subjects will be used to test these hypotheses.

2.3.3 Descriptive Endpoints

The descriptive endpoints specified in Section 1.4.3 will be summarized with descriptive statistics based on methods in Sections 2.2.1 and 2.2.2. Descriptive endpoints such as adverse events will be analyzed

descriptively in the attempted population, descriptive endpoints including valve-related long-term events will be analyzed descriptively in the implanted population (described in Section 2.1.2) in whom a functional Navitor Valve remains implanted at the time of assessment. Besides analyses stated above, additional analyses will be performed for the following descriptive endpoints.

2.4 Sample Size Calculations

The sample size (which includes attrition) required for evaluation of the primary safety endpoint and primary effectiveness endpoint are 262 and 434 subjects, respectively. The primary effectiveness endpoint requires a larger sample size (N=434) and therefore determines the overall sample size of the trial.

2.5 Timing of Analysis

The analysis in the primary analysis cohort for regulatory approval submission will be conducted after (1) the first 262 consecutively registered subjects have been followed for 12 months[8], (2) all registered subjects[9] have been followed for 30 days[10], and (3) 400 patient-years of follow up have been completed. The first 262 consecutively registered subjects will be used for the hypothesis testing of the primary safety endpoint, and all registered subjects will be used for the hypothesis testing of the primary effectiveness endpoint.

2.6 Trial Success

The trial will be considered successful if both the primary safety and effectiveness endpoints are met.

2.7 Subgroups for Analysis

Subgroup analysis will be performed to examine the results of the primary endpoints across baseline risk categories, specifically by risk group (intermediate vs low risk), and sex (male vs female). For each subgroup, KM estimates on the primary safety endpoint event will be reported along with 95% confidence intervals, while proportional rate estimates on the primary effectiveness endpoint event will be reported along with 95% exact confidence intervals.

2.8 Multiplicity Issues

The study will be successful if both primary safety and effectiveness endpoints are met. If both primary endpoints are met, fixed sequence procedure in the pre-specified order of secondary endpoints listed below will be used.

1. The secondary endpoint (#1) of change in mean transvalvular gradient between baseline and 12 months.

[8] This includes subjects who die, withdraw, or are lost to follow-up before 365 days.
[9] If more than 434 subjects are registered before enrollment completion for this cohort, all registered subjects will be included in the hypothesis testing of the primary effectiveness endpoint.
[10] This includes subjects who die, withdraw, or are lost to follow-up before the 30-day follow-up visit.

[redacted]

2. The secondary endpoint (#2) of change in mean effective orifice area between baseline and 12 months.
3. The secondary endpoint (#3) of change in KCCQ quality of life score between baseline and 12 months.

If one hypothesis test in the secondary endpoint sequence is not statistically significant, the subsequent tests will not be performed. Hence, no additional multiplicity adjustment is needed.

2.9 Sensitivity Analysis

For the primary safety endpoint, sensitivity analysis will be conducted including all CEC adjudicated death or fatal stroke/stroke with disability events regardless of relationship to COVID-19 to assess the impact of the pandemic. The first 262 consecutively registered subjects will be used for this analysis. Additionally, sensitivity analysis for the primary safety endpoint will be conducted including all registered subjects and all available follow-up, both with and without COVID-19 censoring.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

All analyses in this section will be performed in the primary analysis cohort, the roll-in cohort, and the ViV cohort.

3.1 Baseline and Demographic Characteristics

The following baseline and demographic variables will be summarized for the subjects registered: gender, age, ethnicity, race, surgical risk, medical co-morbidities, arrhythmia history, previous pacemaker implant, history of smoking, implant procedural characteristics, etc.

3.2 Adverse Events

All of the adverse device effects, serious adverse device effects, UADEs, USADEs will be summarized for all subjects who registered in this trial in terms the number of events and the percentage of subjects with events per MedDRA coding. All CEC adjudicated adverse events will also be summarized for all subjects who registered in the trial in terms the number of events, the percentage of subjects with events. Moreover, COVID-19 related AEs will be summarized in terms of number of events, the percentage of subjects with events per AE term.

3.3 Subject Early Termination

Subject early termination reasons including deaths, withdrawals, lost-to-follow-up, etc. will be summarized at all scheduled visits.

3.4 Protocol Deviation

For subjects in whom a protocol deviation was reported, protocol deviations will be summarized in terms of number of deviations and number of subjects with deviations by type of deviation. COVID-19 related protocol deviations will also be reported.

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

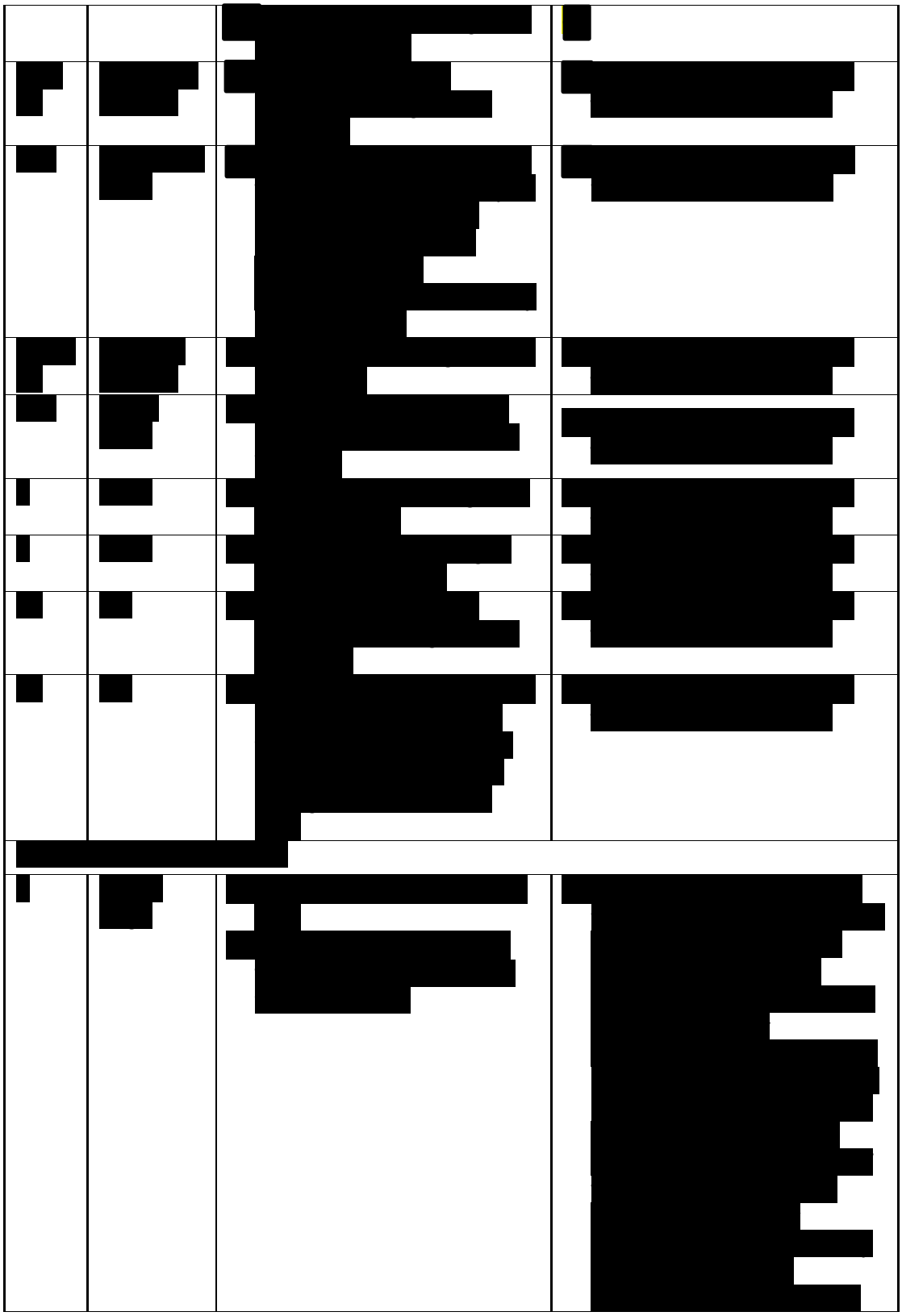
All analyses will be performed using SAS® for Windows, version 9.4 or higher.

[redacted]

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
AE	Adverse Event
AP	Attempted Population
AS	Aortic Stenosis
CEC	Clinical Events Committee
CIP	Clinical Investigation Plan
IP	Implanted Population
KCCQ	Kansas City Cardiomyopathy Questionnaire
KM	Kaplan-Meier
LTF	Lost-to-follow-up
NYHA	New York Heart Association
PG	Performance Goal
PPI	Permanent Pacemaker Insertion
PVL	Paravalvular Leak
SAE	serious adverse event
SAP	statically analysis plan
TAVI	Transcatheter Aortic Valve Implantation
TIA	Transient Ischemic Attack
UADE	Unanticipated adverse device effect
UCB	Upper Confidence Bound
USADE	Unanticipated serious adverse device effect
ViV	Valve-in-Valve

6.0 APPENDIX A: STATISTICAL ANALYSIS PLAN REVISIONS



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