BIO-CONDUCT: BIOTRONIK Conduction System Pacing with the Solia Lead

Statistical Analysis Plan
Version 1.0
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1 Introduction

This statistical analysis plan (SAP) for the BIO-CONDUCT study contains definitions of analysis populations and statistical methods for the analysis of the study data. This SAP further specifies the pre-planned analyses as outlined in the August 10, 2022 protocol version. The SAP is applicable to clinical study reports that include statistical analysis testing of the primary endpoints and/or secondary endpoint 1, as well as subgroup analysis and poolability analysis.

The BIO-CONDUCT study was designed to evaluate the safety and effectiveness of the BIOTRONIK Solia S pacing lead when implanted in the left bundle branch (LBB) area.

2 Synopsis of Study Design and Procedures

2.1 Study Objectives

2.2 Study Design

BIO-CONDUCT is a prospective, non-randomized, multi-center, investigational device exemption (IDE) study. This clinical investigation is designed to enroll up to 260 subjects who will be followed for at least 12 months post-implant at up to 25 clinical study sites within the United States (U.S.). The design allows for pooling of data with other prospectively collected data sources to supplement the LBB area pacing population to achieve the sample size of 260 subjects with 3 months of follow-up needed for primary safety endpoint 1 analysis. Thus, the number of prospectively enrolled subjects in the BIO-CONDUCT study may be less than 260. At least 50% of the subjects included in the analysis will be from the BIO-CONDUCT study.

2.2.1 Primary Endpoints

Primary Endpoint 1: Serious adverse device effect (SADE)-free rate through 3 months post-implant

The purpose of primary endpoint 1 is to evaluate the overall incidence of serious Solia S LBB lead related adverse device effects and serious implant procedure events related to the Solia S LBB lead that occur through 3 months post-implant. The parameter of interest is the Solia S LBB lead complication-free rate, which will be calculated as the number of subjects without one or more complications divided by the total number of study subjects successfully enrolled and subjects undergoing an unsuccessful implant attempt who have a qualifying primary safety endpoint event in percent.

Primary Endpoint 2: Implant success

The purpose of primary endpoint 2 is to evaluate the implant success rate of the Solia S lead in the LBB area. The parameter of interest is the percentage of subjects with Solia S placed successfully in the LBB area divided by the total number of consented study subjects in whom an implant of Solia S in the LBB area was attempted. The definition of implant success is provided in Section 4.1.2.

2.2.2 Secondary Endpoints

One powered secondary endpoint and 4 descriptive secondary endpoints are planned.

1. Quality of Life (QOL) from baseline through 12 Months Post-Implant

The purpose of secondary endpoint 1 is to evaluate the improvement in QOL for subjects with the Solia S lead implanted in the left bundle branch (LBB) area. The parameter of interest is the change in the physical function SF-36 (36-Item Short Form Health Survey) QOL scale from pre-implant baseline to 12 months post-implant, which will be calculated as the mean change from baseline for all subjects that complete both the baseline QOL and 12-month QOL questionnaire.

2. SADE-free rate for Solia S LBB lead through 6- and 12-months post-implant
3. Solia S LBB lead pacing threshold at 3-, 6-, and 12-month follow-up visits
4. Solia S LBB lead R-wave sensed amplitude at 3-, 6-, 12-month follow-up visits
5. Solia S LBB lead pacing impedance at 3-, 6-, 12-month follow-up visits

2.2.3 Additional Data of Interest

Additional information is collected to characterize the study population, implanted system, and progress of the clinical investigation. These include demographics, medical history, cardiovascular medications, ECG characteristics, implanted device information, device programming, Home Monitoring transmission success, non-Solia S LBB area related adverse events, reasons for inability to place or achieve capture with Solia S in LBB area, revisions to implanted systems, results for returned product analysis, compliance to protocol, and change in QOL scales.

2.2.4 Other Planned Analyses

Other planned analyses include subgroup analysis (age ≥65 years), poolability analysis to assess the primary outcomes across sites and regions (U.S. and outside of U.S.), and analyses to determine differences in outcomes based on sex and race.

3 General Analysis Considerations

The planned analyses described here will be performed when the data required to complete the analysis is available. A pivotal analysis and interim report of primary endpoint 1 and primary endpoint 2 is planned and will support other analysis required for a PMA submission. Analysis of secondary endpoint 1 and subgroup analysis will be performed after all patients have completed the 12-month study visit or exited the study.

For annual progress reports, the results of completed analyses will be provided when available. If the planned analysis time point has not yet been met, progress toward the analysis and current available data will be presented using descriptive statistics within the annual progress report.

3.1 Statistical Methods

Descriptive statistics will be used to present and summarize the data collected in the clinical study. Frequency distributions (counts and percentages) and cross tabulations will be

presented for discrete variables. Means, standard errors, and ranges will be presented for continuous variables. Proportions will be calculated using known non-missing values. All statistical tests and/or confidence intervals will be performed at $\alpha = 0.05$ (2-sided).

For reporting of adverse events, descriptive statistics that describe the percentage of subjects experiencing an adverse event and rate of adverse event as events per subject-year will be provided. The total number of ITT subjects and cumulative duration of follow-up completed for the subjects as of the date of the report will be utilized to calculate the descriptive statistics.

Analysis of SADE-free rates for Solia S and procedure related events will be based on Clinical Events Committee (CEC) adjudicated event data. Analysis of the rest of the endpoints will be based on site-reported data.

3.2 Analysis Populations

All clinical data will be analyzed based upon the pre-defined analysis populations as outlined in Table 1. Additional analysis population considerations for specific analysis are included within the analysis method details (Section 4).

Table 1: Study Analysis Populations

Analysis Population	Definition
Intent-to-Treat (ITT) – Primary Endpoint 1 (Safety), Secondary Endpoint 2	This ITT population is defined as • all enrolled subjects (subjects with successfully implanted Solia S in the LBB area) and • subjects with an unsuccessful implant attempt of the Solia S in the LBB area who had a qualifying primary safety endpoint event prior to their exit from the study.
Intent-to-Treat (ITT) – Primary Endpoint 2 (Efficacy)	This ITT population is defined as • all enrolled subjects (subjects with successfully implanted Solia S in the LBB area) and • subjects with an unsuccessful implant attempt of the Solia S in the LBB area.
Intent-to-Treat (ITT) – Secondary Endpoint 1 (QOL), Secondary Endpoints 3-5	This ITT population is defined as • all enrolled subjects (subjects with successfully implanted Solia S in the LBB area)

3.3 Handling of Missing Data

All reasonable methods will be taken to ensure a minimum of missing data, including site monitoring, training, and corrective actions, if required, ongoing review of collected data for accuracy and completeness, and repeated, documented attempts to contact subjects with missing study visits. Any reasons for missing data or withdrawal from the study will be documented when possible.

If warranted, the impact of missing data on conclusions about the primary study endpoints will be examined in sensitivity analyses, which may include multiple imputation methods.

For secondary endpoint 1, missing QOL data at either the baseline or 12-month follow-up visit affects the number of subjects that can be included in the analysis. It is anticipated that subjects may either forget or choose not to answer one or more of the questions in the QOL. In some cases, subjects may also provide two answers for one or more of the questions. There is no appropriate method to correct these QOL questionnaires after the subject completes the visit.

If needed to ensure sufficient subjects to analyze secondary endpoint 1, an analysis using the last observation carried forward principle and/or average replacement for missing QOL answers or QOL questions with multiple answers may be performed. Additionally, last observation carried forward may be used in cases for which the QOL questionnaire is not completed at the 12-month visit. If there are more than 10% of subjects with missing answers, an assessment of the cause for the missing answers will be performed. If the assessment is such that a random cause can be assumed, then a multiple imputation technique that accounts for variability in imputation will be utilized. Additionally, where missing data are imputed, sensitivity analyses will be completed.

3.4 Interim Analysis

A pivotal analysis and interim report of the primary endpoint data is planned after 3-month follow-up data is collected for the BIO-CONDUCT study patients and the minimum sample size for primary endpoint 1 and primary endpoint 2 has been met. In addition to analyzing primary endpoints 1 and 2, the interim report will also summarize the additional data collected at time of analysis, including but not limited to Solia S LBBA lead measurements and non-Solia S adverse event rates. Poolability analysis for sites and regions, as well as analysis by sex and gender, will also be completed at time of interim analysis.

Further interim analyses are not planned and there are no statistical criteria to stop the study early. Thus, no adjustment of the significance level is planned due to the pivotal analysis.

3.5 Study Success

For the study to be considered successful, both primary endpoints must be met to control the type I error at the 1-sided 0.025 level. Secondary endpoint 1 will only be tested if both primary endpoints are successful.

4 Analysis Methods

4.1 Endpoint Analyses

4.1.1 Primary Endpoint 1 - Serious Adverse Device Effect (SADE)-Free Rate Through 3 Months Post-Implant

The purpose of primary endpoint 1 is to evaluate the serious lead related adverse device effects related to Solia S lead utilized or attempted to be implanted in the LBB area and

serious implant procedure events related to the Solia S LBB lead that occur through 3 months post-implant.

The following hypotheses have been defined to evaluate the primary endpoint "Serious adverse device effect (SADE)-free rate through 3 months post-implant":

H_o: The serious adverse device effect (SADE)-free rate through 3 months post-implant is less than or equal to 87.5%

SADE-free rate ≤ 87.5%

H_a: The serious adverse device effect (SADE)-free rate through 3 months post-implant is greater than 87.5%

SADE-free rate > 87.5%

Primary endpoint 1 will be evaluated by performing an exact, one-sided binomial proportion test comparing the observed proportion (overall SADE-free rate through 3 months) to the performance goal of 87.5%. The lower, two-sided 95% confidence bound for the overall SADE-free rate must be greater than 87.5% to reject the null hypothesis (H_o), which would demonstrate evidence that the SADE-free rate is significantly higher than 87.5%.

For the primary endpoint 1 analysis, ITT population subjects who have at least 76 days of follow-up (corresponding to the earliest potential in-window 3-month visit) or experienced the primary safety endpoint will be included. A Kaplan-Meier survival analysis (time-to-event) for the primary endpoint outcome will also be performed.

Subjects without a primary safety endpoint event with less than 76 days of follow-up will be excluded from the Kaplan-Meier survival analysis and the binomial proportion test to avoid overestimation of the SADE-free rate.

Sample Size Determination for Primary Endpoint 1

Prior studies evaluating the safety of Solia S when implanted in the right ventricle has demonstrated a high SADE-free rate, between 94.3% and 98.5% (Master Study of the Siello Pacemaker Lead and Siello IDE Clinical Study, data on file). When implanting in the LBB area, the expected safety needs to consider the change in implant location. A summary of published data that includes safety information for leads implanted in the LBB area is presented in Table 2.

Table 2: LBB Area Pacing—Published Safety Results

Study	Mean Follow-up Duration (months)	Total Implanted Subjects (n)	Subjects without SADE (n)	SADE-Free Rate	95% CI – Lower Bound
Su L et al. 2021	18.6	618	600	97.1%	95.4%
Vijayaraman P et al. 2019	5.2	93	87	93.6%	86.4%
De Pooter J et al. 2021	3.0	44	39	88.6%	75.6%
Li X et al. 2019	3.0	30	29	96.6%	81.9%

Based on this information, it is anticipated the Solia S lead will have a safety profile similar to published literature for leads implanted in the LBB area with an expected SADE-free rate of at least 93.0%. The assumed performance (93%) and performance goal of 87.5% are compared to the published safety results in Figure 1.

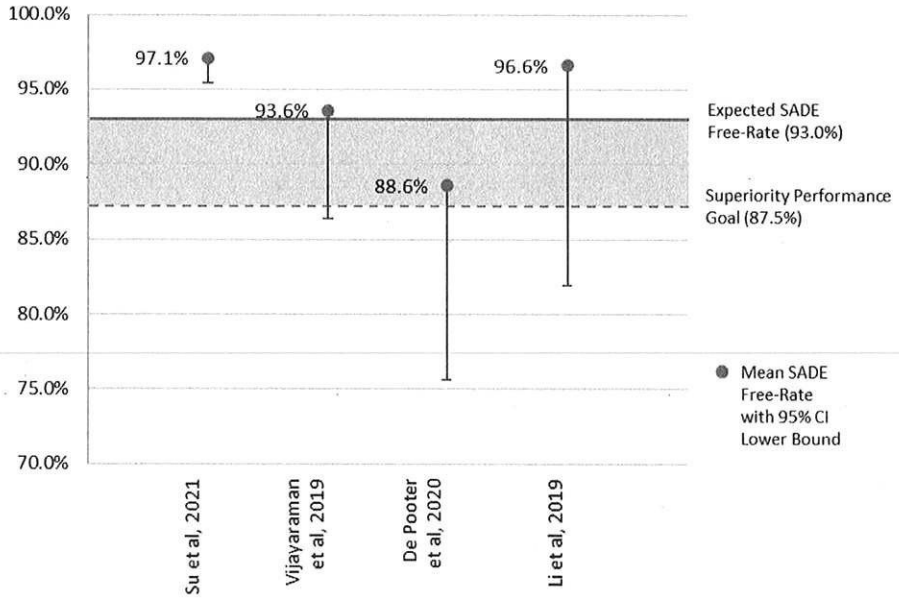

Figure 1: Assumed Safety Performance Compared to Published Results

The estimated sample size required to evaluate primary endpoint 1 is based on a superiority comparison of overall Solia S lead serious adverse device effect free-rate to 87.5% through 3 months post-implant. The sample size for primary endpoint 1 was calculated based on the following assumptions.

- Study Design: Non-randomized
- Type I error (alpha): 0.025 (one-sided for superiority)
- Statistical power: 80%
- Performance Goal for SADE-Free Rate through 3 months post-implant: 87.5%
- Expected SADE-Free Rate through 3 months post-implant: 93% (Based on Literature Review/Master Study)
- Test basis: Exact binomial test
- Attrition Rate: 5%

For primary safety endpoint 1, a total of 247 evaluable Solia S leads would be required to demonstrate superiority to a SADE-free rate of 87.5%. Assuming a 5% attrition rate, a total of 260 (= 247 / 0.95) patients with a Solia S lead would be required to be enrolled to evaluate Primary Safety Endpoint 1.

Justification of Pooling for Primary Endpoint 1

Justification of pooling data from other prospectively collected data sources will include the following considerations:

- Design of study including but not limited to inclusion/exclusion criteria, follow-up visit schedule, and required procedures/data collection
- Implanted devices included in the study
- Criteria for success of Solia S LBB area implants
- Study organization and level of monitoring
- Availability of subject level data and, when required, documentation supporting reported adverse events

Data from studies that are determined to be similar to BIO-CONDUCT with regards to the considerations above may be pooled for analysis of primary endpoint 1. A poolability analysis will be conducted to examine heterogeneity (Section 4.4).

Specifically, it is planned that for evaluation of primary safety endpoint 1, data from subjects in the BIO|MASTER.Selectra 3D study (NCT04323670) with a successful Solia S lead LBB area implant will be pooled with data from the BIO-CONDUCT study. The BIO|MASTER.Selectra 3D study was a multi-center, prospective, non-randomized post-market study designed to evaluate the clinical safety, performance, and handling of the Selectra 3D catheter when used for conduction system pacing implants (His bundle or LBB area) of the Solia S lead. Additionally, performance and safety of the Solia S lead was collected. A total of 157 subjects were enrolled into the BIO|MASTER.Selectra 3D study from October 8, 2020 to November 18, 2021 across 10 study sites in Europe, Asia, and Australia.

Only subjects enrolled into the BIO|MASTER.Selectra 3D study with a successful Solia S lead LBB area implant and at least 76 days of follow-up or with a Solia S lead LBB area implant attempt and qualifying primary safety endpoint event will be included in pooled analysis with the BIO-CONDUCT ITT population. All potential endpoint events occurring in the BIO|MASTER.Selectra 3D study (i.e., serious Solia S LBB lead events and serious procedure related events) will be adjudicated by the BIO-CONDUCT CEC and adjudication outcomes will be utilized for the analysis of primary endpoint 1.

4.1.2 Primary Endpoint 2 – Implant Success

The purpose of primary endpoint 2 is to evaluate the implant success rate of Solia S lead in the LBB area.

The following hypotheses have been defined to evaluate the primary efficacy endpoint:

H_0: The implant success rate of Solia S lead in the LBB area is less than or equal to 80%.

Implant Success Rate $\leq$ 80%

H_a: The implant success rate of Solia S lead in the LBB area is greater than 80%.

Implant Success Rate > 80%

Primary endpoint 2 will be evaluated by performing an exact, binomial test comparing the observed proportion (implant success rate) to the performance goal of 80%. The lower, two-sided 95% confidence bound for the overall implant success rate must be greater than 80% to reject the null hypothesis (H_o), which would demonstrate evidence that the rate of successful Solia S LBBAP implants is significantly higher than 80.0%.

Definition of Implant Success

Implant success is defined as successful placement in the LBB area with a pacing threshold of less than or equal to 2.5 V at 0.4 ms and a mean sensing value of greater than or equal to 2.0 mV in the final lead position. Evaluation of the mean sensing value is not required for patients that are pacing dependent.

For the BIO-CONDUCT study, successful placement in the LBB area is defined as: a) presence of two or more of the criteria listed below as determined and documented by the investigator, with b) at least one of Criterion #1 or #2 being met. (Huang W et al. 2019, Vijayaraman et al. 2021, De Pooter et al. 2020, Wu et al. 2021):

1. Paced QRS morphology that presents with a right bundle branch block (RBBB) pattern
2. Peak LV activation time (stimulus to peak of the R wave in leads V4 to V6) of < 90ms at high and low-output pacing
3. Presence of LBB potentials (LBB-V intervals of 15 to 35ms)
4. Demonstration of output-dependent non-selective LBBAP and selective LBBAP at near threshold outputs

Sample Size Determination for Primary Endpoint 2

Expectations for implant success are based on published findings for LBB area pacing (Table 3).

Table 3: LBB Area Pacing—Published Implant Success Results

Study	Total Subjects (n)	Subjects with successful implant (n)	Success Rate	95% CI – Lower Bound
Su L et al. 2021	632	618	97.8%	96.3%
Padala S et al. 2020	341	305	89.4%	85.7%
Li X et al. 2021	246	235	95.5%	92.1%
Vijayaraman P et al. 2019	100	93	93.0%	86.0%
Wang J et al. 2020	66	61	92.4%	83.1%
De Pooter J et al. 2020	50	44	88.0%	75.8%
Li X et al. 2019	33	30	90.9%	75.7%
Zhang S et al. 2021	33	29	87.9%	72.1%
Huang W et al. 2020	63	61	96.8%	88.5%

It is expected that the Solia S when implanted in the LBB area will have an implant success of 88.0%, which is similar to published rates. The assumed performance (88.0%) and performance goal of 80.0% are compared to the published safety results in Figure 2.

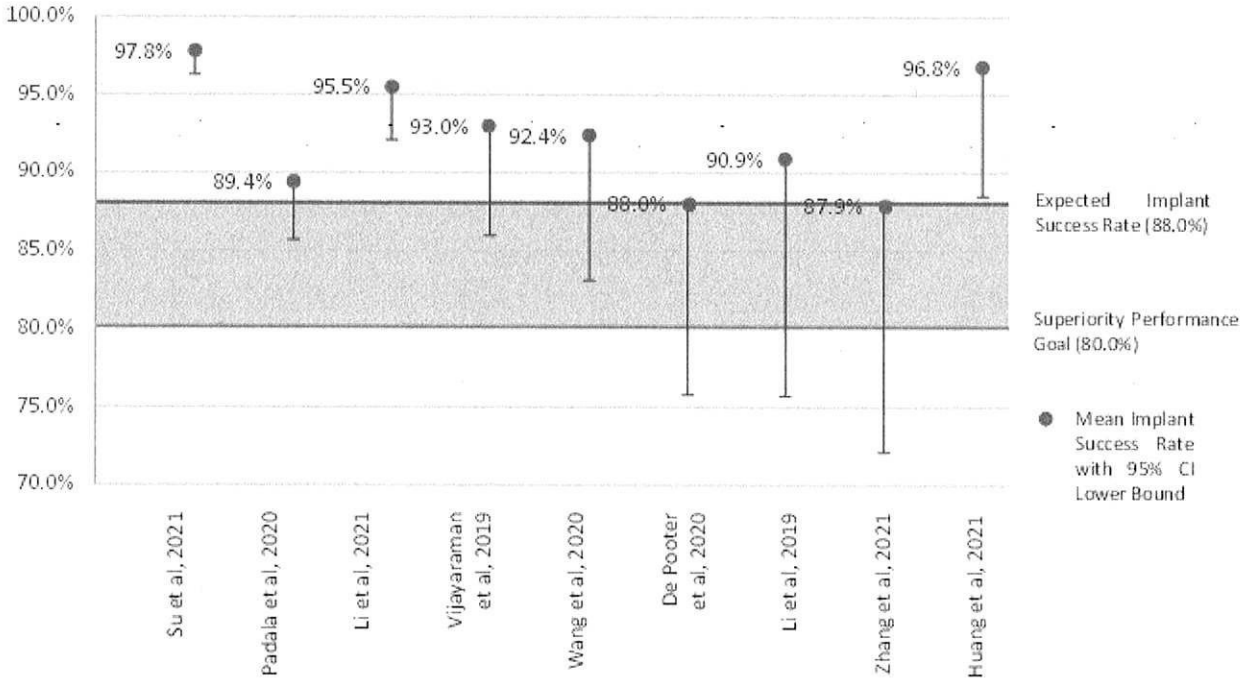

Figure 2: Assumed Implant Success Compared to Published Results

The estimated sample size required to evaluate primary endpoint 2 is based on a superiority comparison of overall Solia S leads successfully implanted to 80%. The sample size for primary endpoint 2 was calculated based on the following assumptions.

- Study Design: Non-randomized
- Type I error (alpha): 0.025 (one-sided for superiority)
- Statistical power: 80%
- Performance Goal for Successful Implant Rate: 80%
- Expected Successful Implant Rate: 88%
- Test basis: Exact binomial test
- Attrition Rate: 5%

For primary endpoint 2, a total of 175 evaluable Solia S leads would be required to demonstrate superiority to a successful implant rate of 80%. Assuming a 5% attrition rate, a total of 184 (= 175 / 0.95) patients with a Solia S lead would be required to be enrolled to evaluate primary endpoint 2.

4.1.3 Secondary Endpoint 1: Quality of Life (QOL) Through 12 Months Post-Implant

The purpose of secondary endpoint 1 is to evaluate the improvement in QOL for patients with successful Solia S lead implantation in the LBB area. Specifically, the physical function scale of the SF-36 will be used as it has been shown to be the best all-around measure of physical health (Ware JE Jr. et al. 2000). The QOL scale is standardized such that a higher score indicates better physical health.

The following hypotheses have been defined to evaluate the improvement in quality of life:

H_0: The improvement in quality of life through 12 months post-implant for subjects with successful Solia S lead implanted in the LBB area is less than or equal to 2.8

$$\text{Improvement in QOL}_{\text{Physical Function Scale}} \leq 2.8$$

H_a: The improvement in quality of life through 12 months post-implant for subjects with successful Solia S lead implanted in the LBB area is greater than 2.8

$$\text{Improvement in QOL}_{\text{Physical Function Scale}} > 2.8$$

Secondary endpoint 1 will be evaluated by performing an exact one-sample t-test comparing the mean improvement in QOL from baseline to 12 months post-implant to the performance goal of 2.8. The lower, two-sided 95% confidence bound for the improvement in QOL must be greater than 2.8 to reject the null hypothesis (H_0), which would demonstrate evidence that the improvement in QOL is significantly higher than 2.8.

For the secondary endpoint 1 analysis, ITT population subjects with evaluable QOL paired baseline and 12-month measurements will be included. Subjects for which a baseline or 12-month physical function QOL score cannot be calculated, either due to missing or incomplete QOL data, will be excluded from the analysis.

Sample Size Determination for Secondary Endpoint 1

Prior studies evaluating the quality of life in elderly patients receiving dual-chamber pacemakers with standard RV pacing have demonstrated modest improvement (ranging from 2.7 to 4; weighted mean of 2.8) in QOL as assessed by the SF-36 physical function scale from baseline (pre-implant) to 12 months post-implant (Fleischmann KE et al. 2006, Yu CM et al. 2014). More recently, Li H et al. (2021), found patients experiencing pacemaker-induced cardiomyopathy that were upgraded from RV pacing to LBB area pacing had a higher score in the physical function scale by 18.2 points at 12 months post-upgrade. At 24 months post-implant, in a crossover study, Kronborg MB et al. 2014 showed a 5-point improvement as measured by the physical function scale comparing His or para-His pacing to RV pacing. However, this improvement was not shown to be statistically significant. Other studies on conduction system pacing have noted improved QOL in patients receiving this therapy (Lustgarten DL et al. 2015, Occhetta E et al. 2006).

Based on this information, it is anticipated that patients with successful LBB area pacing with the Solia S lead will have an improvement in QOL, as measured by the SF-36 Physical Function score, of at least 10 from pre-implant baseline to 12 months post implant. This improvement in the Physical Function Score with LBB area pacing using a Solia S lead is the expected improvement due to receiving a pacemaker system (pre-implant baseline to RV pacing, average improvement in QOL score = 2.8) plus the additional expected benefit due to utilizing LBB area pacing as compared to RV pacing (expected improvement in QOL score = 7.8; combining LBB vs RVp from Li H et al. and Kronborg MB et al, weighted mean = 7.8). For the sample size calculation, an expected improvement in the Physical function Score was rounded to 10.

The estimated sample size required to evaluate secondary endpoint 1 is based on a superiority comparison of the improvement in QOL (physical function scale) to the expected improvement with RV pacing of 2.8 points. The sample size for secondary endpoint 1 was calculated based on the following assumptions.

Assumptions:

- Study Design: Non-randomized
- Type I error (alpha): 0.025 (one-sided for superiority)
- Statistical power: 80%
- Standard deviation: 30
- Performance Goal for $QOL_{\text{Physical Function Scale}}$ Improvement: 2.8
- Expected $QOL_{\text{Physical Function Scale}}$ Improvement: 10
- Test basis: Exact one-sample t-test

For secondary endpoint 1, 139 evaluable QOL paired baseline and 12-month measurements would be required to demonstrate superiority to an improved QOL of 2.8 based on a standard deviation of 30. The assumed standard deviation for SF-36 Physical Function Scale score is based on findings from multiple sources using SF-36 for RV pacing (Kronborg MB et al. 2014, Li H et al. 2021, Link MS et al. 2004, Yu CM et al. 2014).

4.1.4 Secondary Endpoint 2: SADE-Free rate through 6 Months and 12 Months Post-Implant

There are no formal hypotheses for secondary endpoint 2. The SADE-free rate at each timepoint will be calculated as the number of subjects without one or more Solia S LBB lead adverse event divided by the total number of study subjects successfully enrolled and subjects undergoing an unsuccessful implant attempt who have a qualifying Solia S LBB lead complication in percent. A Kaplan-Meier survival analysis (time-to-event) for the will also be performed for each timepoint.

For the secondary endpoint 2 analysis at 6 months, ITT population subjects who have sufficient follow-up data (at least 152 days of follow-up, corresponding to the earliest potential in-window 6-month visit) or experienced a Solia S LBB lead adverse event will be included. Subjects without a Solia S LBB lead adverse event who drop out prior to day 152 will be excluded from the analysis.

For the secondary endpoint 2 analysis at 12 months, ITT population subjects who have sufficient follow-up data (at least 335 days of follow-up, corresponding to the earliest potential in-window 12-month visit) or experienced a Solia S LBB lead adverse event will be included. Subjects without a Solia S LBB lead adverse event who drop out prior to day 335 will be excluded from the analysis.

4.1.5 Secondary Endpoints 3 – 5: Solia S Lead Measurements

There are no formal hypotheses for secondary endpoints 3 – 5. Descriptive statistics, including mean, standard deviation, min, and max will be provided for each lead measurement at the visits of interest.

For analysis of secondary endpoint 3 (Solia S LBB pacing threshold at 3-, 6-, and 12-months post-implant), ITT population subjects with threshold data available at the visit of interest will be included. Subjects for which a pacing threshold was not available at a given visit will be excluded from the analysis.

For analysis of secondary endpoint 4 (Solia S LBB R-wave sensed amplitude at 3-, 6-, and 12-months post-implant), ITT population subjects with R-wave sensed data available at the visit of interest will be included. Subjects for which a R-wave sensed amplitude was not available at a given visit and pacing dependent subjects for which value could not be obtained will be excluded from the analysis.

For analysis of secondary endpoint 5 (pacing impedance at 3-, 6-, and 12-months post-implant), ITT population subjects with impedance data available at the visit of interest will be included. Subjects for which a pacing impedance was not available at a given visit will be excluded from the analysis.

4.2 Analysis of Additional Data of Interest

Additional data of interest will be reported for the relevant ITT analysis population (i.e., safety additional data of interest will utilize the same ITT population as primary endpoint 1; lead implant information will utilize the same ITT population as primary endpoint 2; remaining additional data of interest will utilize same ITT population as secondary endpoints

1 and 3 -5). For each analysis, only subjects with the data of interest available at implant or visit will be included. Subjects for which data is not available will be excluded from the analysis.

4.3 Subgroup Analysis

A sub-group analysis evaluating impact of age at consent (< 65 years, ≥ 65 years) may be conducted for the primary and secondary endpoints after all patients have completed the 12-month study visit. As the purpose of this analysis is to evaluate the impact of age on the outcomes, there is no formal hypothesis for this subgroup analysis.

4.4 Poolability Analysis

Poolability analyses will examine the heterogeneity of the primary endpoints across clinical sites within the U.S. and across regions (U.S. and outside of U.S.). For each analysis, sites with less than 5 subjects enrolled will be combined into one or more pseudo-sites for purposes of analysis. Starting with the site with the lowest enrollment, subjects will be successively combined into one or more pseudo-sites until the total number in each pseudo-site is not greater than the median enrollment of sites with greater than 5 subjects enrolled.

The significance of differences in rates for primary endpoint 1 and primary endpoint 2 between U.S. sites will be initially tested using a Kruskal-Wallis test statistic, with an associated p-value of 0.15 or less considered evidence of site differences. In addition, a Cochran-Mantel-Haenszel test with continuity adjustment will be used to assess the poolability across sites. If evidence is found of site differences, then the reasons for the differences will be explored using Cox and logistic regression methods to determine if any baseline subject risk factors are explanatory.

Once U.S. site poolability is confirmed, the analysis will be repeated to test region poolability (U.S. and outside of U.S.) for primary endpoint 1.

Poolability analysis will be occur after analyses for the primary endpoints has been completed.

4.5 Sex, Race, and Region Analysis

Any differences between sexes or race in primary endpoint 1 and primary endpoint 2 study results will be analyzed and reported. There are no pre-specified tests of the statistical significance for differences in sex and race. These analyses will be completed once analysis for the primary endpoints has been completed.

Region analysis (U.S. vs. outside of U.S.) will be conducted to confirm poolability as noted above (Section 4.4).

5 Deviations from the SAP

Any changes to the planned statistical analyses made prior to study completion will be documented in an amended Statistical Analysis Plan approved prior to implementation. Changes from the planned statistical methods after the study is completed will be documented in the clinical study report along with a reason for the deviation.

6 Signatures

BIOTRONIK, Inc. Signatures and Date

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