CELESTIAL

Post Approval Registry

Corox OTW, Endocardial, Left VEntricular STerold LeAd, BipoLar

NCT00810264
Study Protocol
November 16, 2010

BIOTRONIK
excellence for life
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CELESTIAL
Post Approval Registry
(**C**orox OTW, **E**ndocardial, **L**eft V**E**ntricular **ST**ero**I**d Le**A**d, Bipo**L**ar Post Approval Registry)

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CELESTIAL POST-APPROVAL REGISTRY

PROTOCOL SIGNATURE PAGE

The signature below constitutes the receipt and review of the CELESTIAL protocol and any attachments, and provides the necessary assurances that this registry will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations, ICH and GCP guidelines.

PRINCIPAL INVESTIGATOR:

Signed: _____ Date: _____

Name (please print)

_____ _____

Signature Date:

PROTOCOL SUMMARY

Title:	CELESTIAL Post-Approval Registry
Design:	This study is a long-term post approval registry designed to follow at least 2500 patients implanted with BIOTRONIK's Corox BP left ventricular lead. Each patient will be followed for 5 years.
Purpose:	The purpose of this post-approval registry is to confirm long-term safety and successful biventricular pacing for BIOTRONIK's Corox BP left ventricular (LV) pacing leads as used in conjunction with any BIOTRONIK CRT pulse generator (CRT pacemaker (CRT-P) or CRT defibrillator (CRT-D)). The evaluation of safety will be based on the analysis of Corox BP LV lead related adverse events. The CELESTIAL post-approval registry will provide data to permit characterization of any LV lead failures contributing to patients losing CRT. Additionally, acute and chronic LV lead parameters for pacing thresholds and impedance will be evaluated.
Patient Population:	Patients who require treatment for advanced heart failure through any CRT-P or CRT-D. Patient must be successfully implanted with a BIOTRONIK CRT system, including a Corox BP LV lead, from 7-180 days prior to enrollment.
Enrollment:	This post approval registry will include a minimum of 2500 patients from up to 100 centers. The collection of data will continue for five years for each enrolled subject.
Clinical Sites:	Up to 100 sites in the United States and internationally.
Primary Endpoints:	The purpose of Primary Endpoint 1 is to evaluate the overall incidence of serious adverse events related to the Corox BP LV leads. The purpose of Primary Endpoint 2 is to evaluate the incidence of each type of serious adverse event that contributes to Primary Endpoint 1.
Secondary Endpoint:	The following secondary endpoints will also be evaluated during the study: 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 Table 4) through 5 years post-enrollment. 3. Pacing threshold, sensing and impedance measurements for the Corox BP leads at scheduled CELESTIAL registry follow ups through 5 years post-enrollment
Sponsor:	BIOTRONIK, Inc. Clinical Studies Department 6024 SW Jean Road Lake Oswego, Oregon 97035

1. INTRODUCTION

1.1 NAME OF DEVICE

This study is a FDA required post approval registry for the BIOTRONIK's Bipolar Over-the-Wire (OTW) steroid-eluting left ventricular (LV) pacing leads: Corox OTW Bipolar (BP), Corox OTW-S BP, and Corox OTW-L BP, further referred to as Corox BP LV lead throughout this protocol. For this study, the Corox BP LV lead is utilized in conjunction with any market-released BIOTRONIK Cardiac Resynchronization Therapy (CRT) device.

1.2 OVERVIEW AND BACKGROUND

1.2.1 Overview

The purpose of this post-approval registry is to confirm long-term safety and reliability of the Corox BP LV lead as used in conjunction with any BIOTRONIK Cardiac Resynchronization Therapy pacemaker or defibrillator (CRT-P or CRT-D). The CELESTIAL post-approval registry will provide data to fully characterize LV lead failures, from implant through 5 years, including those failures contributing to patients losing CRT therapy. Safety will be evaluated based on the analysis of Corox BP LV lead related adverse events, specifically but not limited to conductor fractures and insulation failures. Acute and chronic LV lead parameters for sensing, pacing thresholds, and impedance will be evaluated from enrollment through 5 years post implant, along with analysis of the connector block of the pulse generator at any device change-out. Reporting of all Adverse Events will be performed twice a year in order to identify and characterize any trend in adverse events, failure modes or failure rates. At least 2500 patients will be enrolled in this post-approval registry, and each patient will be followed for five years.

All devices included in the CELESTIAL post approval registry are legally marketed and are not investigational products. These devices are being prescribed by physicians according to approved FDA indications for use. There is no off-label use of these devices in the CELESTIAL post approval registry.

All patients will be screened to ensure they are eligible to participate, and will sign an informed consent prior to enrollment into the registry. The informed consent is designed to allow the collection of all pertinent LV lead data at implant and up to the time of enrollment. During this study, the CRT devices will be programmed to provide cardiac resynchronization therapy. Additionally, all patients will continue to receive conventional pharmacological therapy for the treatment of CHF and tachyarrhythmias.

1.2.2 Background

BIOTRONIK developed the Corox BP LV leads for use in biventricular pacing systems. These leads are polyurethane coated and designed to minimize any system related restrictions regarding implantation. Corox BP LV lead can be introduced into the coronary venous system either by stylet or guidewire. Furthermore, the guidewire can be introduced into the lead body from either end (distal or proximal). Sensing and pacing through the lead can be programmed in various configurations, allowing optimal parameters to be programmed according to each individual patient.

Each of these leads is offered with a different type of fixation. The Corox OTW BP has a three dimensional pre-shaped helical tip to achieve a stable position in larger veins, while Corox OTW-S BP has a tip with a bend at the distal end for stable placement in smaller veins ('wedge position'). Finally, the Corox OTW-L BP has a dual-curve shape that is designed to achieve a stable position in larger veins.

The CELESTIAL Post Approval Registry is designed to document the clinical experience of the Corox BP LV leads in the United States and internationally as required by the FDA through P070008, dated May 12, 2008.

1.2.3 Prior Clinical Experience

1.2.3.1 everesT Study Overview

The clinical investigation everesT: "Evaluation of the new BIOTRONIK Resynchronization+ICD System" evaluated the safety and effectiveness of the Lumax HF-T 300 and 340 CRT-D, as well as the safety and effectiveness of the Corox OTW BP and Corox OTW-S BP polyurethane coated LV leads. The Lumax devices and Corox BP LV leads are legally marketed in Europe and this multi-center study was conducted as a post-market registry to gather sufficient safety and effectiveness data for regulatory purposes outside the EU.

While the everesT investigation was designed to study both Lumax devices and Corox BP LV leads, only everesT results from the Corox OTW BP and Corox OTW-S BP LV leads are presented in this summary.

For the Corox BP LV lead portion of the everesT clinical study, the primary effectiveness endpoint was implant success rate of the Corox BP LV leads compared to a pre-defined threshold. Additionally, the evaluation of effectiveness was based on an equivalence (non-inferiority) comparison between the implant success rate of the Corox BP LV leads and rates reported in prior studies for endocardial LV leads. The evaluation of safety was based on analysis of the incidence of Corox BP LV lead related adverse events, defined as any complications or observations judged by the investigator to be in probable relationship with the Corox BP LV lead.

1.2.3.2 Corox OTW-L BP Pre-Market Evaluation Overview

The Corox OTW-L BP Pre-Market Evaluation (PME) was completed to assess the clinical performance of the Corox OTW-L BP lead. The study was performed by collecting acute and chronic lead parameters, investigator assessment, and lead related observations. Lead data were collected at implant, hospital pre-discharge and 1-month follow-up. This pre-market evaluation was conducted as an observational registry without pre-defined endpoints or sample size calculations.

1.2.3.3 Implant Success Rate Comparison

Left ventricular lead placement success rates are dependent on several key factors, including: lead design, patient coronary vein anatomy, physician expertise, and familiarity of placing LV leads.

During the everesT study, Corox OTW BP LV leads were successfully implanted in 91.5% of patients (97/106), and Corox OTW-S BP LV leads were successfully implanted in 89.5% of patients (34/38). Overall, the Corox OTW BP and Corox OTW-S BP LV leads were successfully implanted in 91.0% of patients (131/144). During the Corox OTW-L BP LV lead PME, 82.6% of patients (71/86) were successfully implanted with the lead. Table 1 compares the implant success rates of the Corox BP LV leads to other published study results.

Table 1: Implant Success Rate Comparison

LV Lead	N
BIOTRONIK Corox OTW and Corox OTW-S BP LV leads (everesT)	131/144 (91.0%)
BIOTRONIK Corox OTW-L BP LV leads (Corox OTW-L BP PME)	71/86 (82.6%)
BIOTRONIK Corox OTW UP Steroid	121/132 (91.7%)
St. Jude Aescula 1055K (P030035)	125/146 (85.6%)
St. Jude Aescula 1055K (P030054)	155/175 (88.6%)
St. Jude QuickSite 1056K (P030035)	153/162 (94.4%)
Medtronic Attain Models: 2187, 2188, 4189 (P010031)	374/424 (88.2%)
Guidant Easytrak Models: 4510, 4511, 4512, 4513 (P010012)	448/517 (86.7%)

1.2.3.4 Corox BP LV Lead Measurements

At implant and all routine follow-ups during the everesT clinical study and the Corox OTW-L PME, investigators were required to use the implanted pulse generator to obtain ventricular lead measurements, including pacing thresholds and lead impedance. All measurements were made with a pulse width of 0.5 milliseconds. Intra-operative data were measured with an external pacing system analyzer or through the pulse generator.

Table 2 provides a summary of Corox BP LV lead pacing thresholds as well as lead impedance measurements obtained during the these 2 studies. The everesT data presented in the first two columns represent combined data from both Corox OTW BP and Corox OTW-S BP LV leads. The last 2 columns reflect data from the Corox OTW-L BP LV lead PME.

Table 2: Corox BP LV Lead: Pacing Parameters

	Corox BP (everesT) Pacing Threshold (Volts @ 0.50 ms)	**Corox BP (everesT) Lead Impedance (Ohms)**	**Corox OTW-L BP Pacing Threshold** (Volts @ 0.5 ms)	**Corox OTW-L BP Lead Impedance** (Ohms)
Implant				
Number of Tests	121	115	31	30
Mean ± SD	1.2 ± 0.9	839 ± 262	1.0 ± 0.7	723 ± 191
Range	0.2 - 4.5	362 -1720	0.3 - 3.6	470 - 1164
Pre-discharge Follow-up				
Number of Tests	128	121	32	32
Mean ± SD	1.5 ± 1.3	732 ± 219	1.0 ± 0.6	681 ± 216
Range	0.3 - 7.5	305 -1748	0.3 - 2.6	316 - 1273
One-month Follow-up				
Number of Tests	108	103	28	31
Mean ± SD	1.3 ± 1.2	806 ± 245	1.1 ± 0.7	745 ± 185
Range	0.3 - 7.5	374 -1652	0.3 - 3.2	427 - 1164
Three-month Follow-up				
Number of Tests	99	94	N/A	N/A
Mean ± SD	1.2 ± 1.1	788 ± 202	N/A	N/A
Range	0.4 - 5.2	346 -1379	N/A	N/A
Six-month Follow-ups				
Number of Tests	15	15	N/A	N/A
Mean ± SD	0.8 ± 0.6	886 ± 194	N/A	N/A
Range	0.4 - 2.7	646 -1407	N/A	N/A

All lead impedance and pacing threshold values observed in the everesT study and the Corox OTW-L BP LV lead PME are clinically acceptable. Low pacing thresholds and appropriate lead impedance values may allow the physician to program lower outputs while maintaining an adequate safety margin, thereby potentially extending the service life of the pulse generator.

1.2.3.5 Freedom from Corox BP LV Lead Related Complications

During the everesT clinical study, the freedom from Corox BP LV lead related complications post-implant was studied. The results were compared to a predetermined performance criterion and to the results of other similar prospective LV lead clinical trials. Patients who terminated the study before completing all follow-up procedures were included up to the point of their study exit. During the Corox OTW-L BP LV lead PME, adverse events data were collected through at least 4 weeks for each enrolled subject, although none were reported.

Freedom from Corox BP LV lead related adverse events compares favorably with results from other manufacturers. Table 3 presents freedom from Corox BP LV lead related adverse events along with other published results.

Table 3: Comparison of Freedom from Adverse Events in the Corox BP LV Lead to Other Published Study Results

Study	Results
BIOTRONIK Corox OTW BP	97.9% * 2 complications in 97 pts
BIOTRONIK Corox OTW-S BP	100% * 0 complications in 34 pts
BIOTRONIK Corox OTW-L BP	100% † 0 complications in 32 pts
BIOTRONIK Corox OTW UP Steroid (helix)	92.9% 8 complications in 8 pts.
St. Jude QuickSite 1056K LV lead (P030054)	96.1% * 8 complications in 6 pts.
St. Jude Aescula 1055K LV lead (P030035)	88.2% 25 complications in 24 pts.
Medtronic Attain LV lead Models 4189 (P010031)	85.1% 49 complications in 44 pts.
Guidant Easytrak LV Lead Models 4510, 4511, 4512, 4513 (P010012)	87.8% 53 complications in 517 pts.

*Freedom from LV lead related complications at 3 months
† Freedom from LV lead related complications at 1 month

1.3 DEVICE DESCRIPTIONS

1.3.1 Corox BP LV Leads

The Corox BP LV leads are a guidewire or stylet delivered, transvenous, steroid-eluting family of leads for LV pacing and sensing. A standard 0.014 inch guidewire can be introduced from either the distal or proximal end into the lead body. This allows alternate usage of a stylet or guidewire until the lead is advanced and properly fixated in a coronary vein. The leads are equipped with a “true” stylet stop near the tip, which allows full straightening of, and maximal load transmission to, the distal end of the lead with a stylet. An integrated distal tip seal situated inside the lead body prevents intrusion of fluids into the lead lumen during implantation.

The MP35N/Ag lead conductor core is insulated with silicone and externally coated with polyurethane up to the beginning of the helix. A steroid / silicone collar behind the tip electrode is designed to slowly elute 0.5 mg of dexamethasone acetate (DXA). A second steroid / silicone collar is located next to the ring and slowly elutes 0.5 mg of dexamethasone acetate (DXA).

The leads are available in two different lengths (77 & 87 cm), which are designated as Corox OTW (-S or -L) 75-BP and Corox OTW (-S or -L) 85-BP, respectively; dedicated implant tools include several ScoutPro guiding catheters and Galeo guidewires with varying designs, as well as commercially available balloon catheters to facilitate coronary sinus angiography for visualization of the venous anatomy.

1.3.1.1 Corox OTW BP

This LV lead model has a helically pre-shaped distal end designed to provide atraumatic fixation within a coronary vessel (Figure 1 left). The tip is electrically active with an area of 5.0 mm^2 and a diameter of 5.85 F (1.95 mm). The electrically active ring has an area of 8.0 mm^2 and a diameter of 5.85 F. The tip and ring electrodes are separated by 18 mm. To improve pacing and sensing, both electrodes are fractally coated with iridium to enhance charge transfer between the conductive sections of the lead and the electrolyte.

1.3.1.2 Corox OTW-S BP

This LV lead model has a bend in the distal end enhanced with a silicone screw to provide atraumatic fixation within a narrow coronary vessel (Figure 1 right). The tip is electrically active with an area of 5.0 mm^2 and a diameter of 5.85 F (1.95 mm). The electrically active ring has an area of 8.0 mm^2 and a diameter of 5.85 F. The tip and ring electrodes are separated by 18 mm. To improve pacing and sensing, both electrodes are fractally coated with iridium to enhance charge transfer between the conductive sections of the lead and the electrolyte.

1.3.1.3 Corox OTW-L BP

The Corox OTW-L BP is a subsequent model of the currently marketed Corox OTW BP and Corox OTW-S BP leads. The Corox OTW-L BP lead features design elements inherited from the predecessor models, such as electrode shape, size and spacing,

however, the Corox OTW-L BP has a new passive fixation structure (Figure 1 bottom). This structure is a dual-curved pre-shape, covering approximately 5 cm of the distal aspect of lead, and is designed to achieve a stable position in larger veins.

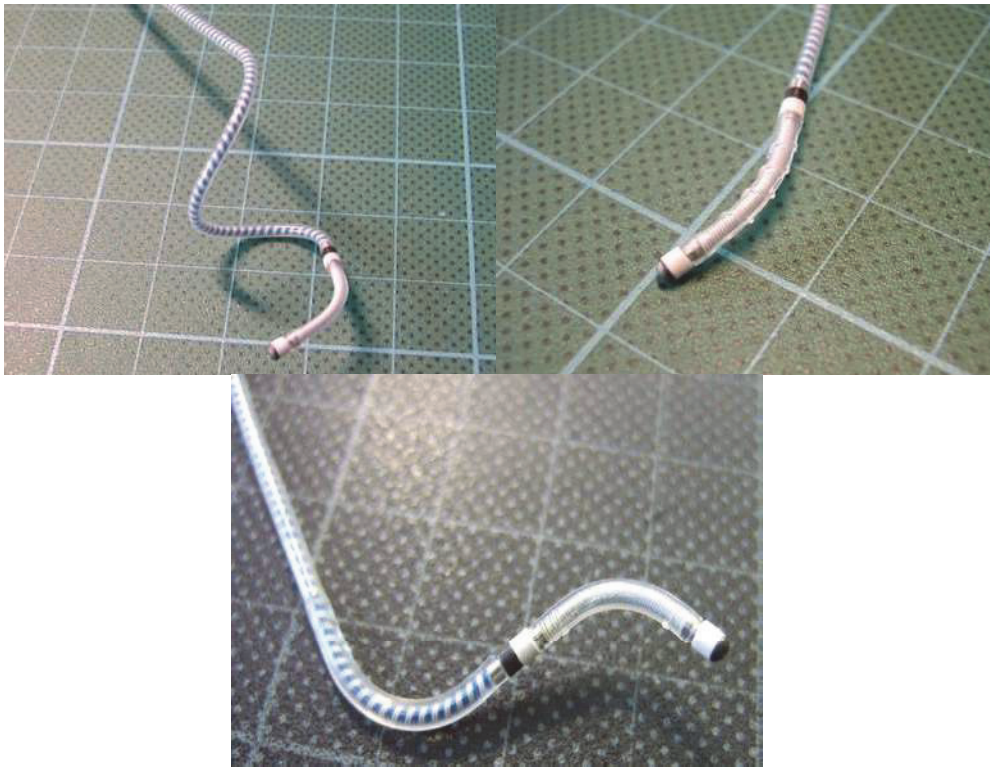

Figure 1: Corox BP LV Leads

2. STUDY DESIGN

The CELESTIAL post-approval registry is a multi-center, prospective, non-randomized, 5 year data collection registry. The registry is designed to gather long term safety and reliability data on BIOTRONIK's Corox BP LV leads. All patients enrolled into the clinical study will have an implanted BIOTRONIK CRT system, including a Corox BP LV lead, and will be enrolled from 7-180 days after successful CRT implantation or system revision.

Patients will be followed for 5 years post-implant, and are meant to be seen according to each institution's standard of care, but not to exceed a follow up time frame of (1) every 6 months for CRT pacemakers (CRT-Ps) or (2) every 4 months for CRT defibrillators (CRT-Ds). At enrollment, information will be collected regarding patient medical history, demographics, and other secondary data or data of interest specifically pertaining to the implant and status of the LV lead. At each follow up, a determination will be made whether the system is providing appropriate biventricular pacing. Additionally, the electrical parameters of the left ventricular lead will be collected, and any LV lead related adverse event will be documented.

The primary safety endpoints are constructed to capture all LV lead-related serious adverse events (SAEs) that require additional invasive intervention to resolve. Individual analysis of each serious adverse event (SAE) will be conducted and reported throughout the study. The low probability of SAE mandates the registry study size of a minimum of 2000 patients.

A secondary effectiveness endpoint will utilize a responder analysis of the success/failure of the CRT generator implanted with the Corox BP LV lead to deliver long-term biventricular pacing through 5 years post-implant.

2.1 STUDY ENDPOINTS

This clinical investigation includes the assessments of two primary safety endpoints related to the Corox BP LV leads, and several secondary endpoints that include an evaluation of the long-term delivery of biventricular pacing by BIOTRONIK CRT study devices. The hypotheses associated with the primary safety endpoints are presented below.

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

The purpose of primary endpoint 1 is to evaluate the overall incidence of serious adverse events that require additional invasive intervention to resolve, related to the Corox BP LV leads implanted with either BIOTRONIK CRT-P or CRT-D devices.

Primary safety endpoint 1 is constructed to capture all LV lead-related serious adverse events, not limited to fractures and insulation failures, but excluding those well documented adverse events that do not reflect a LV lead failure.

The following serious adverse events have been collected and reported by each LV lead manufacturer in their respective Summary of Safety and Effectiveness Data Reports (P050045, P050023, P030035, P010031, P010015, and P010012). While these SAEs will not be counted toward primary endpoint, they will be collected and analyzed as pre-specified secondary endpoints.

Table 4: Adverse Event Exclusions

Adverse Event Exclusions	Estimates of rates from prior studies
Inability to place LV Lead	10 - 14%
Lead dislodgements up to 180 days post implant procedure	1.9 - 9%
High LV pacing threshold, intermittent LV capture, no capture of LV lead	3.6 - 5.6%
Diaphragmatic/pectoral stimulation	0.2 - 2.9%
Infection	1.6 - 2.3%
Atrial lead, ICD lead, or generator adverse events requiring additional interventions	1.6 - 36.8%
Non LV lead related hospitalizations	27.4 - 48.9%
Non LV lead related death	6.2 - 18.9%
Implant procedure related complications such as CS dissection, CS perforation, pneumothorax, arrhythmias, cardiac tamponade, hematoma	1.5 - 13.3%
LV lead related thrombosis	<0.5%
Implant damage to LV lead (e.g. accidental cut to lead body during pocket revision, device replacement, etc.)	0.2 - 0.9%
Twiddler's syndrome	0.2%

Assuming that the expected Corox BP LV lead-related serious adverse event rate (proportion of subjects with at least one SAE), excluding the above, is 7.5% or less, then 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 BP 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 BP 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).

2.3 PRIMARY ENDPOINT 2: SAFETY OF COROX BP LV LEADS – 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 BP 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 BP LV Leads at 5 years post-enrollment is not equal to 1%

SAEIndividual ≠ 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.

2.4 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 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.

2.5 ADDITIONAL DATA OF INTEREST

In addition to the data collected in order to support the pre-defined endpoints, the CELESTIAL post approval registry will also collect other data of interest:

1. Patient implant data (collected retrospectively from medical chart review)
2. Demographic information
3. All cause adverse events
4. BIOTRONIK RA and RV/ICD lead electrical performances
5. Returned product analyses

6. Extraction experience
7. Comparison of data collected between Home Monitoring and in-office device interrogations

2.6 REGISTRY SIZE

The estimated sample size requirement is based on both primary safety endpoints: a noninferiority comparison of the overall SAE free-rate to 92.5% at 5 years, excluding those SAEs listed in 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.

The required sample sizes for the two primary safety endpoints are summarized in Table 5.

Table 5: Primary Safety Endpoints Sample Sizes

	Primary Safety Endpoint 1: Overall SAE free-rate	Primary Safety Endpoint 2: Individual SAE rates
Sample Size of Evaluable Patients	240	1000
Total with 50% Loss to Follow-Up over 5 years	480	2000

Due to the addition of the Corox OTW-L BP in the study, the total sample size was increased to 2500 to allow for sufficient enrollment of patients with this lead.

Study attrition

For the sample size calculation, a maximum loss to follow-up of 10% per year (50% over 5 years) was assumed. The loss to follow-up rate encompasses all causes for subjects to be exited from the study, including subject death, device explants, patient directed withdrawals, physician directed withdrawals, and loss of contact with the subject. BIOTRONIK will make every effort to limit the loss to follow-up, for reasons other than subject death and device explants unrelated to device design or performance, to less than 20% of the total registry enrollment cohort.

Minimum cohort size

The pre-specified secondary analysis will be conducted as an ad hoc analysis, meaning no testable hypothesis is being stated. Therefore, the minimal cohort size to analyze each lead model is based on an assumption of an equal 1/3 distribution of each lead model being enrolled in the CELESTIAL Registry. For the evaluation of the Corox OTW-L BP lead, a minimum of 600 evaluable subjects will be necessary.

2.7 DATA 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 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.

Primary safety endpoint 1 will be evaluated by performing an exact, noninferiority test comparing a binomial proportion (overall SAE free-rate at 5 years) to 92.5%, with a noninferiority delta of 5%. Equivalently, the upper, one-sided 95% confidence bound for the absolute difference between the overall SAE free-rate and 92.5% must not exceed 5%.

The evaluation of primary safety endpoint 2 will be based on the exact, two-sided 95% confidence interval for the observed, individual SAE rates at 5 years. The upper bound of these 95% confidence intervals must be less than 1%.

The secondary endpoint of successful biventricular pacing will be summarized as a success rate at each of the scheduled CELESTIAL follow-up visits through 5 years post-enrollment, together with the associated exact, 95% confidence intervals.

The secondary endpoint of other SAEs at 5 years, which were excluded from the primary safety analyses (listed in Table 5), will also be summarized as SAE rates together with their associated exact, 95% confidence intervals.

The secondary endpoints of pacing threshold and impedance measurements for the Corox BP LV leads will be summarized at scheduled visits where they were evaluated, using standard measures, including means, standard deviations, medians, minimums, and maximums.

The secondary endpoint for overall incidence of serious adverse events that meet the primary endpoint 1 criteria will be evaluated separately for each Corox BP lead model using the criteria established for primary safety endpoint 1 and 2.

2.7.1 Trend Analyses

The primary safety endpoints are evaluated at 5 years post-enrollment against pre-specified performance levels (92.5% for overall freedom from Corox BP LV lead-rated SAEs, 1% for individual SAE rates). To monitor the ongoing incidence of any potential SAEs against the accumulating follow-up exposure post-enrollment, Kaplan-Meier actuarial survivor curves will be prepared at the reporting intervals for these safety outcomes. Root causes for any failures, regardless of the incidence rates, will be investigated.

If the observed cumulative survival rates fall below the 5-year target values (92.5% of overall freedom from SAEs, 99% for individual SAEs) at any time during the study, or are projected to fall below the target values, then BIOTRONIK will summarize the observed data and the results of its failure investigations, and report the findings to the FDA at or before the next scheduled status report. If at any time a single unanticipated serious adverse event or device failure, or combination of events, is believed to have implications regarding the safety of current or future patients, then this will be reported immediately to the FDA.

2.7.2 Missing Data

The reasons for any missing data in the study will be documented. The sponsor will examine both missing-data patterns, which describe which values are observed and which are missing, and the missing-data mechanisms, which concern the relationship between missingness and the values of variables in the study data set [R.J.A. Little and D.B. Rubin, 2002, Statistical Analysis with Missing Data, 2nd edition, Wiley and Sons].

For evaluation of the primary study endpoints (safety endpoints 1 and 2), only patients who achieve 5 years of follow-up or have experienced a serious adverse event prior to 5 years will be included in the evaluation of the associated hypotheses. The secondary endpoint of other SAEs at 5 years, excluded from the primary safety analyses, will be analyzed in similar manner. There will be no imputation for these missing adverse event outcomes.

For purposes of Kaplan-Meier actuarial analyses, described in Section 2.7.1 Trend Analyses, all SAE data on enrolled patients will be included, with follow-up time censored at the time of withdrawal or last completed follow-up visit.

Secondary endpoints, which include successful biventricular pacing, pacing thresholds, sensing and impedance measurements will be analyzed in two ways. Initially, all available results will be summarized by scheduled visit through the 5 years of study follow-up. Afterwards, a last value carried forward (LVCF) will be used to estimate the values at the final 5-year follow-up evaluation.

2.8 STUDY ORGANIZATION

2.8.1 Electronic Data Capture (EDC)

MedNet Solutions Incorporated is a privately-held company that specializes in Web-based clinical database and data management technology. MedNet's responsibility is to partner with BIOTRONIK in the development, implementation, and on-going support of a system for an eClinical Solution including EDC of clinical trial data for the CELESTIAL post-approval registry. MedNet will configure a web-based eClinical system to meet the specific goals and needs of BIOTRONIK for the CELESTIAL registry. MedNet will host the Oracle database utilized for the EDC system. This system is 21 CFR Part 11 compliant and will be the conduit for the electronic case report form (eCRF) data entry, data validation, and access to real-time configured functions, tools, and reports for BIOTRONIK, specified investigational sites, and any other parties authorized by BIOTRONIK.

3. PROTOCOL REQUIREMENTS

3.1 PATIENT POPULATION

This post approval registry will include a minimum of 2500 patients from up to 100 centers. The collection of data will continue for five years for each enrolled subject.

The investigator is responsible for screening all potential patients and selecting those who are appropriate for registry inclusion. The patients selected for participation should be from the investigator's general patient population according to the inclusion and exclusion criteria described below. Patients declining participation will be documented on a screen failure log describing the primary reason.

3.1.1 Indications

Corox BP LV Lead

The Corox OTW BP, Corox OTW-S BP, and Corox OTW-L BP left ventricular pacing leads are bipolar steroid-eluting leads, intended for permanent implantation in the left ventricle via the coronary veins to provide pacing and/or sensing when used in conjunction with a compatible IS-1 pulse generator.

In this post-approval registry, any legally-marketed BIOTRONIK CRT device may be used (e.g. CRT-D: Lumax HF-T and any future CRT-D; CRT-P: Stratos LV and any future CRT-P).

3.1.2 Contraindications

Corox BP LV Lead

The use of the Corox BP LV leads is contraindicated under the following circumstances:

- Coronary sinus anomalies
- Tissue in the coronary sinus area that has been damaged by an infarction
- Any anomalies of the venous system that preclude transvenous implantation of the lead
- Patient cannot tolerate a single systemic dose of up to 1.0 mg of dexamethasone acetate (DXA)

3.1.3 Inclusion Criteria

To support the objectives of this post-approval registry, patients are required to meet the following inclusion criteria prior to enrollment:

- Successfully implanted BIOTRONIK CRT system, including a Corox BP LV lead, from 7-180 days prior to enrollment.
- Able to understand the nature of the registry and give informed consent

- Available for follow-up visits on a regular basis at the investigational site
- Age greater than or equal to 18 years

3.1.4 Exclusion Criteria

To support the objectives of this registry, the exclusion criteria at the time of patient enrollment include:

- Enrolled in any IDE clinical study
- Planned cardiac surgical procedures or interventional measures within the next 6 months
- Expected to receive a heart transplant within 1 year
- Life expectancy less than 1 year
- Presence of another life-threatening, underlying illness separate from their cardiac disorder
- Pregnancy
- Inability to provide date of implant, devices implanted, age, gender, and whether the patient experienced any protocol-defined adverse events since implant

3.2 POST APPROVAL REGISTRY DESIGN

3.2.1 Procedure

This is a prospective registry involving a minimum of 2500 subjects from up to 100 centers. Subjects will be enrolled 7-180 days after successful implantation of a BIOTRONIK CRT device utilizing a Corox BP LV lead. At enrollment, each registry patient should have CRT programmed “ON”. Additionally, BIOTRONIK Home Monitoring should be activated in all subjects. Standard Home Monitoring reports will be available to investigators. Home monitoring data can be utilized to assist in triage and diagnosis of LV lead-related adverse events.

3.2.2 Study Visits

The specific visits that are part of this registry are provided in the following bullets, and the procedures are described in more detail in the following sections:

- Screening Visit
- Enrollment
- Routine and unscheduled follow-ups through 5 years post-implant (every subsequent follow up that is scheduled according to each institution’s standard of care)

3.2.3 Screening Visit

Prior to enrollment, the patient's background and history must be reviewed in order to ensure they are an appropriate candidate for the registry. In addition, all patients must satisfy the inclusion and exclusion criteria prior to enrollment, including having an implanted BIOTRONIK CRT system utilizing a Corox BP LV lead. After the patient has passed this screening process, informed consent must be obtained from the patient prior to initiating any registry-related procedures.

The following are required at this visit:

- Ensure registry candidacy by answering inclusion and exclusion criteria
- Administer Informed consent

3.2.4 Enrollment Visit (within 30 days of screening visit)

After Informed Consent has been obtained and the patient has been determined to be eligible for the registry, data is collected in the Enrollment Visit. Typically the Screening Visit and the Enrollment Visit happen concurrently.

The following are required at the Enrollment Visit:

- Collect retrospective implant information from medical chart review
    - Date of implant
    - Implant approach/method, and venous access
    - Implant location of pulse generator and implanted leads
    - Implant procedure durations, if available
- Collect patient demographics (gender, height, weight, etc.)
- Medical history of patient
    - Bradycardia or ICD indication with Heart Failure
    - NYHA classification
    - LVEF %, if available; date and method obtained
- Collect information on implanted system (pulse generator and leads manufacturer/model, serial numbers, etc.)
- Record electrical parameters of the implanted leads
- Record any cardiac related adverse event between implant and the enrollment visit

Programming parameters should be set to best suit the needs of the patient. If adequate system function, including effective CRT, cannot be obtained, the patient should not be enrolled in this registry.

3.2.5 Routine and Unscheduled Follow-Ups

Patients enrolled in the CELESTIAL post approval registry can be implanted with either a CRT Pacemaker (CRT-P) or a CRT Defibrillator (CRT-D). Follow-up schedules for these devices vary by practice, but typically occur every 3-4 months for a CRT-D and every 6 months for a CRT-P. Therefore patients will be seen for routine follow-up visits per their institutional standard of care, but not to exceed every 6 months. All scheduled follow up windows are ± 1 month.

Any time a patient is seen outside of a required follow-up window according to each site's pre-determined specific follow-up scheduling practice, that visit is considered an unscheduled follow-up. Each site Principal Investigator (PI) and Clinical Research Coordinator (CRC) will be trained to identify and schedule follow-ups to meet this expectation. Additionally, the EDC will provide assistance in identifying properly scheduled follow-ups according to this protocol by assisting in the selection of the proper electronic Case Report Form (eCRF).

The following are required at each follow-up visit:

- Interrogate programmed parameters
- Determine lead electrical parameters
- Evaluate device diagnostics and programmed parameters to ensure CRT is programmed "ON" and the device is correctly providing CRT therapy
- Record % of CRT pacing
- Determine if there are any cardiac-related Adverse Events. If there are, complete the Adverse Event eCRF
- Complete all appropriate eCRF's

4. STUDY DOCUMENTATION AND DATA COLLECTION

4.1 ELECTRONIC CASE REPORT FORMS (eCRFs)

Original data will be collected from each investigational site and recorded into a secure Electronic Data Capture (EDC) application hosted by MedNet Solutions, Minneapolis, Minnesota, and audited and monitored by BIOTRONIK.

Information from electronically delivered source data (e.g. programmers) will be captured and stored in a validated environment until the end of the study.

The investigator will be required to use his/her electronic signature to verify the content of the data reported in the eCRFs.

Patient follow-up is required for all subjects enrolled in this clinical registry. The follow-up visit date is based on the Corox BP LV lead implant date, and are to be used for:

- Screening Visit
- Enrollment (7-180 days after Corox BP LV lead implant or lead revision)
- Medical History and Implant (at enrollment)
- Routine follow-ups (every 3-4 months for a CRT-D and every 6 months for a CRT-P, ± 1 month)
- Unscheduled cardiac related physician or hospital visits
- Final 5 Year follow-up (± 1 month)
- All cause Adverse Events
- Study Exit
- Patient Non-Compliance

4.2 DATA QUALITY CONTROL

BIOTRONIK will monitor study data closely. At any time, reports can be generated on data completion and missing data by the sponsor and by approved research personnel at each investigational site. An EDC system will be used to track received and expected follow-up data and eCRFs for each participant. This system provides the capability to monitor the status, volume, and disposition of data as well as to identify data completed, due, overdue, and backlogged. In addition, all study data will undergo extensive automatic edit and plausibility checks which provide information to the investigational sites to help improve and maintain data quality control procedures designed to detect inaccuracies and inconsistencies.

4.3 PATIENT RETENTION

Although the CELESTIAL Study sample size has been calculated with a 10% patient attrition rate per year (50% in 5 years), patient retention in a 5 year study may pose additional, unforeseen challenges. Therefore, BIOTRONIK has provided additional tools in an effort to minimize the number of patients that are lost to follow-up. The EDC system includes an overview of each patient's follow-up schedule, including the tolerance windows for each follow-up. The EDC system also provides a patient follow-up scheduling tool in the form of a Visit Scheduler Report. This report allows research personnel to become alerted to and track all study patients that should be scheduled for upcoming follow-ups. Additionally, the EDC system will automatically provide a bi-weekly action item list to each site coordinator in the form of email, which includes all patients that are due for scheduling.

Finally, to ensure protocol and follow-up compliance at all participating investigational sites, BIOTRONIK monitors will conduct monitoring visits (see Section 7). Monitoring visits include a review of patients that may be lost to follow-up.

5. PATIENT CONSENT

Patient participation in this registry is voluntary. It is required that all patients sign an IRB approved Patient Information and Consent Form (ICF) prior to participation in the registry. Patient informed consent must be obtained before enrollment and any protocol related procedures. To assist with the consent process, BIOTRONIK will provide a template patient ICF to participating sites.

The investigator is required to inform the sponsor and the reviewing IRB within 5 days if any patient was not appropriately consented to participate in the registry. The sponsor is then required to report any failure to obtain patient consent to the FDA within 5 working days of learning of such an event.

6. CONFIDENTIALITY AND RISK ANALYSIS

6.1 PATIENT DATA CONFIDENTIALITY

All information sent to BIOTRONIK pertaining to each patient will be kept confidential at BIOTRONIK and is subject to FDA audit. Reports submitted to the physician or publications of registry results will not make any reference to patient names.

In order to verify the study data and ensure study integrity, monitors from BIOTRONIK, the FDA, and the reviewing Investigational Review Board (IRB) may review and/or copy the study records.

6.2 RISKS AND RISK MINIMIZATION

This is a post-approval registry conducted using legally marketed devices implanted according to their approved labeling. BIOTRONIK foresees no additional risks associated with this registry beyond those stated in the labeling for the respective pulse generators and leads.

7. MONITORING

7.1 SUMMARY

BIOTRONIK, Inc. is the "sponsor" of the clinical registry. A sponsor is defined as an entity that initiates but does not conduct a post-approval registry. BIOTRONIK's responsibility as the post-approval registry sponsor is to ensure protocol and regulatory compliance through periodic monitoring of the investigation. BIOTRONIK has determined that this clinical investigation is not a significant risk study, as it concerns only legally marketed devices that are used in accordance with approved labeling. However, BIOTRONIK requires IRB review and a Patient Information and Consent form for all after-market research.

7.2 REGISTRY MONITORS

Registry monitors are trained, qualified, and designated by BIOTRONIK management to oversee the progress of a registry at the clinical site. The address for submitting clinical data to BIOTRONIK for this registry is:

BIOTRONIK, Inc.
Attn: CELESTIAL Registry
Clinical Studies Department
6024 Jean Road
Lake Oswego, Oregon 97035

Clinical data may also be submitted by fax to: (800) 723-9220
For technical assistance 24 hours a day, call: (800) 284-6689

7.3 MONITORING

A monitor may visit the post-approval registry site periodically throughout the registry. The sponsor may also require the presence of personnel from BIOTRONIK at follow-up procedures outlined by this protocol in order to assist the investigator and other site personnel. During periodic monitoring visits, assessment of the study site will include the following:

- Completion and submission of the required eCRFs and other applicable registry documentation
- Continued acceptability of the facilities
- Adherence to the clinical protocol
- Adherence to the applicable FDA regulations regarding the obligations of the investigator and maintenance of records

7.4 REGISTRY COMPLETION

BIOTRONIK will notify the post-approval registry site upon completion or termination of the registry or of the investigator's participation. At the sponsor's request, an investigator will return any equipment and pertinent information in their possession. The sponsor will provide a final report to each investigational site as required by FDA regulations. After FDA has agreed to terminate this registry, BIOTRONIK personnel will conduct a registry closure visit. During this final visit, BIOTRONIK will verify records and ensure that the investigator understands any applicable regulatory requirements, including those related to record retention. The investigator must retain records related to the registry for a period of 2 years after the investigation is completed.

7.5 DEVIATION FROM THE INVESTIGATIONAL PLAN

The investigator is required to conduct this registry in accordance with the signed investigator agreement and clinical protocol. The investigator shall notify the sponsor and reviewing IRB in writing no later than 5 working days after any significant deviation from the post approval registry that has occurred to protect the life or physical well being of a subject in an emergency. Except in such emergency, prior approval by the sponsor is required for significant deviations from the post-approval registry.

BIOTRONIK categorizes protocol non-compliance instances as either violations or deviations. Both protocol violations and deviations will be reported to FDA in the form of progress reports as necessary.

Protocol violations are defined as instances where the protocol requirements and/or regulatory guidelines were not followed, and are generally more serious in nature. Protocol violations are considered to potentially affect the scientific soundness of the study and/or the rights, safety, or welfare of subjects. Protocol violations include, but are not limited to, failure to obtain consent and patient inclusion/exclusion violations. These violations will be reported to FDA in accordance with applicable regulatory timelines, and the site must notify the reviewing IRB. Protocol violations must also be reported to the sponsor via Case Report Forms.

Protocol deviations are deviations from the requirements of the protocol in such a manner whereby data may not be usable or is not available. Protocol deviations are less serious in nature and do not require IRB notification as long as they do not effect the rights, safety, or welfare of the registry patient. Protocol deviations from the post-approval registry must be reported to the sponsor via Electronic Data Capture.

7.6 ADVERSE EVENTS

The investigator will be required to assess the association of each reported adverse event to the implant procedure, implanted system including the generator, any lead, or the Corox BP LV lead. For each of these relationships, the investigators will indicate whether the Adverse Event is not related, related, possibly related, or unknown.

All Adverse Events will be adjudicated by the Clinical Events Committee (see Section 7.7 Clinical Events Committee). The Clinical Events Committee (CEC) will have the responsibility to adjudicate all Adverse Events into one of the following three final classifications: related, not related, or unknown.

In evaluation of the two primary safety endpoints, the estimates of SAE rates will be based on the number of patients with at least one related SAE as a proportion of total patients with no SAEs, related SAEs, or unrelated SAEs. Patients with a final adjudicated relatedness SAE classification of unknown will not have that individual unknown event contribute to or be included in the evaluation of primary safety endpoint 1 (overall complication-free rate). Patients with an adjudicated relatedness SAE classification of unknown for a specific type of individual SAE will not have that individual unknown event contribute to or be included in the evaluation of that type of SAE in primary safety endpoint 2. However, for purposes of Kaplan-Meier actuarial analyses, described in Section 2.7.1 Trend Analyses and Section 2.7.2 Missing Data, all SAE data on enrolled patients will be included, with follow-up time censored at the time of withdrawal or last completed follow-up visit.

For the purposes of this registry, an adverse event is considered to be implant related if any one of the following occurred:

- Coronary sinus dissection
- Coronary sinus perforation
- Pneumothorax
- Arrhythmias
- Cardiac Perforation with or without tamponade
- Non-healing pocket dehiscence requiring intervention
- Hematoma
- Other event requiring surgical intervention

Additionally, for purposes of this registry, an adverse event is considered to have occurred at any point if both of the following conditions are met:

Condition One (definitions can be found in Appendix A: Definition of Terms)

- Infection
- Cardiac perforation with or without tamponade
- Lead dislodgment
- High pacing threshold, intermittent capture, no lead capture
- Diaphragmatic/pectoral stimulation
- Lead impedance out of range, high impedance
- Lead impedance out of range, low impedance
- Lead related thrombosis
- Implant damage to lead (e.g. accidental cut to lead body during pocket revision, device replacement, etc.)
- Premature battery depletion
- Suspected lead failure
- Suspected generator failure
- Twiddler's Syndrome
- Lead undersensing or loss of sensing
- Skin erosion

Condition Two:

- Lead pacing polarity or pacing mode reprogrammed due to suspected lead failure
- Lead surgically repositioned
- Lead surgically explanted
- Lead surgically replaced
- Lead surgically abandoned
- Lead abandoned and pacing disabled
- Lead use continued based on medical judgment despite a known clinical performance issue
- Other lead related surgery performed

Note: If Condition One is corrected by reprogramming the pulse generator or lead (other than changing the polarity or pacing mode) and no other invasive action was taken, then the event will not be considered an adverse event and should not be reported. Similarly, programming changes in pacing polarity/vector or pacing mode that are not due to a suspected lead failure will likewise not be considered an adverse event and should not be reported. For example, electrical reprogramming of the pacing polarity to eliminate diaphragmatic stimulation will not be considered an adverse event.

The adverse events that the IRB considers reportable are dependent on the particular IRB. The protocol-defined Adverse Events not related to the Corox BP LV lead are detailed in Table 4. To avoid underreporting, BIOTRONIK recommends that, at a minimum, the investigational site reports the adverse events detailed above that occur during the CELESTIAL post approval study to BIOTRONIK and their IRB.

The investigational site should report the Adverse Event on the Adverse Event eCRF. Additionally, registry sites may report adverse events through MedWatch, FDA's adverse event reporting tool for market-released devices. As defined in BIOTRONIK's internal procedures, these adverse events may be reported by BIOTRONIK through manufacturer's MedWatch reports.

7.7 CLINICAL EVENTS COMMITTEE

A Clinical Events Committee (CEC) consisting of at least 3 independent Electrophysiologists will be established to review and adjudicate all adverse events that occur during the study according to the protocol definitions. The CEC will be blinded to the investigational site and the patient identity. The CEC members will not participate as investigators, in order to minimize any potential bias.

The CEC will create a study specific charter defining the adverse event adjudication process, specifically detailing review guidelines along with appropriate response timelines.

7.8 PATIENT DEATH

Personnel at the investigational site should notify BIOTRONIK as soon as possible concerning any patient death during the investigation. This notification should include a completed Study Exit eCRF and copy of the notification of death (death report) sent to the IRB. The death report should include all of the following, if available:

- date and time of death
- place of death
- identification of the rhythm at the time of death, if known (include any available documentation)
- immediate cause of death
- any other circumstances surrounding the death
- whether the death was device related

Any implanted legally marketed devices that are explanted, including the Corox BP LV lead should be returned to BIOTRONIK for analysis.

7.9 IRB APPROVAL

Institutional Review Board (IRB) approval is required from each site prior to participation in this clinical registry. Patient enrollment may not begin until the IRB and BIOTRONIK have granted approval for the registry site. IRB approval is also required throughout the duration of this clinical investigation. If IRB approval is withdrawn for a site, BIOTRONIK must be notified within 5 working days.

7.10 OTHER INSTITUTIONS AND PHYSICIANS

This investigational registry is not transferable to other institutions attended by the investigator unless prior approval is obtained from both BIOTRONIK and the appropriate IRB. Only approved investigators are authorized to participate in the registry. However, there are certain situations where an investigator might not be immediately available to provide the necessary medical care for a patient with a registry device (e.g. when a patient goes to the emergency room for medical treatment). In any such situations, the IRB and investigator must continue to provide oversight for that patient's medical care and rights as a research subject. BIOTRONIK will ensure that the necessary support personnel are available to any physician providing immediate care for a patient in order to answer questions about the device and provide guidance in collecting the necessary documentation required for the post-approval registry. Documentation obtained will then be forwarded to the approved investigator for review and signature.

8. RECORDS AND REPORTS

8.1 INVESTIGATOR RECORDS

The physician is required to maintain the following accurate, complete, and current records pertaining to this post-approval registry:

- All correspondence relating to the registry: e.g. with another investigator, IRB, the sponsor, a monitor, or the FDA
- Records of each patient, including case history, data forms, patient consent, and supporting documentation
- A copy of the registry protocol
- Signed investigator or research agreement
- A copy of the IRB letter approving the research registry
- A copy of the IRB approved Patient Information and Consent form
- All clinical forms and documentation, including:

– a copy of the signed patient consent form
– all supporting documentation for data entered into the EDC
– records of any adverse device effects, including supporting documentation
– records pertaining to patient deaths during the investigation
– documentation and rationale for any deviations from the clinical protocol
– any other records required by the sponsor

8.2 INVESTIGATOR REPORTS

The investigator is responsible for the accurate and timely preparation (review and/or signature) and submission of the reports cited below:

- Withdrawal of IRB approval and the reason for withdrawal. An investigator should report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the site investigator's participation in an investigation.
- Informed consent. If an investigator enrolls a patient without obtaining informed consent, the investigator will report such enrollment to the sponsor and the reviewing IRB within 5 working days after the event occurs.
- Notification of patient death during the post-approval registry
- Annual progress reports prepared for the IRB

- Notification of any deviations from the investigational protocol
- Final summary report prepared for the IRB
- Other: an investigator will, upon request by a reviewing IRB, the FDA, or BIOTRONIK, provide accurate, complete, and current information about any aspect of the registry

The table below is a chart outlining the responsibilities, including time constraints, for submitting the above reports.

Type of Report	Prepared by Investigator for:	Time Constraints of Notification
Patient Death During Investigation	BIOTRONIK, IRB	BIOTRONIK as soon as possible and as required by reviewing IRB
Patient Withdrawal	BIOTRONIK	Within 5 working days
Withdrawal of IRB Approval	BIOTRONIK	Within 5 working days
Progress Report	BIOTRONIK, IRB	Submitted not less than yearly
Significant Deviations from Investigational Plan	BIOTRONIK, IRB	Within 5 working days after emergency to protect life or physical well-being of the patient, otherwise prior approval by sponsor is required
Informed Consent Not Obtained	BIOTRONIK, IRB	Within 5 working days of use
Final Summary Report	BIOTRONIK, IRB	Within 3 months after completion or termination of the registry

8.3 SPONSOR RECORDS

The sponsor, BIOTRONIK, will maintain the following records:

- All correspondence that pertains to the investigation with investigator(s), IRB, and FDA
- Investigator agreements, financial disclosures, and current curriculum vitae
- Name and address of each investigator and each IRB that is involved with the investigation
- Adverse events and complaints
- Electronic Case Report Form data
- Completed patient Informed Consent Forms
- Clinical investigational plan (protocol) and report of prior investigations
- Monitoring reports
- Clinical progress reports

8.4 SPONSOR REPORTS

The sponsor is responsible for preparing the following reports:

Type of Report	Prepared by Sponsor for:	Time Constraints of Notification
Withdrawal of IRB Approval	FDA, all reviewing IRBs, and participating investigators	Within 5 working days of receipt of notice of withdrawal of approval
Withdrawal of FDA Approval	Reviewing IRBs and participating investigators	Notification will be made within 5 working days
Progress Report	FDA, all reviewing IRBs	A periodic progress report will be submitted every six months. The report will include: • All reported AEs • AE trend analysis • Patient accountability, including enrollment, and follow-up status
Recall and Disposition	FDA, all reviewing IRBs	Notification will be made within 30 working days and will include the reasons for any request that an investigator return, repair or otherwise dispose of any devices
Final Report	FDA, all reviewing IRBs, and participating investigators	Notify FDA within 30 working days of the completion or termination of the investigation. A final report will be submitted within 6 months after completion or termination of the registry.
Failure to Obtain Informed Consent	FDA	A copy of the investigator's report will be submitted within 5 working days of notification of use

APPENDIX A: DEFINITION OF TERMS

AE (Adverse Event) - an unwanted effect detected in participants. The term is used whether or not the effect can be attributed to the leads in the registry. For the purposes of this registry, BIOTRONIK classifies an AE as either related to the Corox BP lead or not related to the lead.

ACC/AHA – American College of Cardiology/American Heart Association

Cardiac Perforation – Penetration of the lead tip through the myocardium (including microperforation), either clinically suspected or confirmed by chest x-ray, fluoroscopy, echocardiogram, intracardiac electrogram and/or visually

Clinical Failure – Inability of the Corox BP LV lead to correctly sense or pace in the heart, not attributable to a mechanical malfunction of the lead or pulse generator that remains unresolved despite reprogramming and/or repositioning.

CFR – Code of Federal Regulations

Conductor Fracture – See Lead Fracture

Confirmed Failure – A Corox BP LV lead having clinically relevant characteristics that are outside the performance limits established by BIOTRONIK while implanted and in service, as confirmed by analysis, except for changes in characteristics that are due to induced malfunctions. Lead damage caused during or after explant is not considered a failure.

Complication - an adverse event that requires additional invasive intervention to resolve

Coronary Sinus Dissection – A tear that occurs in the wall of the coronary sinus

Coronary Perforation - Penetration of the lead tip through the coronary sinus, either clinically suspected or confirmed by chest x-ray, fluoroscopy, echocardiogram, intracardiac electrogram and/or visually

CHF (Congestive Heart Failure) – a condition where the heart is not able to pump sufficient amounts of blood to meet the body's need

CRT-P – Cardiac Resynchronization Therapy Pacemaker

CRT-D - Cardiac Resynchronization Therapy Defibrillator

Defibrillation Impedance – The total opposition of current that presents in the circuit utilized to shock an arrhythmic heart back into a normal rhythm. Defibrillation impedance is considered abnormal if the measurement is ≤ 20 Ohms or ≥ 200 Ohms

Diaphragmatic/Pectoral Stimulation – Clinical observation of inadvertent nerve/muscle stimulation other than cardiac muscle.

eCRF – electronic Case Report Form

EDC – Electronic Data Capture system

Elevated Threshold – Either of the following definitions constitute an Elevated Threshold:

1. At implant, pacing thresholds for the permanently programmed electrode that are greater than 3.0 Volts at 0.5 ms., or

2. At follow-up, pacing thresholds for the permanently programmed electrode that are greater than 3.5 Volts at 0.5 ms.

ERI – Elective Replacement Indicator

Exit Block – The failure of an intact pacing system to capture the heart because the stimulation threshold exceeds the output of the pacemaker

Explanted (LV Lead) – Surgical removal of an LV lead during the acute implant stage, whereby the lead has not been chronically implanted and can be easily removed by simple traction

Extracted (LV Lead) - Surgical removal of a chronically implanted LV lead

Failure to Capture or Loss of Capture – Intermittent or complete failure to achieve cardiac stimulation at programmed output delivered outside of the cardiac refractory period

High Pacing Threshold – Sudden and significant increase compared to the previous measured threshold value

IDE – Investigational Device Exemption

Insulation Breach/Break – Visual, electrical, or radiographic evidence of a disruption or break in the insulation of a lead

IRB – Investigational Review Board

Lead Dislodgment or Lead Migration – Radiographic, electrical or electrocardiographic evidence of electrode displacement from the original implant site or electrode displacement that adversely affects pacing, and/or lead performance

Lead Fracture – Visual, electrical and/or radiographic evidence of mechanical break within the lead conductor (connectors, coils and/or electrodes)

Lead impedance out of range – Pacing impedance is considered abnormal if a measurement is ≤ 200 Ohms or ≥ 2000 Ohms

Loss of Sensing/Undersensing– Intermittent or complete failure to sense any intrinsic events that occur outside the programmed refractory periods at programmed sensitivity settings

LV – Left Ventricular

LV Lead Abandoned, CRT programmed off – The LV lead remains connected to the generator but LV pacing is disabled

Non-healing Pocket Dehiscence – Separation of wound edges around the pocket of the implanted pulse generator that have not healed

NYHA – New York Heart Association, a recognized system of classifying patient condition according to:

I – Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain

II – Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain

III – Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain

IV – Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased

Observation – an adverse event that does not require additional invasive intervention to resolve

Oversensing – Misinterpretation of cardiac or non-cardiac events as cardiac depolarization, such as T waves, skeletal muscle potentials, and extracardiac electromagnetic interference (EMI)

PG (Pulse Generator) – For this registry, the pulse generator must be either a BIOTRONIK CRT-P or CRT-D

Pneumothorax – Air or fluid in the pleural space surrounding the lung leading to collapse or partial collapse of the lung

Premature Battery Depletion – Reaching Elective Replacement indicator (ERI) before the predicted date

Mechanical Failure – Malfunction of the Corox BP LV lead through a break in the conductor, insulation or connector pin leading to loss of CRT therapy

RV/RA/ICD lead – Right Ventricular/ Right Atrial/ Implantable Cardioverter Defibrillator Lead

Significant Increase in Pacing Threshold – One of the following definitions must be met:

1. An observed increase of 2-fold over the first chronic threshold, provided that the resultant threshold is greater than 5 Volts at 0.5 ms, or
2. An observed threshold higher than the maximum output of the device. Currently, this is 7.5 V at 1.5 ms in the Lumax 340 HF-T and Lumax 540 HF-T CRT-D's.

Chronic threshold is defined as the pacing threshold determined at the patient's 3 month follow-up visit.

Skin Erosion – Deterioration of tissue over an implanted device or the movement of a lead toward or through the skin

Suspected Generator Failure – Pulse generator issue that is potentially an electrical malfunction

Suspected Lead Failure – Corox BP LV Lead issue that is potentially a mechanical or electrical malfunction

Tamponade – Compression of the heart caused by blood accumulation in the space between the myocardium and the pericardium

Threshold Rise – An observed threshold increase of 2-fold over the first chronic threshold, provided that the resultant threshold is greater than 3.5 Volts at 0.5 ms. Chronic threshold is defined as the pacing threshold determined at the patient's 3 month follow-up visit.

Thrombosis – The development of a blood clot in a vein or artery

Twiddler's Syndrome – A condition where the pulse generator leads are dislodged by the patient unwittingly rotating the subcutaneous pulse generator

APPENDIX B: TIMELINE

CELESTIAL Post-Approval Registry Timeline

While BIOTRONIK has legally marketed and sold cardiac rhythm management devices for many years, Cardiac Resynchronization Therapy is a relatively new field for BIOTRONIK. Creating a timeline that characterizes patient enrollment where market-share is not clearly understood is challenging, and therefore BIOTRONIK has made the following assumptions:

- FDA protocol approval by November 8, 2008
- Ability to recruit sufficient number of interested centers and enroll 2500 patients within 24 months
- 10% local IRB, 90% central IRB

In addition, BIOTRONIK assumes the approximate timeline:

CELESTIAL Post-Approval Registry Timeline Estimate	Date
FDA Approval of the Corox BP LV Leads (P070008)	May 12, 2008
BIOTRONIK Submission of CELESTIAL Post-Approval Registry	June 10, 2008
FDA Approval of CELESTIAL Post-Approval Registry	November 06, 2008
First IRB Approval	December 08, 2008
First Patient Enrolled	December 19, 2008
5 Clinical Sites open, 19 patients enrolled	February 14, 2009
CELESTIAL 6 Month Interim Post-Approval Registry Status Report submitted	May 08, 2009
50 Sites open, 223 patients enrolled	August 15, 2009
CELESTIAL 12 Month Interim Post-Approval Registry Status Report submitted	November 08, 2009
50-75 Sites open, 541 patients enrolled	February 13, 2010
CELESTIAL 18 Month Interim Post-Approval Registry Status Report submitted	May 08, 2010
50-75 Sites open, 825 patients enrolled	August 12, 2010
CELESTIAL 24 Month Interim Post-Approval Registry Status Report submitted	November 08, 2010
50-75 Sites open, 1104 patients enrolled	December 19, 2010
CELESTIAL 30 Month Interim Post-Approval Registry Status Report submitted	May 08, 2011
75-100 Sites open, 1404 patients enrolled	May 08, 2011
CELESTIAL 36 Month Interim Post-Approval Registry Status Report submitted	November 08, 2011
75-100 Sites open, 1854 patients enrolled	November 08, 2011
75-100 Sites open, 2000 patients enrolled	February 08, 2012
CELESTIAL 42 Month Interim Post-Approval Registry Status Report submitted	May 08, 2012
75-100 Sites open, 2225 patients enrolled	May 08, 2012
75-100 Sites open, 2500 patients enrolled	August 29, 2012
CELESTIAL 48 Month Interim Post-Approval Registry Status Report submitted	November 08, 2012
CELESTIAL 54 Month Interim Post-Approval Registry Status Report submitted	May 08, 2013
CELESTIAL 60 Month Interim Post-Approval Registry Status Report submitted	November 08, 2013
CELESTIAL 66 Month Interim Post-Approval Registry Status Report submitted	May 08, 2014
CELESTIAL 72 Month Interim Post-Approval Registry Status Report submitted	November 08, 2014
CELESTIAL 78 Month Interim Post-Approval Registry Status Report submitted	May 08, 2015
CELESTIAL 84 Month Interim Post-Approval Registry Status Report submitted	November 08, 2015
CELESTIAL 90 Month Interim Post-Approval Registry Status Report submitted	May 08, 2016
CELESTIAL 96 Month Interim Post-Approval Registry Status Report submitted	November 08, 2016
CELESTIAL 102 Month Interim Post-Approval Registry Status Report submitted	May 08, 2017
CELESTIAL Final Post-Approval Registry Status Report submitted	November 08, 2017