Statistical Analysis Plan

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LBBAP Data Collection Registry
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LBBAP Data Collection Registry

Statistical Analysis Plan (SAP)

Version A

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[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) is intended to provide a detailed and comprehensive description of the planned methodology and analysis to be used for clinical investigation plan (CIP) [redacted] the LBBAP Data Collection Registry. This plan is based on the Version B of the Clinical Investigation Plan.

1.2 Clinical Investigation Objectives

The objective of this retrospective chart review study is to evaluate the safety and effectiveness of left bundle branch area (LBBA) pacing/sensing in patients already implanted with the Tendril STS 2088 lead.

1.3 Clinical Investigation Design

This is a retrospective, observational, non-controlled, chart review study designed to evaluate the safety and effectiveness of LBBA pacing/sensing in patients already implanted with the Tendril STS 2088 lead.

Data on a minimum of 220 attempted subjects will be included in order to have 190 evaluable subjects in this registry. The chart review will be conducted at up to 20 centers worldwide. The chart review will be conducted at up to 20 participating centers worldwide.

The clinical investigation is a retrospective chart review and therefore involves no pain, discomfort, fear, and any other foreseeable risk as possible for subjects.

1.4 Endpoints

1.4.1 Primary Safety Endpoint

The primary safety endpoint evaluates freedom from left bundle branch area pacing (LBBAP) lead related serious adverse device effects (SADEs) through 6 months post-implant attempt.

The primary safety endpoint evaluates a LBBAP lead related SADE rate which is an appropriate measure for safety and consistent with the primary safety endpoints used for evaluating performance of the transvenous right ventricular lead. It is appropriate to evaluate the safety through 6 months since it is known that a great majority of complications occur through 3 - 6 months after the implantation.[1]

1.4.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint evaluates the composite success rate of acceptable capture thresholds and sense amplitudes for LBBAP through 6 months post-implant. This analysis will be performed with only patients who are successfully implanted with the Tendril™ STS 2088 lead in the LBBA (see details in CIP section 6.1.2). Acceptable ranges for sensing and pacing are shown below:

Parameter	Acceptable values
Pacing voltage	Pacing threshold ≤ 2.0V
Sense amplitude	LBBA sense amplitude ≥ 5.0 mV or ≥ value at implant

The primary effectiveness endpoint evaluates the ability to pace and sense when the Tendril™ STS 2088 lead is implanted in the LBBA. The evaluation of a composite success rate of acceptable pacing thresholds and sensing amplitudes is similar to the primary effectiveness endpoints used in for a prior transvenous pacing lead (Tendril FSR 1699T). The 6-month timepoint for assessing the primary effectiveness endpoint is an appropriate time period since these electrical measurements have been demonstrated to be stable starting as early as 1 month post-implant.[2]

1.4.3 Descriptive Data and Endpoints

Descriptive data and endpoints are reported using only summary statistics and no hypothesis tests will be performed.

- Demographics (if provided): sex at birth, age range
- Indication for pacemaker or CRT-P/D implant
- Cardiovascular (CV) history and other significant medical conditions
- Procedure and device-related adverse events
- Implant success rate for LBBAP lead and reasons for unsuccessful implant
- Number of repositioning attempts at implant
- Overall procedure time: skin-to-skin
- Implant procedure time: vascular access to lead fixation
- Fluoroscopy time and radiation dose
- Implant tools used (i.e., catheter, stylet, etc.): manufacturer, model#
- Capture threshold, pulse width, sense amplitude, and pacing impedance at all follow-up visits
- Mortality
- QRS duration and morphology (if available)
- NYHA classification (if available)
- LVEF, LVEDV, LVESV (if available)

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

2.1.1 Enrolled Population

This analysis population will include enrolled subjects who have been attempted to implant for the Tendril™ STS 2088 lead in the LBBA.

2.1.2 Successfully Implanted Population

The successfully implanted population includes enrolled subjects who are successfully implanted with the Tendril STS 2088 lead in the left bundle branch area (refer to CIP Section 6.1.2).

2.2 Statistical Methods

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g., age), results will be summarized with the numbers of observations, means, and standard deviations, with quartiles, minimums, maximums, and 95% confidence intervals for the means as per the table mockups.

2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables (e.g. gender, race, 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 estimates.

2.3 Endpoint Analysis

2.3.1 Primary Safety Endpoint

The primary safety endpoint evaluates freedom from LBBAP lead-related SADEs through 6 months post-implant attempt.

The hypothesis is formally expressed as:

H_0: Freedom from LBBAP lead related SADEs ≤ 81.2%
H_1: Freedom from LBBAP lead related SADEs > 81.2%

The primary safety endpoint will be estimated as a binomial proportion and the 97.5% lower confidence bound (LCB) will be calculated using the Clopper-Pearson exact method. The null hypothesis is rejected at the 2.5% significance level if the LCB is greater than the performance goal (PG) of 81.2%. The p-value from a one-sided exact test for the binomial proportion will also be calculated and compared to the 0.025 significance level.

This analysis will be performed on the enrolled population, and the primary safety analysis will use evaluable subjects. Evaluable subjects will include all subjects with an implant attempt with data available for evaluation. Subjects who do not have 6 months data and do not experience a lead-related serious adverse device effect (SADE) prior to 6 months will be excluded from the analysis. Lead-related SADEs that occur through 6 months post attempted implant will be included in the primary safety endpoint analysis. No sensitivity analyses will be performed.

The primary safety endpoint performance goal derivations are provided in Appendix A.

2.3.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint evaluates the composite success rate of acceptable capture thresholds and sense amplitudes for LBBAP through 6 months post-implant. This analysis will be performed with only patients who are successfully implanted with the Tendril STS 2088 lead in the left bundle branch area.

The hypothesis is formally expressed as:

H_0: Composite success rate ≤ 80%
H_1: Composite success rate > 80%

Parameter	Acceptable values
Pacing voltage	Pacing threshold ≤ 2.0V
Sense amplitude	LBBA sense amplitude ≥ 5.0 mV or ≥ value at implant

Success Criteria: A subject will be considered to have met the primary effectiveness endpoint if the pacing threshold voltage ≤ 2.0 V and LBBA sense amplitude is ≥ 5.0 mV or ≥ value at implant through 6 months. For subjects that do not have LBBA amplitude measured due to active tachyarrhythmias or any other heart rhythm conditions or procedures which prevent sensing amplitude from being measured, success will be determined from the pacing threshold only. For subjects that do not have pacing threshold measured, due to active tachyarrhythmias or any other heart rhythm conditions or procedures which prevent pacing threshold from being measured, success will be determined from LBBA amplitude only. Subjects that do not have LBBA amplitude and pacing voltage, both of which are unobtainable due to active tachyarrhythmias or any other heart rhythm conditions or procedures which prevent pacing threshold from being measured, will be excluded from the analysis.

The success rate will be estimated as a binomial proportion and the 97.5% LCB of the rate will be calculated using the Clopper-Pearson exact method. The null hypothesis will be rejected at the 2.5% significance level if the LCB exceeds the PG of 80%. The p-value from a one-sided exact test for the binomial proportion will also be calculated and compared to the 0.025 significance level.

This analysis will be performed on the successfully implanted population, and the primary effectiveness analysis will use the last observation carried forward (LOCF) method. [redacted]

The primary effectiveness endpoint performance goal derivations are provided in Appendix A.

2.3.2.1 Sensitivity Analysis

Sensitivity analysis will be performed on the successfully implanted population using multiple imputation (MI). [redacted]

The multiple imputation model is specified in Appendix B.

2.4 Sample Size Calculations

Data on a minimum of [redacted] attempted subjects will be included in order to have [redacted] evaluable subjects in the registry.

2.4.1 Primary Safety Endpoint

The assumed SADE rate is based on the LBBAP data in the literature. According to data from [redacted], the overall incidence rate of LBBAP lead-related complications was [redacted]

Assuming:

- [redacted] freedom from LBBAP lead-related SADEs (i.e., assumed SADE rate of [redacted])
- [redacted] power
- Binomial exact test
- One-sided alpha of 0.025
- Performance goal of 81.2%
- [redacted] attrition

The minimum sample size to reject the null hypothesis is [redacted] evaluable patients. We assume [redacted] attrition as subjects must have data through 6 months to qualify for enrollment in the study, so the study sample size of [redacted] subjects will be sufficient to evaluate the primary safety endpoint. Evaluable subjects are defined in Section 2.3.1.

The sample size calculation was performed using the PASS 15[4] Tests for One Proportion module.

2.4.2 Primary Effectiveness Endpoint

The assumed success rate is based on the LBBAP data in the literature. Given the lack of individual patient-level data for electrical performance, the overall implant success rate is used as a proxy to evaluate the composite success rate of acceptable capture thresholds and sense amplitudes for LBBAP through 6 months post-implant. According to the meta-analysis of 10 LBBAP studies[3,5-13], the overall range of LBBAP impla[redacted] success rate with consideration of LBBAP electrical performance was [redacted] with [redacted] of success rate from meta-analysis.

Assuming:

- A composite success rate of [redacted]
- [redacted] power
- Binomial exact test
- One-sided alpha of 0.025
- Performance goal of 80%

The minimum sample size to reject the null hypothesis is [redacted] evaluable patients. Assuming approximately [redacted] of subjects will not have a successful LBBAP implant per protocol, and that about [redacted] of subjects will not have evaluable capture threshold and/or sense amplitudes, [redacted] subjects will be enrolled to ensure that [redacted] subjects are evaluable for the primary effectiveness endpoint. Evaluable subjects are defined in Section 2.3.2.

The sample size calculation was performed using the PASS 15[4] Tests for One Proportion module.

2.5 Interim Analysis

No formal interim analyses are planned for this study. As such, no formal statistical rule for early termination of the trial is defined. Interim study reports with descriptive analysis may be produced for regulatory or reimbursement purposes.

2.6 Timing of Analysis

The Sponsor will conduct the primary endpoint analyses when required data collection is complete.

2.7 Study/Trial Success

Success will be declared if both the Primary Safety Endpoint and Primary Effectiveness endpoints are met.

2.8 Subgroups for Analysis

Abbott will also conduct subgroup analyses to estimate the effect of the implanting physician's experience with LBBAP implantation on the primary endpoints. Implanters will be classified as more-experienced or less-experienced based on the number of LBBAP implants they have performed with the Tendril STS 2088 lead. As sites are instructed to enter data consecutively from their first 2088 attempt, implanter experience can be derived by ordering implanter and implant date. We will consider implanters less-experienced with less than 6 implant attempts and more-experienced after they have completed 6 or more implant attempts.

As some subjects will be implanted with non-Abbott, market-approved pacemaker, defibrillator, and/or CRT devices used in combination with the Tendril 2088 lead, another subgroup analysis will be performed to determine the effect of manufacturer on the primary endpoints. In this analysis, subjects implanted with non-Abbott devices will be compared to subjects implanted with Abbott devices.

Other subgroup analyses may be performed on an ad hoc basis to understand outcomes for specific indications and patient populations.

2.9 Handling of Missing Data

The primary safety endpoint analysis will include evaluable subjects only. The primary effectiveness endpoint analysis will use [redacted] All other outcome measures will be based on the available data, with no imputation for missing values.

2.9.1 Partial Dates

Partial dates with a missing day (ex: --APR2022) will be imputed to the first of the month, 01APR2022. Dates with a missing month (ex: 25---2020) will be imputed to January (25JAN2020), and dates with a missing day and month (ex: -----2021) will be imputed to the first of the year (01JAN2021).

2.10 Poolability Issue

Poolability analyses of the primary effectiveness endpoint and primary safety endpoint will be conducted by site. To evaluate the site effect on each endpoint, site will be tested against an alpha level of 0.15 using logistic regression model. Sites must have at least 10 or more subjects to be included in the

poolability analyses. If a poolability model does not converge, the number of subjects needed to be included in the analysis will be raised until the model converges.

If there is evidence of inconsistency of either endpoint across the sites, subject's demographics, medical history, and baseline characteristics may be examined.

In addition to the poolability analysis by site, an analysis of poolability by geography will be conducted in which sites are grouped into 3 geographic regions: United States, European Union, and Asia Pacific. To evaluate the geographic effect on each endpoint, geography will be tested against an alpha level of 0.15 using logistic regression model.

2.11 Multiplicity Issues

To control the family-wise type I error rate, both primary endpoints must be met to declare study success.

2.12 Sensitivity Analysis

Sensitivity analyses will be performed on the primary effectiveness endpoint using multiple imputation (Appendix B). No sensitivity analyses will be conducted on the primary safety endpoint.

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

Baseline and demographic variables will be summarized for enrolled subjects, and may include, but not be limited to: sex at birth, age, cardiac disease history, implant procedural characteristics, etc.

3.2 Adverse Events

All of the adverse device effects, serious adverse device effects, will be summarized for all subjects who enrolled in this trial in terms the number of events and the percentage of subjects with events.

3.3 Subject Early Termination

This is a retrospective chart review study, so there will be no case of subject early termination.

3.4 Protocol Deviation

Protocol deviations will be summarized for subjects in whom a protocol deviation was reported.

3.5 Descriptive Endpoints or Additional Data

Descriptive endpoints and additional data are reported using only summary statistics and no hypothesis tests will be performed.

These data points will be reported for the Enrolled Population:

- Demographics (if provided): sex at birth, age range
- Indication for pacemaker or CRT-P/D implant
- Cardiovascular (CV) history and other significant medical conditions
- Procedure and device-related adverse events

- Implant success or failure for an LBBAP lead and if not successful, reasons for unsuccessful implant
- Number of repositioning attempts at implant
- Overall procedure time: skin-to-skin
- Implant procedure time: vascular access to lead fixation
- Fluoroscopy time and radiation dose
- Implant tools used (i.e., catheter, stylet, etc.): manufacturer, model#
- Mortality

These data points will reported for the Implanted Population:

- Capture threshold, pulse width, sense amplitude, and pacing impedance at all follow-up visits
- QRS duration and morphology (if available)
- NYHA classification (if available)
- LVEF, LVEDV, LVESV (if available)

4.0 DOCUMENTATION AND OTHER CONSIDERATIONS

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

4.1 Changes from CIP planned analyses

Due to the small number of subjects anticipated in the registry who will be implanted with a non-Abbott pacemaker, defibrillator, and/or CRT devices, the analyses comparing the primary endpoints by device manufacturer will be conducted descriptively (Section 2.8) instead of via the poolability analysis specified in the Clinical Investigation Plan Addendum for Investigational Sites Participating in France (CL1022010).

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
CIP	Clinical Investigation Plan
LBBA	Left Bundle Branch Area
LBBAP	Left Bundle Branch Area Pacing
LCB	Lower Confidence Bound
LOCB	Last Observation Carried Backward
LOCF	Last Observation Carried Forward
MI	Multiple Imputation
PG	Performance Goal
SADE	Serious Adverse Device Effects
SAP	Statistical Analysis Plan

6.0 REFERENCES

[redacted]

7.0 APPENDICES

APPENDIX A: JUSTIFICATION/DERIVATION OF ASSUMPTIONS

Primary Safety Endpoint Performance Goal Derivation

[redacted]

Primary Effectiveness Endpoint Performance Goal Derivation

[redacted]

References

[redacted]

APPENDIX B: Multiple Imputation of the Primary Effectiveness Endpoint

[redacted]

APPENDIX C: STATISTICAL ANALYSIS PLAN REVISIONS

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]