CELESTIAL

Post Approval Registry

Corox OTW, Endocardial, Left VEntricular STerold LeAd, BipoLar

Protocol Version: November 16, 2010

NCT00810264
Statistical Analysis Plan
April 26, 2019

BIOTRONIK
excellence for life
6024 Jean Road
Lake Oswego, OR 97035

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1. INTRODUCTION

The CELESTIAL study is a post-approval registry of the BIOTRONIK Corox OTW BP, Corox OTW-S BP, and Corox OTW-L BP Left Ventricular (LV) pacing leads, also referred to as "Corox LV". For this study, the Corox lead is utilized in conjunction with any US market-released BIOTRONIK CRT-D or CRT-P devices. The study is conducted to confirm the long-term safety and effectiveness of the Corox LV leads as used in conjunction with a BIOTRONIK Cardiac Resynchronization Therapy (CRT) device. The study also provides data to permit characterization of any Corox LV lead failures contributing to subjects losing CRT therapy. The Corox LV leads are capable of providing permanent pacing therapy to the left ventricle in a CRT system. Subjects enrolled in this study will be followed for five years post-implant.

1.1 SAMPLE SIZE AND POWER

The estimated sample size requirement is based on both primary safety endpoints: a noninferiority comparison of the overall serious adverse event (SAE) free-rate to 92.5% at 5 years, excluding those SAEs listed in Protocol Table 4, and a non-powered, superiority comparison for those individual lead-related SAE to 1% at 5 years. The sample size for primary safety endpoint 1 was calculated based on the following assumptions:

Assumptions for primary safety endpoint 1

- Study Design: nonrandomized registry
- Type I error (alpha): 0.05 (one-sided for noninferiority)
- Statistical power: 80%
- Noninferiority delta: 5%
- Estimated SAE-Free Rate at 5 years: 92.5% for Corox BP LV Leads

For primary safety endpoint 1, a total of 240 evaluable subjects implanted with Corox BP LV leads would be required to demonstrate the noninferiority within 5% of a SAE free-rate of 92.5%. Assuming a 50% loss to follow-up rate over 5 years of follow-up, a total of 480 (240/0.5) subjects would be required to evaluate primary safety endpoint 1. Enrollment will seek to achieve 240 evaluable subjects for each of the Corox BP LV leads.

Assumptions for primary safety endpoint 2

- Estimated individual SAE rate at 5 years: 0.4%
- Allowable two-sided, upper 95% confidence bound: 1%

For primary safety endpoint 2, a total of 1000 subjects would be required to demonstrate a two-sided, upper 95% confidence bound of 1%, assuming an expected individual SAE rate of 0.4% (no more than 4 patients with an SAE out of 1000). Assuming a 50% loss to follow-up rate over 5 years (10% per year), a total of 2000 (1000/0.5) enrolled patients would be required for evaluation of primary safety endpoint 2.

2. STUDY ENDPOINTS

2.1 PRIMARY ENDPOINT 1: SAFETY OF COROX BP LV LEADS PACING – OVERALL COMPLICATION-FREE RATE

The primary safety endpoint will be evaluated in the following testable hypothesis in a noninferiority format.

H_o: The serious adverse event-free rate (SAEFR) for the Corox LV Leads at 5 years post-enrollment is inferior to 92.5%

$SAEFR + \delta \leq 92.5\%$

H_a: The serious adverse event-free rate (SAEFR) for the Corox LV Leads at 5 year post-enrollment is not inferior to 92.5%

$SAEFR + \delta > 92.5\%$

Where, (δ) is the clinically significant difference for establishing noninferiority. A rejection of the null hypothesis would indicate that the serious adverse event-free rate is not inferior to 92.5% within (δ).

2.2 PRIMARY ENDPOINT 2: SAFETY OF COROX BP LV LEADS PACING – INDIVIDUAL COMPLICATION RATES

Each of the individual types of serious adverse events contributing to primary safety endpoint 1 will be evaluated separately in the following superiority hypotheses:

H_o: The individual serious adverse event rate (SAEIndividual) for a given type of SAE for the Corox LV Leads at 5 years post-enrollment is equal to 1%

$SAEIndividual = 1\%$

H_a: The individual serious adverse event rate (SAEIndividual) for a given type of SAE for the Corox LV Leads at 5 years post-enrollment is not equal to 1%

$SAEIndividual \neq 1\%$

If the two-sided, 95% upper confidence bound is no more than 1% for individual serious adverse events, then the null hypothesis will be rejected for that SAE type.

2.3 SECONDARY ENDPOINTS

There were no pre-specified formal hypotheses established for the following secondary endpoints:

1. Successful biventricular pacing in a BIOTRONIK CRT device at scheduled CELESTIAL registry follow-up visits through 5 years post-enrollment
2. Serious adverse event rates for SAEs excluded from primary safety endpoint (listed in Protocol Table 4) through 5 years post-enrollment.
3. Pacing threshold, sensing and impedance measurements for the Corox BP leads at scheduled CELESTIAL registry through 5 years post-enrollment
4. Individual electrical parameters of the Corox OTW BP LV lead, the Corox OTW-S BP LV lead, and the Corox OTW-L BP LV lead.
5. Overall incidence of serious adverse events that meet the primary endpoint 1 criteria will be evaluated separately for each Corox BP lead model.

6. Incidence of individual types of serious adverse events contributing to primary endpoint 2 will be evaluated separately for each Corox BP lead model.

2.4 FDA Requested Ad Hoc Analysis

The FDA had requested an ad hoc analysis sin P070008/R4, which includes: chronic events that occur at 30 or more days post-implant; lead dislodgements occurring 30 or more days post-implant; elevated LV pacing threshold, intermittent LV capture, and no capture of LV lead occurring 30 or more days post-implant; diaphragmatic stimulation occurring 30 or more days post-implant; and all LV lead related perforations. This analysis differs from the protocol specified primary endpoint analysis by including adverse events which, per protocol, are excluded from the primary analysis if they occur 30 or more days post-implant, changing the time frame for lead dislodgements from 180 or more days post-implant to 30 or more days post-implant, including all LV lead related perforations, and excluding other events that occur within less than 30 days of implant. In addition, all subjects with an elevated pacing threshold obtained at a routine follow-up visit that occurred 30 days or more post-implant are included regardless of whether the event met the criteria for a protocol defined adverse event.

3. ANALYSIS POPULATIONS

The primary and secondary endpoints analyses will be conducted based on pre-defined populations as described below.

The primary endpoint per-protocol analysis population will be used to conduct the primary endpoints 1 and 2 analyses because these endpoints are based on SAEFR and SAE rates at 5 years post-implant respectively. The secondary endpoint per-protocol analysis population will be used to conduct the secondary endpoints 5 and 6 analyses because these endpoints examine primary endpoints 1 and 2 based on originally implanted lead models; therefore, are examined at 5 years post-implant. The intention-to-treat population will be used to conduct the secondary endpoints 1 through 4 analyses and all additional data of interest because these endpoints are continuous and examine measurements and event rates throughout the study; therefore, are not limited to only examining subjects who complete 5 year follow-up.

3.1 INTENTION-TO-TREAT (ITT) ANALYSIS POPULATION

The intention-to-treat (ITT) population includes all subjects enrolled in the study. The ITT subjects have documentation of informed consented and implant of the Corox LV study lead. This population includes all subjects enrolled in the study.

3.2 PRIMARY ENDPOINT PER-PROTOCOL (PP) ANALYSIS POPULATION

The primary endpoint per-protocol (PP) population is a subset of the ITT population. The primary endpoint PP subjects have experienced a protocol defined primary endpoint AE or have a follow-up visit or system revision date completed 5 years post-implant (defined as a visit completed on or after 45 days prior to the 5 year post-implant date, 1781 days).

3.3 SECONDARY ENDPOINT PER-PROTOCOL (PP) ANALYSIS POPULATIONS

The secondary endpoint per-protocol subjects are a subset of the primary endpoint PP population, who are separated by the originally implanted Corox LV lead models. Subjects with a Corox LV lead replacement resulting in a change in lead model (e.g. Corox OTW-S BP to Corox OTW-L BP) and experiencing an event after the replacement will be analyzed with the originally implanted lead.

3.3.1 Corox OTW BP (Helical) PP Analysis Population

The Corox OTW BP (helical) PP subjects are originally implanted with a Corox OTW BP (helical) lead and have experienced a protocol defined primary endpoint AE or have a follow-up visit or system revision date completed 5 years post-implant (defined as a visit completed on or after 45 days prior to the 5 year post-implant date, 1781 days).

3.3.2 Corox OTW-S BP (Screw) PP Analysis Population

The Corox OTW BP-S (screw) PP subjects are originally implanted with a Corox OTW BP-S (screw) lead and have experienced a protocol defined AE or have a follow-up visit or system revision date completed 5 years post-implant (defined as a visit completed on or after 45 days prior to the 5 year post-implant date, 1781 days).

3.3.3 Corox OTW-L BP (Dual-Curve) PP Analysis Population

The Corox OTW BP-L (dual-curve) PP subjects are originally implanted with a Corox OTW BP-L (dual-curve) lead and have experienced a protocol defined primary endpoint AE or have a follow-up visit or

system revision date completed 5 years post-implant (defined as a visit completed on or after 45 days prior to the 5 year post-implant date, 1781 days).

4. POOLABILITY ANALYSIS

For both primary safety endpoints 1 and 2, pooling of data from the Corox OTW BP, Corox OTW-S BP, and Corox OTW-L BP LV leads will be justified as part of the final data analysis. The differences in outcomes for the Corox OTW BP, Corox OTW-S BP, and Corox OTW-L BP LV leads will be tested using an exact, Chi-square test. If the sample size is too small to use a Chi-square test, Fisher's Exact test will be used to evaluate the differences in outcomes instead. If no evidence is found of differences between the Corox OTW BP, Corox OTW-S BP, and Corox OTW-L BP LV leads ($p > 0.05$), then the results will be considered poolable for purposes of testing the protocol hypotheses associated with the two primary endpoints. If evidence of differences is found for a given endpoint, then the hypotheses for that endpoint will additionally be tested separately for each LV lead.

5. DESCRIPTION OF STATISTICAL METHODS

5.1 PRIMARY ENDPOINT 1: SAFETY OF COROX BP LV LEADS PACING – OVERALL COMPLICATION-FREE RATE

Primary endpoint 1 will be evaluated by performing an exact, noninferiority test comparing a binomial proportion (overall serious adverse event free-rate at 5 years) to 92.5%, with a noninferiority delta of 5% (87.5%). A lower 95% confidence limit greater than 87.5% will be considered evidence of statistical significance. A p-value will also be reported. This endpoint will be evaluated using the subject population defined in section 3.2 Primary Endpoint Per-Protocol (PP) Analysis Population.

5.2 PRIMARY ENDPOINT 2: SAFETY OF COROX BP LV LEADS PACING – INDIVIDUAL COMPLICATION RATES

Primary endpoint 2 will be evaluated based on the exact, two-sided 95% confidence interval for the observed, individual serious adverse event rates at 5 years. The upper bound of these 95% confidence intervals must be less than 1%. This endpoint will be evaluated using the subject population defined in section 3.2 Primary Endpoint Per-Protocol (PP) Analysis Population.

5.3 SECONDARY ENDPOINTS

There are no formal hypothesis tests associated with the secondary endpoints.

5.3.1 Secondary Endpoint 1

Secondary endpoint 1 examines the successful biventricular pacing in a BIOTRONIK CRT device at scheduled CELESTIAL registry follow-up visits. The mean, standard deviation, minimum, and maximum of the biventricular pacing percentage will be reported for each visit. This endpoint will be evaluated using the subject population defined in section 3.1 Intention-to-Treat (ITT) Analysis Population.

5.3.2 Secondary Endpoint 2

Secondary endpoint 2 examines the rates of serious adverse events excluded from primary safety endpoint. The serious adverse event rates will be reported along with a Kaplan-Meier actuarial graph and case summary will be reported to assess this endpoint. The estimated freedom from adverse event at 5 years along with the standard error and 95% confidence intervals will also be reported. This endpoint will be evaluated using the subject population defined in section 3.1 Intention-to-Treat (ITT) Analysis Population.

5.3.3 Secondary Endpoint 3

Secondary endpoint 3 examines the sensing, pacing threshold, and pacing impedance measurements for the Corox LV leads at scheduled CELESTIAL registry follow-up visits. The mean, standard deviation, median, minimum, and maximum of each measured values be reported for each visit. This endpoint will be evaluated using the subject population defined in section 3.1 Intention-to-Treat (ITT) Analysis Population.

5.3.4 Secondary Endpoint 4

Secondary endpoint 4 examines the individual electrical parameters of the Corox OTW BP LV lead, the Corox OTW-S BP LV lead, and the Corox OTW-L BP LV lead. The electrical parameters presented will be the sensing, pacing threshold, and pacing impedance measurements for each lead model at scheduled CELESTIAL registry follow-up visits. The mean and standard deviation of each measured value will be

reported for each visit. This endpoint will be evaluated using the subject population defined in section 3.1 Intention-to-Treat (ITT) Analysis Population.

5.3.5 Secondary Endpoint 5

Secondary endpoint 5 examines the overall incidence of serious adverse events that meet primary endpoint 1 criteria as separated by each Corox LV lead model. The overall incidence of the serious adverse events meeting primary endpoint 1 criteria will be reported for each lead model using the subject population defined in section 3.3 Secondary Endpoint Per-Protocol (PP) Analysis Populations.

Similar to primary endpoint 1, secondary endpoint 5 will also be evaluated by performing an exact, noninferiority test comparing a binomial proportion (overall serious adverse event free-rate at 5 years) to 92.5%, with a noninferiority delta of 5% (87.5%). A p-value will also be reported.

Additionally a Kaplan-Meier actuarial graph and case summary will be reported for each lead model. Furthermore, the estimated freedom from adverse event at 5 years along with the standard error and 95% confidence intervals will also be reported for each lead model.

5.3.6 Secondary Endpoint 6

Secondary endpoint 6 examines the individual incidence of serious adverse events that meet primary endpoint 1 criteria as separated by each Corox LV lead model. The individual incidence of the serious adverse events meeting primary endpoint 1 criteria will be reported for each lead model using the subject population defined in section 3.3 Secondary Endpoint Per-Protocol (PP) Analysis Populations.

Similar to primary endpoint 2, secondary endpoint 6 will also be evaluated based on the exact, two-sided 95% confidence interval for the observed, individual serious adverse event rates at 5 years. The upper bound of these 95% confidence intervals will be compared to 1%.

5.4 FDA Requested Ad Hoc Analysis

The FDA requested ad hoc analysis examines the overall incidence of events defined in section 2.4. The FDA defined event rates will be reported along with a Kaplan-Meier actuarial graph and case summary will be reported to assess this analysis. The estimated freedom from adverse event at 5 years along with the standard error and 95% confidence intervals will also be reported. This endpoint will be evaluated using the subject population defined in section 3.1 Intention-to-Treat (ITT) Analysis Population.

5.5 Figures, Tables, and Listings Templates

Refer to the CELESTIAL Final Clinical Report Template

5.6 Adherence and Retention Analysis

A 50% loss to follow-up over 5 years (10% per year) will be assumed.

5.7 Additional Sub-Group Analyses (If Applicable)

No additional sub-group analyses are pre-specified. If any additional sub-group analyses are done, descriptive statistics only will be reported with no hypotheses tests.

6. REFERENCES

1. Kaplan, E. L. & Meier, P. (1958). Non Parametric Estimation from Incomplete Observations. Journal of the American Statistical Association, Vol. 53(282); 457-481.
2. Peto, R. & Pike, M. C., Armitage, P. et al. (1977). Design and analysis of randomized clinical trials requiring prolonged observation of each patient. Part II: Analysis and Examples. British Journal of Cancer, Vol. 35(1); 1-39.

7. SIGNATURES

BIOTRONIK, Inc. Signatures **Date**

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