# Protocol for the SIELLO Clinical Study


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**SIELLO Clinical Study**

# PROTOCOL SIGNATURE PAGE

The signature below constitutes the receipt and review of the SIELLO Clinical Study protocol and any attachments, and provides the necessary assurances that this study 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: _____

Name (please print)

_____ _____

Signature Date

# SUMMARY

| | |
|---|---|
| **Title:** | SIELLO Clinical Study |
| **Design:** | This clinical study is a combined Pre-Market Study and Post-Approval Registry that will enroll up to 2124 subjects implanted with BIOTRONIK's Siello pacing lead in the atrium and/or ventricle.<br><br>The Pre-Market study is designed to follow a total of 986 leads (430 atrial and 556 ventricular) in up to 986 subjects from implant through 12 months post implant. The pre-market analysis will occur once 387 Siello atrial leads and 500 Siello ventricular leads have reached the 12-month follow-up time point.<br><br>In order to meet FDA's objective of a large subject cohort prospectively followed to confirm long-term safety of the Siello pacing lead, BIOTRONIK will continue enrollment for a long-term Post-Approval Registry designed to follow a total of 2124 leads (combined atrial and ventricular) in up to 2124 subjects for a target follow-up time of 5 years post implant. A minimum number of 1694 right ventricular leads will be enrolled in the study. |
| **Purpose:** | The purpose of the Pre-Market Study is to demonstrate the safety and effectiveness of the BIOTRONIK Siello pacing lead. The evaluation of safety will be based on the analysis of the Siello lead-related adverse events in a follow-up time of 12 months post implant. The evaluation of effectiveness will be based on the analysis of the success rate of the implanted system including one or two Siello leads to sense and deliver pacing at 12 months post-implant.<br><br>The purpose of the Post-Approval Registry is to confirm long-term safety of the BIOTRONIK Siello pacing lead. The evaluation of safety will be based on the analysis of Siello pacing lead-related adverse events in a follow-up time of 5 years post implant. Additionally, acute and chronic lead parameters for pacing and sensing thresholds and impedance will be evaluated. |
| **Subject Population:** | Subjects who require treatment for bradycardia requiring the implantation of a pacemaker system including an atrial and/or a ventricular pacing lead. Subjects need to be enrolled in the study before implantation of a BIOTRONIK system, including one or two Siello leads. |
| **Enrollment:** | The Pre-Market Study will include up to 986 subjects from up to 75 centers. Data on a total of a minimum of 887 leads (387 atrial and 500 ventricular) will be collected for 12 months post implant. Subjects enrolled in the Pre-Market Study will continue to be followed in the Post-Approval Registry.<br><br>The Post-Approval Registry will include up to 2124 subjects from up to 75 centers. The collection of data on a total of a minimum of 1253 leads (combined atrial and ventricular) will continue for five years post implant. |
| **Clinical Sites:** | Up to 75 sites in the United States. |

| | |
|---|---|
| **Primary Endpoints:** | The purpose of primary endpoints 1 and 2 for pre-market analysis is to evaluate the overall incidence of adverse events related to the atrial and ventricular Siello leads within 12 months post-implant. The purpose of primary endpoint 3 is to evaluate the overall success rate of the implanted system including one or two Siello leads to sense and deliver pacing at 12 months post-implant. Primary endpoints 1, 2 and 3 will be evaluated once 387 Siello atrial leads and 500 Siello ventricular leads have reached the 12-month follow-up time point.<br><br>The purpose of primary endpoint 4 is to evaluate the overall incidence of adverse events related to the Siello lead in the primary RV lead position within 5 years post implant. The purpose of primary endpoint 5 is to evaluate the incidence of each type of adverse event that contributes to primary endpoint 4, within 5 years post implant. |
| **Secondary Endpoint:** | The following secondary endpoints will also be evaluated during the study:<br>1. 5-year Adverse Event-Free Rate for the Secondary (RA) lead position<br>2. Individual Adverse Event Rates for the Secondary (RA) lead position at 5-years<br>3. Pacing threshold, sensing and impedance measurements for the atrial and ventricular Siello leads at 12-months post-implant<br>4. Success rate of the implanted system including a Siello lead to deliver long-term pacing through 5 years post-implant<br>5. Adverse event rates for AEs excluded from primary safety endpoint through 5 years post-implant.<br>6. Pacing threshold, sensing and impedance measurements for the Siello leads through 5 years post-implant |
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# 1. INTRODUCTION

## 1.1 NAME OF DEVICE

This protocol includes a Pre-Market Study (IDE) phase and an FDA required Post-Approval Registry phase for BIOTRONIK's Siello S (active fixation), further referred to as Siello lead throughout this protocol. Under this protocol, the Siello lead is utilized in conjunction with any market-released BIOTRONIK Evia pacemaker device (P950037/S72, dated May 7, 2010 and P950037/S92, dated February 11, 2011).

## 1.2 OVERVIEW AND BACKGROUND

### 1.2.1 Overview

The purpose of this observational study is to confirm safety and reliability of the Siello lead as used in conjunction with any BIOTRONIK Evia pacemaker device. The study will provide data to characterize lead-related adverse events, from implant through 12 months post implant to support a pre-market analysis. In addition, the study will provide data to fully characterize Siello lead failures, from implant through 5 years as a post-approval registry. Safety will be evaluated based on the analysis of all Siello lead-related adverse events. Acute and chronic lead parameters for sensing, pacing thresholds, and impedance will be evaluated from implant through 12 months post implant for the pre-market analysis and 5 years post implant for a post-approval registry analysis. 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. Up to 2124 subjects will be enrolled in this Post-Approval Registry, to gather data on a minimum total of 253 atrial and 1000 ventricular leads followed for five years post implant.

In this study the Siello lead is considered an investigational device. All other devices included in the study are legally marketed. All devices are being prescribed by physicians according to approved indications for use.

All subjects will be pre-screened to ensure they are eligible to participate, and will sign an informed consent prior to enrollment into the study. The informed consent form will inform the subject regarding the collection of all pertinent subject, device and lead data from implant through 5 years post implant.

### 1.2.2 Background

The Siello S lead (active fixation) is a transvenous, bipolar, endocardial lead designed for permanent atrial or ventricular stimulation and sensing. The Pre-Market Study and Post-Approval Registry are designed to document the clinical experience of the Siello lead in the United States as required by the FDA.

### 1.2.3 Prior Clinical Experience

The Siello lead is similar to BIOTRONIK's Setrox lead. Data from the previous clinical studies including the Siello lead and the Setrox lead are presented in this section.

#### 1.2.3.1 Setrox OUS Study

BIOTRONIK conducted a Post Market Surveillance study outside the United States on the Setrox S active fixation lead. The Post Market Surveillance (PMS) study was designed to evaluate the long term performance of the Setrox S lead based on a large subject population (n = 414 subjects). The sensing and pacing behavior was evaluated as well as the rate of device related complications over a period of at least 2 years (and up to 3 years). From the first implant in September 2006, 627 Setrox S leads (283 atrial, 344 ventricular) were implanted in 414 subjects. The mean atrial and ventricular pacing threshold at 24 months was 0.8 V and 0.9 V, respectively. The study reported a complication rate of 2.1% (13 lead-related complications) with 9 complications occurring within the first 4 days after implantation.

#### 1.2.3.2 CELESTIAL and GALAXY Studies

BIOTRONIK is currently conducting two studies in the US on FDA approved leads (CELESTIAL, a post-approval study for the Corox OTW BP family of LV leads; and GALAXY, an after-market study for the Linox family of ICD leads), both of which include patients with the Setrox S lead implanted as the brady lead for the pacing system. The Setrox S data collected to date from these two studies was extracted and summarized in an interim report. The report contains data from the 956 CELESTIAL and 960 GALAXY subjects who have been implanted with a right atrial Setrox S lead enrolled as of September 16, 2011 for CELESTIAL and March 26, 2012 for GALAXY. The sensing and pacing behavior was evaluated as well as the rate of device related complications over the available follow-up period. The mean atrial pacing threshold ranges from 0.6V to 0.8V. The mean atrial sensing amplitude ranges from 2.4 to 2.8 mV. The mean atrial lead impedance ranges from 541 to 613 Ohms. The reported complication rate at this interim analysis is 1.4% (27 lead-related complications) with 11 complications occurring within 90 days of implant.

#### 1.2.3.3 Siello European Study

BIOTRONIK completed a Post Market Evaluation in Europe which was designed to demonstrate the clinical effectiveness and safety of the Siello S active and Siello JT/T passive pacemaker lead family. This summary includes data on the Siello S active fixation lead. From July 30, 2009 (first implant procedure) to November 15, 2010 (day of last follow-up in the report), data was collected on 191 Siello S leads in 126 subjects. The sensing and pacing behavior was evaluated as well as the rate of device related complications over a period of 1 year.

The mean atrial pacing threshold at the 12 month follow-up of the Siello S lead was 0.8 V ± 0.3 V. The mean atrial sensing amplitude at 12 months was 4.2 mV ± 2.0 mV and

the mean atrial impedance at 12 months was 573 Ohm ± 98 Ohm. All atrial lead measurements also showed stable performance over the 12 month study period.

The mean ventricular pacing threshold at the 12 month follow-up of the Siello S lead was 0.9 V ± 0.5 V. The mean ventricular sensing amplitude at 12 months was 14.1 mV ± 8.2 mV and the mean ventricular impedance at 12 months was 624 Ohm ± 94 Ohm. All ventricular lead measurements also showed stable performance over the 12 month study period.

The Siello S complication free rate at 3 months was 96.8% with a confidence interval of [91.9%, 99.0%]. All complications were ventricular lead dislocations with successful repositioning of the lead within 3 months of implant. Five subjects died, but according to the investigators these deaths were not related to the Siello lead.

#### 1.2.3.4 Other Studies

The following adverse events on active fixation leads have been collected and reported in several Summary of Safety and Effectiveness Data Reports and manuscripts.

**Table 1: Historical Adverse Events**

| Adverse Events Exclusions | Estimates of rates from prior studies (Atrial) | Estimates of rates from prior studies (Ventricle) | Estimates of rates from prior studies (A or V - no distinction) |
|---|---|---|---|
| Lead dislodgement | 0 - 7.8% | 4.00% | 0 - 7.8% |
| Elevated pacing threshold, undersensing, oversensing, loss of capture | 1.9 - 10.68% | 9.04% | 0.08 - 10.68% |
| Implant procedure-related lead complications (lead reversed in header, loss of slack in leads) | 2.60% | | 2.60% |
| Implant procedure-related medical complications (e.g. Pleural effusion, pneumothorax, tamponade, cardiac perforation, edema, pericardial effusion, hematoma of the pocket, chest pain, venous occlusion) | 0.63 - 6% | 0.47 - 5.06% | 0.01 - 6% |
| Pocket infection | 2.06% | | 0.56% |
| Extracardiac stimulation | 0.5 - 0.56% | 1.13% | 0.01 - 1.13% |
| VA Crosstalk | | | 3.10% |
| Atrial fibrillation | 0.56 - 14.29% | | |
| Pulmonary embolism | 0.50% | | 0.50% |
| Non lead-related death | 0 - 9.2% | 0.00% | 0 - 37.86% |

Sources:
- Summary of Safety and Effectiveness Data Report P020030
- Summary of Safety and Effectiveness Data Report P030036
- Boston Scientific CRM Product Performances Report, published Nov 30, 2009
- Kistler P. M., Liew G. and Mond H. G., Long-term performance of active-fixation pacing leads: a prospective study, Pacing Clin Electrophysiol 2006; 29: 226–230.
- Luria D., Bar-Lev D., Gurevitz O., Granit H., Rotstein Z., Eldar M. and Glickson M., Long-term performance of screw-in atrial pacing leads: a randomized comparison of J-shaped and straight leads, Pacing Clin Electrophysiol 2005; 28: 898–902.
- Sterlinski M, Przybylski A, Maciag A, Syska P, Pytkowski M, Lewandowski M, et al. Subacute cardiac perforations associated with active fixation leads. Europace. 2009;11: 206-212.

## 1.3 DEVICE DESCRIPTIONS

### 1.3.1 Siello Leads

The Siello S is a family of 6F, steroid-eluting, transvenous, endocardial and bipolar active-fixation leads with an extendable/retractable and electrically active screw. The Siello S is manufactured, like its predecessor the Setrox S lead, in three different models (45, 53 and 60 cm length). It has an isodiametric structure and silicone insulation. The inner and outer conductors consist of quadruple wire coils. Siello S has a diameter of 5.9 F and is covered by a polyurethane overlay for improved gliding. It has an IS-1 connector and a 10 mm pole distance. The area between tip and ring is flexible in order to minimize the perforation risk. The fixation screw of the Siello S is electrically active and has a fractal iridium coating. The screw can be extended by 1.8 mm and has an active surface area of 4.5 $mm^2$. The ring electrode of Siello S has a surface area of approximately 17.4 $mm^2$ and is fractally coated with iridium. The Siello S has a dexamethasone eluting steroid collar containing 0.85 mg dexamethasone acetate. The accessories that are delivered with the lead are identical to the accessories of the Setrox S.

**Figure 1: Siello Lead**

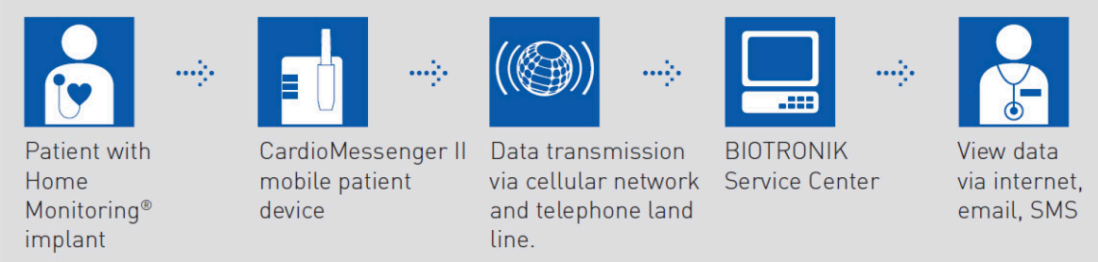
### 1.3.2 BIOTRONIK Home Monitoring

Current expert consensus advocates 3- to 12-month device evaluations either in-person or by remote monitoring[1].

Home Monitoring is a communication system which allows the automatic transmission of diagnostic subject data from the device to the physician at any time. The technology implements the use of wireless communications to provide the physician with daily subject monitoring and trend analysis information between office follow-up visits. A block diagram of the transmission path is shown in Figure 2, and the transmission steps are described as follows:

- Communication starts with the implant, which activates a very low power RF transmitter circuitry integrated within the pulse generator.
- The subject device accepts subject data from the implant and transfers this digital information using a cellular short messaging system (SMS) or telephone landline connection to a BIOTRONIK service center for evaluation.
- The BIOTRONIK Service Center receives incoming data and generates a customized summary which is available to the physician online via secure Internet access, or can be forwarded to the physician via FAX.

**Figure 2: Home Monitoring Transmission Path**




BIOTRONIK conducted the TRUST study to evaluate the safety and effectiveness of Home Monitoring. BIOTRONIK received FDA approval (P050023/S020, approved May 12, 2009) of the following labeling claims regarding Home Monitoring:

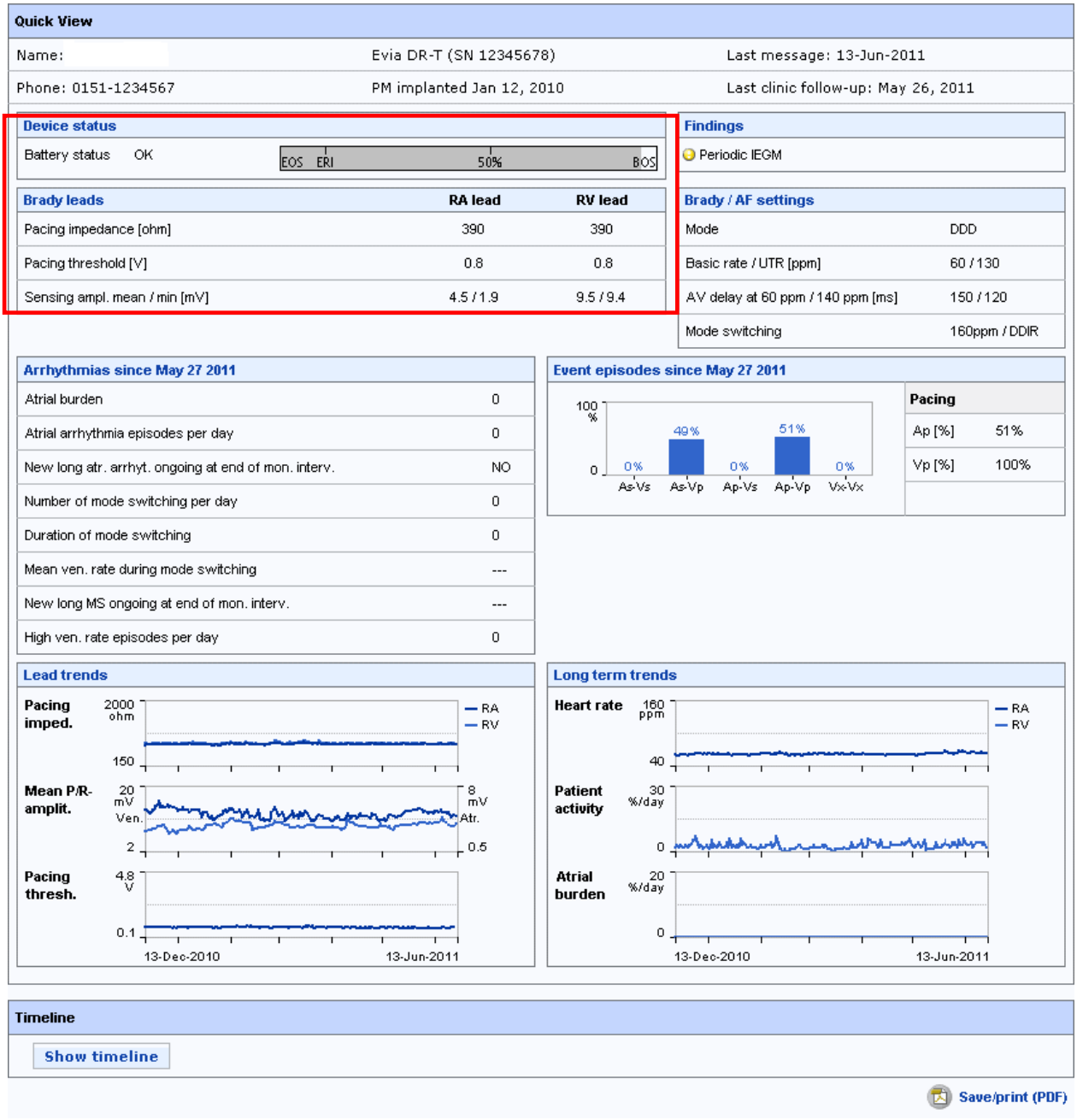
- BIOTRONIK Home Monitoring information may be used as a replacement for device interrogation during in-office follow-up visits.
- A strategy of care using BIOTRONIK Home Monitoring with office visits when needed has been shown to extend the time between routine, scheduled in-office follow-ups of BIOTRONIK implantable devices in many patients. Home Monitoring data is helpful in determining the need for additional in-office follow-up.

[1] Wilkoff BL, et al. HRS/EHRA expert consensus on the monitoring of cardiovascular implantable electronic devices (CIEDs): description of techniques, indications, personnel, frequency and ethical considerations. *Heart Rhythm* 2008;5:907-25

- BIOTRONIK Home Monitoring-patients—who are followed remotely with office visits when needed—have been shown to have similar numbers of strokes, invasive procedures and deaths as patients followed with conventional in-office follow-ups.
- BIOTRONIK Home Monitoring provides early detection of arrhythmias.
- BIOTRONIK Home Monitoring provides early detection of silent, asymptomatic arrhythmias.
- Automatic early detection of arrhythmias and device system anomalies by BIOTRONIK Home Monitoring allows for earlier intervention than conventional in-office follow-ups.
- BIOTRONIK Home Monitoring allows for improved access to patient device data compared to conventional in-office follow-ups since device interrogation is automatically scheduled at regular intervals.

In the Evia pacemakers, Home Monitoring provides event and system information similar to what is currently available during office follow-up visits. The highlighted information in the Home Monitoring Quick View Summary Report, Figure 3, displays the study related follow-up data automatically transmitted on a daily basis including: battery status, pacing impedance, pacing threshold, sensing amplitude (mean/min) for both the atrial and ventricular leads. In addition, Home Monitoring provides automatic daily information on arrhythmias, lead trends, current device programming, event episodes, and long term trends.

## Figure 3: Home Monitoring Quick View Summary Report



# 2. STUDY DESIGN

This is a multi-center, prospective, non-randomized study designed to gather safety data on BIOTRONIK's Siello S leads. All subjects enrolled into the study will have an implanted legally marketed BIOTRONIK Evia pacemaker system including one or two Siello leads.

At enrollment, information will be collected regarding subject medical history and demographics. Implant data will include lead measurements, implant technique and lead positioning. Subjects will be seen for an in-office follow-up at 3, 6, and 12 months post-implant. At these follow-ups, a determination will be made whether the system is able to provide appropriate pacing and sensing. Additionally, the electrical parameters of the Siello leads will be collected, and any Siello lead-related adverse events will be documented.

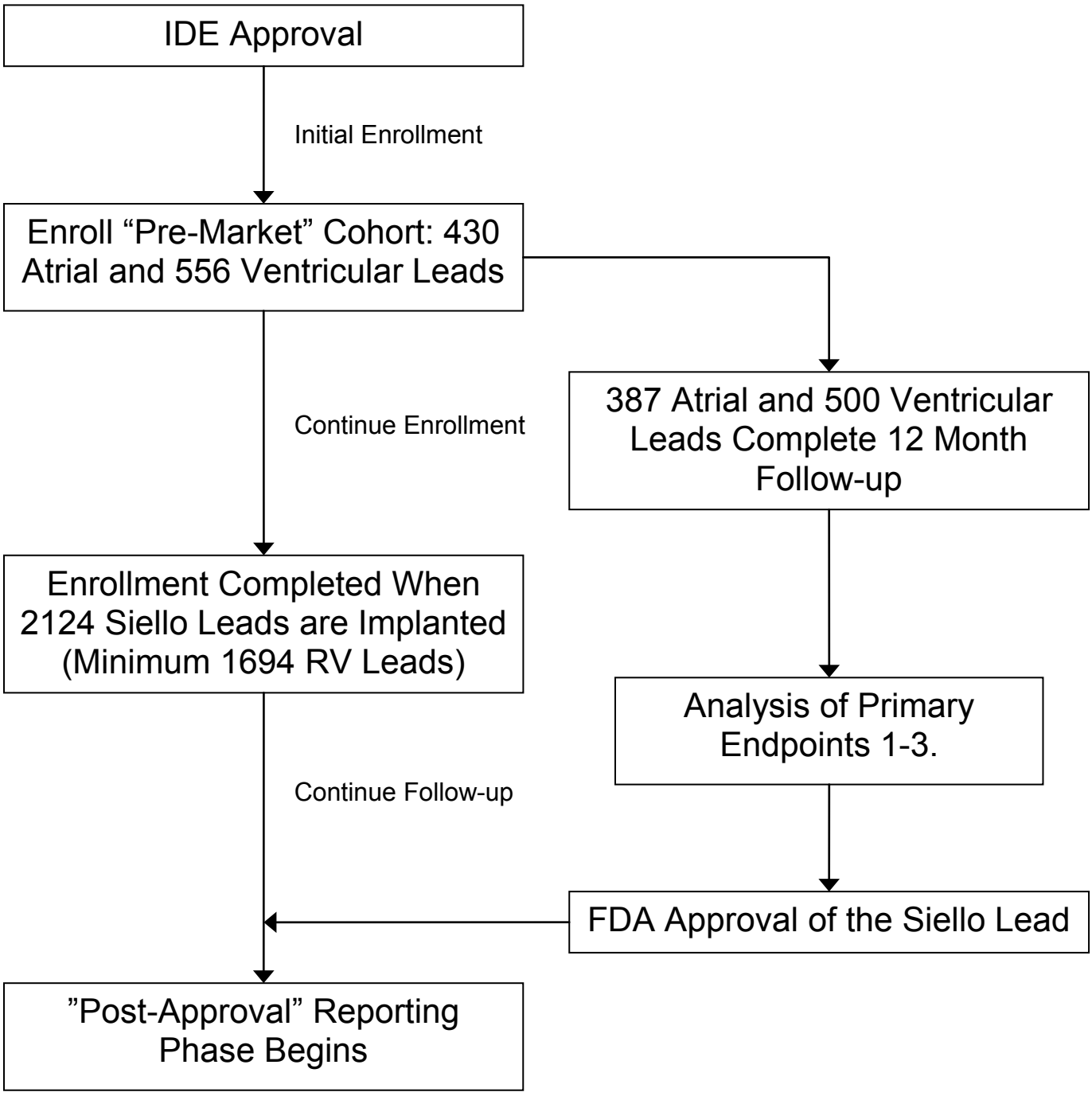
Subjects will continue to be followed for 5 years post-implant. Subjects with a Home Monitoring system may be seen for an in-office follow-up at least every 12 months and be followed by Home Monitoring between in-office follow-ups at least every 6 months. Subjects without a Home Monitoring system will be seen for an in-office follow-up at least every 6 months. At each follow-up, a determination will be made whether the system is able to provide appropriate pacing and sensing. Additionally, the electrical parameters of the Siello leads will be collected, and any Siello lead-related adverse event will be documented.

The primary safety endpoints are constructed to capture all Siello lead-related adverse events (AEs) that require additional invasive intervention to resolve within 12 months post-implant (premarket analysis), and 5 years post-implant (post-approval analysis). Individual analysis of each adverse event (AE) will be conducted and reported throughout the study. Primary endpoint 3 will analyze the success rate of the implanted system including a Siello lead to deliver long-term pacing through 12 months post implant. Analysis for the pre-market primary endpoints will occur once 387 Siello atrial leads and 500 Siello ventricular leads have reached the 12-month follow-up time point. In order to meet FDA's objective of a large subject cohort prospectively followed to confirm long-term safety of the Siello pacing lead, BIOTRONIK will continue enrollment for a long-term Post-Approval Registry designed to follow a minimum total of 1253 leads (combined atrial and ventricular) in up to 2124 enrolled subjects for a target follow-up time of 5 years post implant. A minimum number of 1694 right ventricular leads will be enrolled in the study.

Secondary endpoints will analyze the success rate of the implanted system including a Siello lead to deliver long-term pacing through 5 years post-implant, adverse event rates for AEs excluded from primary safety endpoint through 5 years post-implant, as well as pacing threshold, sensing and impedance measurements for the Siello leads through 5 years post-implant. The low probability of AE mandates the study size of a minimum of 1253 total atrial and ventricular leads in up to 2124 enrolled subjects.

The study design is summarized in Figure 4.

**Figure 4: Flowchart of Study Design**



## 2.1 STUDY ENDPOINTS

This study includes the assessments of four primary safety endpoints related to the atrial and ventricular Siello leads, and several secondary endpoints that evaluate the effectiveness of the BIOTRONIK system including one or two Siello leads. The hypotheses associated with the primary safety endpoint are presented below.

Success Criteria

The Pre-Market evaluation at 12 months will be considered a success, if the safety endpoints (Primary Endpoints 1 and 2) and effectiveness endpoint (Primary Endpoint 3) are met.

The Post-Market evaluation at 5 years will be considered a success, if the Pre-Market evaluation is successful and the long-term safety endpoints (Primary Endpoints 4 and 5) are met.

### 2.1.1 Primary Endpoint 1: Atrial Siello Lead Safety – 12-Month Adverse Event-Free Rate (Pre-Market Analysis)

The purpose of primary endpoint 1 is to evaluate the overall incidence of adverse events related to the Siello leads (as defined in Section 10.4) implanted in the atrium with a BIOTRONIK Evia pacemaker device.

Assuming that the expected atrial Siello lead-related adverse event rate at 12 months post-implant (proportion of subjects with at least one AE in the timeframe from implant through 12 months post-implant), excluding the adverse events listed above, is 6.0% or less, then the primary safety endpoint will be evaluated in the following testable hypothesis in superiority format.

$H_o$: The adverse event-free rate (AEFR) for the atrial Siello leads at 12 months post-implant is less than or equal to 94.0%

$$AEFR \leq 94.0\%$$

$H_a$: The adverse event-free rate (AEFR) for the atrial Siello leads at 12 months post-implant is greater than 94.0%

$$AEFR > 94.0\%$$

A rejection of the null hypothesis would demonstrate evidence that the adverse event-free rate is greater than 94.0%.

### 2.1.2 Primary Endpoint 2: Ventricular Siello Lead Safety – 12-Month Adverse Event-Free Rate (Pre-Market Analysis)

The purpose of primary endpoint 2 is to evaluate the overall incidence of adverse events related to the Siello leads (as defined in Section 10.4) implanted in the ventricle with a BIOTRONIK Evia pacemaker device.

Assuming that the expected ventricular Siello lead-related adverse event rate at 12 months post-implant (proportion of subjects with at least one AE in the timeframe from implant through 12 months post-implant), excluding the adverse events listed above, is 6.0% or less, then the primary safety endpoint will be evaluated in the following testable hypothesis in superiority format.

$H_o$: The adverse event-free rate (AEFR) for the ventricular Siello leads at 12 months post-implant is less than or equal to 94.0%

$AEFR \leq 94.0\%$

$H_a$: The adverse event-free rate (AEFR) for the ventricular Siello leads at 12 months post-implant is greater than 94.0%

$AEFR > 94.0\%$

A rejection of the null hypothesis would demonstrate evidence that the adverse event-free rate is greater than 94.0%.

### 2.1.3 Primary Endpoint 3: Siello Lead Effectiveness – Success rate of the implanted system including one or two Siello leads to sense and deliver pacing at 12-months post-implant (Pre-Market Analysis)

The purpose of primary endpoint 3 is to evaluate the overall success rate of the implanted system including one or two Siello leads to sense and deliver pacing at 12-months post-implant.

Successful sensing performance at 12 months is the demonstrated ability to appropriately sense without an intervention for undersensing (i.e. Siello lead-related adverse event for lead undersensing or loss of sensing) in the period from implant to 12 months, except for normal pulse generator reprogramming. Successful pacing is the demonstrated ability at 12 months to deliver a stimulation pulse with capture, without an intervention (i.e. Siello lead-related adverse event for intermittent capture or no lead capture) other than normal pulse generator reprogramming. Success is determined at the subject level. If both atrial and ventricular leads have been implanted, then both must have successful sensing and pacing performance. The success rate will be tested in the following hypotheses:

$H_o$: The rate of successful sensing and pacing (Rate) in subjects receiving the Siello leads at 12 months post-implant is less than or equal to 97%

$Rate \leq 97\%$

$H_a$: The rate of successful sensing and pacing (Rate) in subjects receiving the Siello leads at 12 months post-implant is greater than 97%

$Rate > 97\%$

A rejection of the null hypothesis would demonstrate that the rate of successful sensing and pacing is greater than 97%.

### 2.1.4 Primary Endpoint 4: Siello Lead Safety – 5-Year Adverse Event-Free Rate for Primary (RV) Lead Position (Post-Approval Analysis)

The purpose of primary endpoint 4 is to evaluate the overall incidence of adverse events related to the Siello leads (as defined in Section 10.5) implanted in the primary RV position with a BIOTRONIK pacemaker device.

Assuming that the expected Siello lead-related adverse event rate at 5 year post-implant (proportion of subjects with at least one AE in the timeframe from implant through 5 year post-implant) is 7.5% or less, then the primary safety endpoint will be evaluated in the following testable hypothesis in superiority format.

$H_o$: The adverse event-free rate (AEFR) for subjects receiving the Siello leads at 5 years post-implant is less than or equal to 92.5%

$$AEFR \leq 92.5\%$$

$H_a$: The adverse event-free rate (AEFR) for subjects receiving the Siello leads at 5 year post-implant is greater than 92.5%

$$AEFR > 92.5\%$$

A rejection of the null hypothesis would demonstrate that the adverse event-free rate is greater than 92.5%.

### 2.1.5 Primary Endpoint 5: Siello Ventricular Lead Safety – Individual Adverse Event Rates for Primary (RV) Lead Position (Post-Approval Analysis)

Each of the individual types of adverse events contributing to primary safety endpoint 4 will be evaluated separately in the following superiority hypotheses:

$H_o$: The individual adverse event rate (AEIndividual) for a given type of AE for the Siello Ventricular Leads at 5 years post-implant is equal to 1%

$$AEIndividual = 1\%$$

$H_a$: The individual adverse event rate (AEIndividual) for a given type of AE for the Siello Ventricular Leads at 5 years post-implant is not equal to 1%

$$AEIndividual \neq 1\%$$

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

### 2.1.6 Secondary Endpoints

There are no formal tests of hypotheses associated with secondary endpoints 1-6.

1. 5-year Adverse Event-Free Rate for Secondary (RA) lead position
2. Individual Adverse Event Rates for Secondary (RA) lead position at 5-years
3. Pacing threshold, sensing and impedance measurements for the atrial and ventricular Siello leads at 12-months post-implant.
4. Success rate of the implanted system including one or two Siello leads to deliver long-term pacing through 5 years post-implant.
5. Adverse event rates for AEs excluded from primary safety endpoint 4; through 5 years post-implant.
6. Pacing threshold, sensing and impedance measurements for the Siello leads through 5 years post-implant.

### 2.1.7 Additional Data of Interest

In addition to the data collected in order to support the pre-defined endpoints, the SIELLO Pre-Market Study will also collect other data of interest:

1. Subject implant data
2. Demographic information
3. Returned product analyses
4. Extraction experience

## 2.2 STUDY SIZE

The estimated sample size requirement for primary safety endpoints 1 and 2 are based on a superiority comparison of the overall AE free-rate to 94.0% at 12 months. The sample size for primary safety endpoint 1 and 2 was calculated based on the following assumptions:

<u>Assumptions for primary safety endpoints 1 and 2</u>

- Study Design: nonrandomized study
- Test basis: exact binomial test
- Type I error (alpha): 0.025 (one-sided for superiority)
- Statistical power: 80%
- Estimated AE-Free Rate at 12 months: 97.0% for both RV and RA Siello Leads
- Performance goal for AE-Free Rate at 12 months: 94.0%

For primary safety endpoint 1, a total of 387 evaluable subjects implanted with an atrial Siello lead would be required to demonstrate superiority to an AE free-rate of 94.0%. Assuming a 10% loss to follow-up rate over 12 months of follow-up, a total of 430 (387/0.9) subjects with an atrial lead would be required to be enrolled to evaluate primary safety endpoint 1.

For primary safety endpoint 2, a total of 387 evaluable subjects implanted with a ventricular Siello lead would be required to demonstrate superiority to an AE free-rate of 94.0%.

Since the RV position is the primary lead position, the sample size will be increased to 500 evaluable subjects as recommended by the FDA. Assuming a 10% loss to follow-up rate over 12 months of follow-up, a total of 556 (500/0.9) subjects with a ventricular lead would be required to be enrolled to evaluate primary safety endpoint 2. As subjects may have an atrial and/or ventricular lead implanted, the total number of enrolled subjects may be less than the total of 986 Siello leads (430 + 556).

The estimated sample size for primary effectiveness endpoint 3 is based on a superiority comparison of the overall sensing and pacing success rate to 97% at 12 months. The samples size for primary endpoint 3 was calculated based on the following assumptions:

Assumptions for primary effectiveness endpoint 1

- Study Design: nonrandomized registry
- Test basis: exact binomial test
- Type I error (alpha): 0.025 (one-sided for superiority)
- Statistical power: 80%
- Estimated Successful Sensing and Pacing Rate at 12 months: 99.0% for Siello Leads
- Performance goal for Success Rate at 12 months: 97%

For primary endpoint 3, a total of 432 evaluable subjects would be required to demonstrate superiority to a success rate of 97%. Assuming a 10% loss to follow-up rate over 12 months of follow-up, a total of 480 (432/0.9) subjects would be required to be enrolled to evaluate primary endpoint 3.

The estimated sample sizes required to evaluate primary endpoints 4 and 5 are based on a superiority comparison of the overall primary RV lead position AE free-rate to 92.5% at 5 years, and a non-powered, superiority comparison for those individual lead-related AE to 1% at 5 years. The sample size for primary safety endpoint 4 was calculated based on the following assumptions:

Assumptions for primary safety endpoint 4

- Study Design: nonrandomized registry
- Test basis: exact binomial test
- Type I error (alpha): 0.025 (one-sided for superiority)
- Statistical power: 80%
- Estimated AE-Free Rate at 5 years: 95.0% for Siello Leads
- Performance goal for AE-Free Rate at 12 months: 92.5%

For primary safety endpoint 4, a total of 750 evaluable Siello leads in the primary RV lead position would be required to demonstrate superiority to an AE free-rate of 92.5%. Assuming a 10% loss to follow-up rate per year over 5 years of follow-up (average of 8.2% of original population per year), a total of 1271 ($750/0.9^5$) subjects with a RV lead would be required to be enrolled to evaluate primary safety endpoint 4.

Assumptions for primary safety endpoint 5

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

For primary safety endpoint 5, a total of 1000 evaluable subjects with Siello leads in the primary RV position would be required to demonstrate a two-sided, upper 95% confidence bound of 1%, assuming an expected individual AE rate of 0.4%. Assuming a 10% loss to follow-up rate per year over 5 years of follow-up (average of 8.2% of original population per year), a total of 1694 ($1000/0.9^5$) Siello RV leads would be required for evaluation of primary safety endpoint 5. As stated above, a total of 430 subjects with Siello leads in the RA position will be enrolled for evaluation of Primary Endpoint 1. Of these, 253 ($430/0.9^5$) are expected to have follow-up data available at 5 years. As subjects may have an atrial and/or ventricular lead implanted, the total number of enrolled subjects may be less than the total of 2124 Siello leads (1694 + 430).

The required sample sizes for the five primary endpoints are summarized in Table 2 and Table 3. The total eventual study enrollment will be determined by the number of subjects and leads required to evaluate primary endpoints 1-5.

**Table 2: Primary Endpoints Sample Sizes (Pre-Market Analysis)**

| | **Primary Safety Endpoint 1: Overall Atrial AE free-rate (12 months)** | **Primary Safety Endpoint 2: Overall Ventricular AE free-rate (12 months)** | **Primary Effectiveness Endpoint 3: Overall Siello Lead Pacing and Sensing success rate (12 months)** |
|---|---|---|---|
| **Sample Size of Evaluable Siello leads / subjects** | 387 leads | 500 leads | 432 subjects |
| **Total adjusted for Potential Losses to Follow-Up** | 430 leads | 556 leads | 480 subjects |

**Table 3: Primary Safety Endpoints Sample Sizes (Post-Market Analysis)**

| | Primary Safety Endpoint 4: Overall AE free-rate of primary (Right Ventricular) lead position (5 years) | Primary Safety Endpoint 5: Individual AE rates for primary (Right Ventricular) lead position (5 years) |
|---|---|---|
| **Sample Size of Evaluable Siello leads / subjects** | 750 leads | 1000 leads |
| **Total adjusted for Potential Losses to Follow-Up** | 1271 leads | 1694 leads |

Attrition

For the sample size calculation, a maximum loss to follow-up of 10% per year (41% 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, subject directed withdrawals, physician directed withdrawals, and loss of contact with the subject.

## 2.3 PROTOCOL REQUIREMENTS

### 2.3.1 Subject Population

The study will enroll up to 2124 subjects from up to 75 centers. After the collection of data for evaluation of the Pre-Market Study endpoints, enrollment and follow-up will continue in preparation of the Post-Approval Registry. Expected enrollment at a single site should be at least 20 subjects and will be limited to no more than 15% of the projected total study enrollment (approximately 320 subjects).

The investigator is responsible for pre-screening all potential subjects and selecting those who are appropriate for study inclusion. The subjects selected for participation will be from the investigator's general subject population according to the inclusion and exclusion criteria described below. Subjects declining participation will be documented on a screen failure log describing the primary reason.

Investigators are strongly encouraged to seek an equal enrollment of both men and women at their sites, to ensure that women are adequately represented in the study population and to enable meaningful analyses of results by gender. If less than 40% women are enrolled when the prespecified enrollment is reached, open enrollment will be maintained for women until a proportion of 40% is obtained.

### 2.3.2 Siello S Indications

The BIOTRONIK Siello S lead is a 5.6 French (6F introducer), transvenous, steroid-eluting (0.85 mg DXA), bipolar, IS-1 compatible, active fixation lead intended for permanent sensing and pacing in either the right atrium or right ventricle when used with a compatible pulse generator.

In this study, any currently and future legally-marketed BIOTRONIK Evia pacemaker device (e.g. DR-T, SR-T, HF-T) in combination with one or two Siello leads may be used.

### 2.3.3 Siello S Contraindications

Transvenous endocardial pacing leads are contraindicated in the presence of severe tricuspid valvular disease and in subjects with mechanical heart valves. The Siello S pacing lead is additionally contraindicated for subjects who cannot tolerate a single systemic dose of up to 0.85 mg of dexamethasone acetate (DXA).

### 2.3.4 Inclusion Criteria

To support the objectives of this study, subjects are required to meet the following inclusion criteria prior to enrollment:

- Candidate for de novo implantation of a BIOTRONIK Evia pacemaker system, including one or two Siello leads. Candidate meets recommendation for pacemaker system implant put forth by guidelines of relevant professional societies.
- Able to understand the nature of the study and provide informed consent
- Available for follow-up visits on a regular basis at the investigational site for the expected 5 years of follow-up
- Age greater than or equal to 18 years

### 2.3.5 Exclusion Criteria

To support the objectives of this study, the exclusion criteria at the time of subject enrollment include:

- Enrolled in any other investigational clinical study
- Currently implanted with a pacemaker or ICD device

- 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
- Pregnant at the time of enrollment

## 2.4 STUDY DESIGN

### 2.4.1 Study Procedures

The study will involve up to 2124 subjects from up to 75 centers. Subjects will be enrolled before implantation of a BIOTRONIK system including one or two Siello leads. BIOTRONIK Home Monitoring should be activated in subjects who have a Home Monitoring system. Home Monitoring data can be utilized to assist in triage and diagnosis of lead-related adverse events between scheduled follow-ups. Following the 12-month follow-up, subjects with a Home Monitoring system will be seen for a routine in-office follow-up at least every 12 months and will be followed by Home Monitoring between routine in-office follow-ups at least every 6 months. Subjects without a Home Monitoring system will be seen for a routine in-office follow-up at least every 6 months.

### 2.4.2 Study Visits

The specific visits for the study are:

- Enrollment
- Implant
- 3-Month Follow-up
- 6-Month Follow-up
- 12-Month Follow-up
- Routine Follow-up evaluations (every subsequent six months)
- Interim Follow-ups for Siello lead-related visits
- System Revision

Table 4 summarizes the visit assessment schedule.

**Table 4: Study Visit Assessment Schedule**

| | **Enrollment** | **Implant**[1] | **3 Month Follow-up** (± 1 month) | **6 Month Follow-up** (± 1 month) | **12 Month Follow-up** (± 1 month) | **Routine Follow-up 18-60 Months** (every 6 months ± 1 month)[3] | **System Revision** (if applicable) |
|---|---|---|---|---|---|---|---|
| Informed Consent (enrollment) | X | | | | | | |
| Demographics and Medical History | X | | | | | | |
| Collect Implant Information | | X[2] | | | | | X |
| Device Evaluation | | X | X | X | X | X | X |
| Adverse Event Assessment | | X | X | X | X | X | X |
| Complete eCRF | X | X | X | X | X | X | X |

[1]Implant must be completed within 30 days of informed consent.
[2]If the system was planned to be implanted with a Siello lead, but the Siello lead could not implanted, the subject will exit the study after being followed for a period of 30-days in order to capture any adverse events possibly related to the implant procedure.
[3]Following the 12-month follow-up, subjects using Home Monitoring will be seen for a routine in-office follow-up at least every 12 months and may be followed by Home Monitoring between routine in-office follow-ups at least every 6 months. Subjects not using Home Monitoring will be seen for a routine in-office follow-up at least every 6 months. If a study visit is conducted via home monitoring the site is required to call the subject on the date of the home monitoring data collect and document the Investigators assessment of possible Adverse Events since the last study visit.

### 2.4.3 Study Pre-screening

Prior to enrollment, the subject's background and history must be reviewed in order to ensure they are an appropriate candidate for the study. In addition, all subjects must satisfy the study inclusion and exclusion criteria prior to enrollment, including being a candidate for an implanted BIOTRONIK Evia pacemaker system utilizing one or two Siello leads.

### 2.4.4 Study Enrollment Visit

If the subject has been determined to be eligible for the study, informed consent must be obtained from the subject prior to initiating any study related procedures. The consent process, including discussion of the study, will be documented in the subject's medical record. A subject is considered enrolled in the study upon signing the Informed Consent Form.

After Informed Consent has been obtained, data is gathered during the Enrollment visit.

The following are required at the Enrollment Visit:

- Obtain Informed Consent

- Collect subject demographics (gender, height, weight, etc.)
- Medical history of subject
- Device implant indications
- Complete all appropriate eCRFs

### 2.4.5 Siello Implant

Implant may be completed on the same day enrollment procedures are completed. Otherwise, implant will be completed within 30 days of informed consent being obtained.

The following are required at Implant:

- Collect implant information
  - Date of implant
  - Implant approach/method, and venous access
  - Implant location of pulse generator and implanted leads
  - Implant success
- Collect information on implanted system (pulse generator and leads manufacturer/model, serial numbers, etc.)
- Record electrical parameters of the implanted leads. Perform all pacing threshold measurements at 0.4 ms or 0.5 ms pulse width when feasible.
- Record any lead-related, pulse generator-related and procedure-related adverse events during implant. If any are recorded, complete the Adverse Event eCRF.
- Programming parameters should be set to best suit the needs of the subject.
- Complete all appropriate eCRFs.

If the system was planned to include a Siello lead, but the subject could not be implanted with a lead, the subject will exit the study after being followed for a period of 30-days in order to capture any adverse events possibly related to the implant procedure.

### 2.4.6 3-Month Follow-up

Three months (± 1 month) after implant, subjects will undergo an assessment of their implanted system. The following are required at the 3-month follow-up visit:

- Interrogate programmed parameters.
- Record electrical parameters of the implanted leads. Perform all pacing threshold measurements at 0.4 ms or 0.5 ms pulse width when feasible.

- Evaluate device diagnostics, electrical parameters and programmed parameters to ensure the device is correctly pacing and sensing.
- Determine if there are any lead-related, pulse generator-related or procedure-related adverse events. If any are recorded, complete the Adverse Event eCRF.
- Complete all appropriate eCRFs.

### 2.4.7 6-Month, 12-Month and Subsequent Routine Follow-ups

Six months (± 1 month) after implant and every six months thereafter, subjects will undergo an assessment of their implanted system. Following the 12-month follow-up, subjects using Home Monitoring may be seen for a routine in-office follow-up at least every 12 months and will be followed by Home Monitoring between routine in-office follow-ups at least every 6 months. Subjects not using Home Monitoring will be seen for a routine in-office follow-up at least every 6 months. Additionally, each Home Monitoring follow-up will be accompanied by a follow-up patient-doctor telephone call documenting clinical signs and symptoms.

Each site Principal Investigator (PI) will be trained to identify and schedule follow-ups to meet the required visit expectation. Additionally, the EDC will provide assistance in identifying properly scheduled follow-ups according to this protocol.

The following are required at the 6-month follow-up, 12-month follow-up, and all subsequent routine follow-ups:

- Assess programmed parameters.
- Record electrical parameters of the implanted leads. Perform all pacing threshold measurements at 0.4 ms or 0.5 ms pulse width when feasible.
- Evaluate device diagnostics, electrical parameters and programmed parameters to ensure the device is correctly pacing and sensing.
- Determine if there are any lead-related, pulse generator-related or procedure-related adverse events. If any are recorded, complete the Adverse Event eCRF.
- Complete all appropriate eCRFs.

### 2.4.8 Interim Unscheduled Follow-Ups

Interim unscheduled follow-ups may occur anytime during the study. Data collection is only required for such visits when due to Siello lead-related reasons.

The following should be performed at each interim unscheduled follow-up visit:

- Assess programmed parameters.

- Record electrical parameters of the implanted leads. Perform all pacing threshold measurements at 0.4 ms or 0.5 ms pulse width when feasible.
- Evaluate device diagnostics, electrical parameters and programmed parameters to ensure the device is correctly pacing and sensing.
- Determine if there are any lead-related, pulse generator-related or procedure-related Adverse Events. If any are recorded, complete the Adverse Event eCRF.
- Complete all appropriate eCRFs.

### 2.4.9 System Revision

If a pulse generator and/or lead replacement occurs during the course of the study, information will be collected on the extraction experience (if applicable) and the newly implanted generator or lead(s).

The following are required at a system revision:

- Collect implant information
  - Date of revision
  - Implant approach/method, and venous access
  - Implant location of pulse generator and implanted leads
- Extraction experience (if applicable)
- Collect information on newly implanted system (pulse generator and leads manufacturer/model, serial numbers, etc.)
- Record electrical parameters of the implanted leads. Perform all pacing threshold measurements at 0.4 ms or 0.5 ms pulse width when feasible.
- Record any lead-related, pulse generator-related and procedure-related adverse events during implant. If any are recorded, complete the Adverse Event eCRF.
- Programming parameters should be set to best suit the needs of the subject.
- Complete System Revision and Out of Service (OOS) eCRF for explanted components.

## 2.5 SUBJECT WITHDRAWALS, LOST-TO-FOLLOW-UP

### 2.5.1 Withdrawal of Enrolled Subjects

Once a subject is enrolled, every effort should be made to continue to follow the subject in the study. However, in a trial of this duration, it is inevitable that some subjects will decline to participate further, change geographic location, or become non-compliant with the follow-up schedule. Subjects who are implanted with one or two Siello leads and have all Siello leads explanted that are not replaced with another Siello lead will be withdrawn from the study. However, if a subject is re-implanted with a new Siello lead, the subject will continue to participate in the study based on their original implant date and follow-up schedule.

### 2.5.2 Enrolled Subjects Lost-to-Follow-up

Subjects lost-to-follow-up are those for whom contact is lost despite the investigator's best efforts to locate the subject. Subjects with Home Monitoring systems where contact is lost may continue to be followed via Home Monitoring despite failed efforts to locate the subject for in-office follow-up.

## 2.6 DATA ANALYSIS

The primary analysis population for the study is the intention-to-treat (ITT) population. All subjects who provide informed consent, meet the enrollment criteria, and in whom an attempt is made to implant a Siello lead will be included in the ITT population.

The characteristics of the study population will be described using summary descriptive statistics appropriate to the type of parameter, continuous or discrete, being reported.

Confidence intervals for Adverse Event-Free Rate (AEFR) will be based on Kaplan-Meier estimates for freedom from adverse events together with the associated standard errors.

Primary safety endpoints 1 and 2 will be evaluated by performing an exact, binomial test comparing a binomial proportion (overall AE free-rate at 12 months) to 94.0%. Equivalently, the lower, two-sided 95% confidence bound for the absolute difference between the overall AE free-rate and 94.0% must exceed zero. Primary endpoints 1 and 2 will be evaluated once 387 Siello atrial leads and 500 Siello ventricular leads have reached the 12-month follow-up time point.

Primary effectiveness endpoint 3 of successful sensing and pacing will be evaluated by performing an exact binomial test comparing a binomial proportion (success sensing and pacing rate) to 97.0%. It will also be summarized as a success rate at the 12-month follow-up visit post-implant, together with the associated exact, 95% confidence intervals. Primary endpoints 1, 2 and 3 must all be met for the Pre-market evaluation at 12-months to be considered as success.

The secondary endpoints of pacing threshold, sensing and impedance measurements for the Siello leads at the 12-month visit will be summarized, using standard measures, including means, standard deviations, medians, minimums, and maximums.

Primary safety endpoint 4 will be evaluated by performing an exact binomial test comparing the observed proportion (overall AE free-rate at 5 years) to 92.5%. Equivalently, the two-sided 95% lower confidence bound for the absolute difference between the overall AE free-rate and 92.5% must exceed zero.

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

The secondary endpoint of the 5-year adverse event-free rate for the secondary (RA) lead position will summarized in a Kaplan-Meier survival curve for the follow-up period, with the associated 95% confidence bounds.

The secondary endpoint of the individual adverse event rates for the secondary (RA) lead position will be summarized by the observed, individual AE rates at 5 years and the associated exact, two-sided 95% intervals.

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

The secondary endpoint of other AEs at 5 years, which were excluded from the primary safety analyses, will also be summarized as AE rates together with their associated exact, 95% confidence intervals.

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

## 2.7 TREND ANALYSES

The primary safety endpoints are evaluated at 5 years post-implant against pre-specified performance levels (92.5% for overall freedom from Siello lead-rated AEs, 1% for individual AE rates). To monitor the ongoing incidence of any potential AEs against the accumulating follow-up exposure post-implant, Kaplan-Meier survival 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 AEs, 99% for individual AEs) 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 adverse event or device failure, or combination of events, is believed to have implications regarding the safety of current or future subjects, then this will be reported to the FDA within the statutory timeframes.

## 2.8 MISSING DATA

All possible steps will be taken to minimize missing data in the study, including monitoring of data forms for completeness and efforts to track and maintain contact with study subjects during the follow-up period.

The reasons for any missing data in the study will be documented. BIOTRONIK will examine both missing-data patterns, which describe which values are observed and which are missing, and the missing-data mechanisms, which concerns the relationship between missingness and the values of variables in the study data set[2].

For evaluation of the long-term primary study endpoints (safety endpoints 4 and 5), only subjects who achieve 5 years of follow-up or have experienced an adverse event prior to 5 years will be included in the evaluation of the associated hypotheses. The secondary endpoint of other AEs 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 survival analyses, described in Section 2.7. Trend Analyses, all AE data on enrolled subjects will be included with follow-up time censored at the time of withdrawal or last completed follow-up visit.

Secondary endpoints, which include successful sensing and 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.

## 2.9 POOLABILITY ANALYSES

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

[2] R.J.A. Little and D.B. Rubin, 2002, Statistical Analysis with Missing Data, 2nd edition, Wiley and Sons

BIOTRONIK is not aware of differences in baseline and clinical characteristics between patients with and without Home Monitoring. However, the potential difference between the patients with and without Home Monitoring will be analyzed to demonstrate poolability of the data.

# 3. DATA COLLECTION

## 3.1 ELECTRONIC DATA CAPTURE (EDC)

MedNet Solutions Incorporated is a privately-held company that specializes in web-based clinical data management technology. MedNet will host the EDC system and provide a secure environment that is accessible to authorized individuals through the internet. BIOTRONIK will implement a study specific configuration using this software to meet the data collection requirements of the protocol. The EDC system is 21 CFR Part 11 compliant and is the platform for electronic case report form (eCRF) data entry, clinical data discrepancy resolution, and access to reports for BIOTRONIK, specified investigational sites, and any other parties authorized by BIOTRONIK.

## 3.2 ELECTRONIC CASE REPORT FORMS (ECRFS)

Original data will be collected from each investigational site and recorded into the EDC system, audited and monitored by BIOTRONIK, via completion of eCRFs. The investigator will be required to use an electronic signature to approve the content of the data reported in the eCRFs.

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

Subject follow-up is required for all subjects enrolled in this clinical study. The required follow-up visit dates are based on the Siello lead implant date, and are to be used for the calculation of the dates of the routine follow-up schedule. The following eCRFs will be available in the EDC system:

- Pre-screening
- Enrollment
- Implant
- 3-month follow-up (± 1 month)
- Routine follow-ups (± 1 month)
- Interim Unscheduled follow-up
- Final 5 Year follow-up (± 1 month)
- Adverse Events
- System Revision
- Out of Service

- Study Exit
- Protocol Non-Compliance
- Data Clarification

### 3.3 DATA QUALITY CONTROL

BIOTRONIK will review study data. At any time, reports can be generated on data completion and missing data by BIOTRONIK and by approved research personnel at each investigational site. The 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 in process. 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.

### 3.4 SUBJECT RETENTION

Although the study sample size has been calculated with a 10% subject attrition rate per year (41% total in 5 years), subject retention in a 5 year study may pose additional, unforeseen challenges. BIOTRONIK will provide additional tools to the sites in an effort to minimize the number of subjects that are lost to follow-up. The EDC system includes an overview of each subject's follow-up schedule, including the windows for each follow-up. The EDC system also provides a subject 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 subjects that should be scheduled for upcoming follow-ups. The EDC system will automatically provide a bi-weekly action item list to each site coordinator in the form of email, which includes all subjects that are due for scheduling.

To ensure protocol and follow-up compliance at all participating investigational sites, BIOTRONIK monitors will conduct monitoring visits (see Section 8). Monitoring visits include a review of subjects that may be lost to follow-up.

## 4. SUBJECT CONSENT

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

The investigator is required to inform BIOTRONIK and the reviewing IRB within 5 days if any subject did not provide appropriate consent to participate in the study. BIOTRONIK is then required to report any failure to obtain subject consent to the FDA within 5 working days of learning of such an event.

# 5. SUBJECT DATA CONFIDENTIALITY

All information sent to BIOTRONIK pertaining to each subject will be kept confidential at BIOTRONIK and is subject to FDA audit. Reports submitted to the physician or publications of study results will not make any reference to subject 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. RISKS AND RISK MINIMIZATION

During the Pre-Market Study, the Siello lead is considered an investigational device. All other devices included in the study are legally marketed. All devices are being prescribed by physicians according to FDA approved indications for use.

As with any implantable device, there are always potential risks that accompany the device. The following list provides the potential risks that may occur with the Siello lead in combination with a pacemaker device.

- Air embolism
- Allergic reactions to contrast media
- Arrhythmias
- Bleeding or bruising in the area of the pacemaker implant
- Body rejection phenomena
- Cardiac tamponade
- Chronic nerve damage
- Damage to heart valves
- Device migration
- Elevated pacing thresholds
- Embolism
- Extrusion
- Fluid accumulation
- Hematoma
- Infection
- Keloid formation
- Lead dislodgment
- Lead fracture/ insulation damage
- Lead perforation
- Lead-related thrombosis
- Local tissue reaction / fibrotic tissue formation
- Muscle or nerve stimulation

- Myocardial damage
- Myopotential sensing
- Pacemaker mediated tachycardia
- Pneumothorax
- Pocket erosion
- Swelling in the area of the pacemaker implant
- Ventricular ectopy

BIOTRONIK foresees no additional risks associated with this study beyond those stated in the labeling for the respective pulse generators and leads.

# 7. MONITORING

## 7.1 SUMMARY

BIOTRONIK is the "sponsor" of the clinical investigation. A sponsor is an entity that initiates but does not conduct an investigation. BIOTRONIK's responsibility as the clinical study sponsor is to ensure protocol and regulatory compliance through proper monitoring of the investigation. BIOTRONIK is required to ensure that the investigational device is used under the immediate direction of an investigator. As the investigator, the physician is responsible for conducting the study in accordance with the signed agreement, the investigational plan (protocol), applicable laws, FDA regulations, and any conditions of approval imposed by the reviewing IRB. The primary investigator must also accept responsibility for all aspects of the study including the actions of any co-investigators participating in the study at the investigational site.

## 7.2 MONITORS

Monitors are trained, qualified, and designated by BIOTRONIK management to oversee the progress of a study at the clinical site.

The address for submitting clinical data to BIOTRONIK for this study is:

BIOTRONIK, Inc.
Attn: Siello Clinical Study
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

A monitor will visit the study site periodically throughout the study. BIOTRONIK 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 study 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

# 8. STUDY COMPLETION

BIOTRONIK will notify the study site upon completion or termination of the study or of the investigator's participation. At BIOTRONIK's request, an investigator will return any investigational devices, equipment and pertinent information in their possession. BIOTRONIK will provide a final report to each investigational site as required by FDA regulations. After FDA has agreed to terminate this study, BIOTRONIK personnel will conduct a study 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 study for a period of 2 years after the study is completed.

# 9. DEVIATION FROM THE INVESTIGATIONAL PLAN

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

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 subject inclusion/exclusion violations. These violations will be reported to FDA in accordance with applicable regulatory timelines, and the investigator must notify the reviewing IRB per the IRB's reporting requirements. Protocol violations must also be reported to BIOTRONIK via eCRFs.

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 may not require IRB notification as long as they do not affect the rights, safety, or welfare of the study subject. Protocol deviations during the study must be reported to BIOTRONIK via eCRFs.

# 10. ADVERSE EVENTS

The investigator will be required to assess and classify each reported adverse event related to either the implant procedure, implanted pulse generator, or lead. For each adverse event, the investigator will indicate whether the Adverse Event relatedness to the Siello lead is: not related, related, possibly related, or unknown.

All protocol defined Adverse Events will be adjudicated by the Clinical Events Committee (see Section 10.9 Clinical Events Committee). The Clinical Events Committee (CEC) will have the responsibility to adjudicate the classification of each reported adverse event to either the implant procedure, implanted pulse generator, or lead. For each adverse event, the CEC will indicate whether the Adverse Event relatedness to the Siello lead is: not related, related, possibly related, or unknown.

In evaluation of the four primary safety endpoints for the Pre-Market Study and the Post-Approval Registry, the estimates of AE rates will be based on the number of subjects with at least one related AE as a proportion of total subjects with no AEs, related AEs, or unrelated AEs. Subjects with a final adjudicated related AE classification of unknown will not have that individual unknown event contribute to or be included in the evaluation of primary safety endpoints. However, for purposes of Kaplan-Meier survival analyses, described in Section 2.7 Trend Analyses and Section 2.8 Missing Data, all AE data on enrolled subjects will be included, with follow-up time censored at the time of withdrawal or last completed follow-up visit.

## 10.1 PROCEDURE-RELATED ADVERSE EVENTS

An AE will be classified as procedure-related if any one of the following occurred as a result of the implant procedure:

- Pneumothorax associated with the lead
- Arrhythmias associated with the lead
- Infection
- Cardiac Perforation with or without tamponade associated with the lead
- Non-healing pocket dehiscence requiring intervention
- Hematoma
- Pocket pain
- Lead reversed in header
- Loose set-screw
- Venous occlusion
- Pulmonary embolism
- Damage to lead during procedure (e.g. accidental cut to lead body during pocket revision, device replacement, etc.)
- Lead dislodgement during a procedure (e.g. during pocket revision, device replacement, etc.)

## 10.2 Pulse Generator-Related Adverse Events

An AE will be classified as pulse generator-related if any one of the following occurred:

- Premature battery depletion
- Pulse Generator failure
- Skin erosion
- Twiddler's syndrome

## 10.3 Lead-Related Adverse Events

An AE will be classified as lead-related if any one of the following occurred:

- Lead conductor fracture
- Lead insulation failure
- Lead dislodgment
- High pacing threshold
- Intermittent capture
- No lead capture
- Extracardiac stimulation
- Lead impedance out of range, high impedance
- Lead impedance out of range, low impedance
- Lead-related thrombosis
- Suspected lead failure
- Lead undersensing or loss of sensing

## 10.4 Adverse Events for the Analysis of the Primary Safety Endpoints 1 and 2

If any of the following invasive actions occur in order to resolve an above listed Siello Lead-related AE, the AE will be included in the primary safety endpoint analysis:

- Lead surgically repositioned
- Lead surgically explanted
- Lead surgically replaced
- Lead surgically abandoned
- Other lead-related surgery performed

Alternatively, if any of the following non-invasive actions occur in order to resolve an above listed Siello lead-related AE, the AE will be included in the primary endpoint analysis:

- Lead pacing polarity or pacing mode reprogrammed due to suspected lead failure
- Lead abandoned and pacing disabled due to clinical failure or suspected lead failure
- Lead use continued based on medical judgment despite a known clinical failure or suspected lead failure

AEs that are corrected by reprogramming the pulse generator (other than the above) and resolved without invasive action, will not be considered an adverse event counted towards the primary endpoints. For example, electrical reprogramming of the pacing polarity to eliminate extracardiac stimulation will not be considered an adverse event.

Siello lead-related adverse events meeting the criteria above occurring post implant procedure and prior to hospital discharge (i.e. lead dislodgement post procedure) will be counted as Primary Endpoint adverse events.

Subject deaths as a result of a Siello lead-related AE will be included in the primary endpoint analysis.

In addition, the following two procedure-related adverse events will be included in the analysis of primary endpoints 1 and 2: Pneumothorax associated with the Siello lead and Cardiac Perforation with or without tamponade associated with the Siello lead.

## 10.5 Adverse Events for the Analysis of the Primary Safety Endpoints 4 and 5

If any of the following invasive actions occur in order to resolve an above listed Siello lead-related AE, the AE will be included in the primary safety endpoint analysis:

- Lead surgically repositioned
- Lead surgically explanted
- Lead surgically replaced
- Lead surgically abandoned
- Other lead-related surgery performed

Alternatively, if any of the following non-invasive actions occur in order to resolve an above listed Siello lead-related AE, the Siello lead-related AE will be included in the primary endpoint analysis:

- Lead pacing polarity or pacing mode reprogrammed due to suspected lead failure.
- Lead abandoned and pacing disabled due to clinical failure or suspected lead failure
- Lead use continued based on medical judgment despite a known clinical failure or suspected lead failure

AEs that are corrected by reprogramming the pulse generator (other than the above) and resolved without invasive action, will not be considered an adverse event counted towards the primary endpoints. For example, electrical reprogramming of the pacing polarity to eliminate extracardiac stimulation will not be considered an adverse event.

Subject deaths as a result of a Siello lead-related AEs will be included in the primary endpoint analysis.

Primary endpoints 4 and 5 will exclude 1) lead dislodgements that occur within 30 days after lead implant or a lead revision procedure and 2) high pacing threshold, intermittent capture, no lead capture within 30 days after lead implant or a lead revision procedure

In addition, the following two procedure-related adverse events will be included in the analysis of primary endpoints 4 and 5: Pneumothorax associated with the Siello lead and Cardiac Perforation with or without tamponade associated with the Siello lead.

Table 5 summarizes the adverse events collected and analyzed for the primary endpoints. Adverse event rates for AEs excluded from primary safety endpoint 4 will be evaluated as secondary endpoint 5.

**Table 5: Endpoint Related Adverse Events**

| Adverse Event Relationship | Adverse Event | Primary Endpoints 1 and 2 | Primary Endpoints 4 and 5 |
|---|---|---|---|
| Procedure-Related Adverse Events | Pneumothorax associated with the Siello lead | X | X |
| | Arrhythmias associated with the Siello lead | | |
| | Infection | | |
| | Cardiac Perforation with or without tamponade associated with the Siello lead | X | X |
| | Non-healing pocket dehiscence requiring intervention | | |
| | Hematoma | | |
| | Pocket pain | | |
| | Lead reversed in header | | |
| | Loose set-screw | | |
| | Venous occlusion | | |
| | Pulmonary embolism | | |
| | Damage to Siello lead during procedure (e.g. accidental cut to lead body during pocket revision, device replacement, etc.) | | |
| | Lead dislodgement during a procedure (e.g. during pocket revision, device replacement, etc.). | | |
| Pulse Generator-Related Adverse Events | Premature battery depletion | | |
| | Pulse Generator failure | | |
| | Skin erosion | | |
| | Twiddler's syndrome | | |

| Adverse Event Relationship | Adverse Event | Primary Endpoints 1 and 2 | Primary Endpoints 4 and 5 |
|---|---|---|---|
| Siello Lead-Related Adverse Events[3] | Lead conductor fracture | X | X |
| | Lead insulation failure | X | X |
| | Lead dislodgment | X | X[4] |
| | High pacing threshold | X | X[5] |
| | Intermittent capture | X | X |
| | No lead capture | X | X |
| | Extracardiac stimulation | X | X |
| | Lead impedance out of range, high impedance | X | X |
| | Lead impedance out of range, low impedance | X | X |
| | Lead-related thrombosis | X | X |
| | Suspected lead failure | X | X |
| | Lead undersensing or loss of sensing | X | X |

## 10.6 ADVERSE EVENT REPORTING

The adverse events that an IRB considers reportable are dependent on the particular IRB. To avoid underreporting, BIOTRONIK recommends that, at a minimum, the investigator reports the procedure-related, lead-related, and pulse generator-related adverse events that occur during the SIELLO Pre-Market Study and Post-Approval Registry to BIOTRONIK and the IRB.

The study site will report the Adverse Event on the Adverse Event eCRF. Additionally, study 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.

## 10.7 UNANTICIPATED ADVERSE DEVICE EFFECTS

All devices are subject to problems or failures. As defined in the IDE regulations (21CFR, Part 812.3): "Unanticipated adverse device effect" means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature, severity or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects." It is important to note that random component failures or problems caused by misuse of the product are not considered unanticipated adverse device effects.

[3] Lead-Related Adverse Events must meet one of the invasive or non-invasive actions defined in sections 8.5.4 or 8.5.5 to be included in the primary endpoint analyses.
[4] Analysis of endpoints 4 and 5 exclude lead dislodgements that occur within 30 days after lead implant or a lead revision procedure
[5] Analysis of endpoints 4 and 5 exclude all high pacing threshold, intermittent capture, no lead capture within 30 days after lead implant or a lead revision procedure

If an unanticipated adverse device effect occurs, then the investigator is required to notify the sponsor and the reviewing IRB as soon as possible but no later than 10 working days after the investigator first learns of the event. If the event is serious or life threatening, the sponsor must be notified within 2 calendar days. The sponsor will conduct an immediate evaluation of any unanticipated adverse device effects. Devices that are returned will be sent to BIOTRONIK GmbH in Berlin, Germany for analysis. Those analyses will be trended (as appropriate) and reported to FDA as soon as they are available. The sponsor will notify the FDA, all reviewing IRBs, and participating investigators within 10 working days after notification of the event by the investigator, as required by FDA regulations.

## 10.8 Subject Death

Personnel at the investigational site will notify BIOTRONIK as soon as possible concerning any subject death during the investigation. This notification should include a completed out-of-service eCRF, study exit eCRF death certificate, and a copy of the notification of the death sent to the IRB. If a death certificate is not available, a detailed statement (death report) signed by the investigator must be written. The death report must include all of the following, if available:

- Date and time of death
- Place death occurred
- 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 it was device- or procedure-related

Any implanted devices that are explanted, including the Siello lead and any legally BIOTRONIK marketed device must be returned to BIOTRONIK for analysis, if possible.

## 10.9 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 clinical study site and the subject 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.

# 11. IRB APPROVAL

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

# 12. OTHER GENERAL INFORMATION

## 12.1 LABELING

The study device and its associated components will have a label that will be visible on the pertinent shipping cartons and storage containers. The required labels or manuals will bear the following information:

- Model and serial number of the device (where appropriate)
- Name of the device and the address of BIOTRONIK SE & Co. KG as the manufacturer
- Labeling statement: “Caution: Investigational Device. Limited by United States law to investigational use.”
- All relevant contraindications, hazards, adverse device effects, interfering substances or devices, warnings and precautions.

## 12.2 CONTROL OF THE DEVICE

BIOTRONIK will control the distribution of devices by distributing those devices only to approved investigational centers and approved investigators. BIOTRONIK will also keep records that indicate the place and date of shipment. Devices are not transferable between investigators unless prior approval is obtained from BIOTRONIK.

# 13. OTHER INSTITUTIONS AND PHYSICIANS

This clinical study 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 clinical study. However, there are certain situations where an investigator might not be immediately available to provide the necessary medical care for a subject enrolled in the study (such as a subject emergency room visit for medical treatment). In such situations, the IRB and investigator must continue to provide oversight for that subject’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 subject enrolled in the study in order to answer questions about the device and provide guidance in collecting

the necessary documentation required for the clinical study. Documentation obtained will then be forwarded to the approved investigator for review and signature.

# 14. RECORDS AND REPORTS

## 14.1 INVESTIGATOR RECORDS

Investigators are required to maintain the following accurate, complete and current records relating to this study:

- All correspondence relating to the study with another investigator, an IRB, BIOTRONIK, a monitor, the FDA (e.g., a letter sent from the investigator to the IRB), or any other regulatory agency.
- Records showing receipt, use and disposition of all investigational devices, including:
  - date, quantity, and serial numbers of devices and equipment received
  - names of patients implanted with the investigational device
  - information and serial numbers of devices returned to BIOTRONIK and the reason(s) for return
  - information and serial numbers of devices that are discarded (not returned to BIOTRONIK)
- All clinical forms and documentation, including:
  - A copy of the signed subject consent form
  - All procedure and follow-up report forms, including supporting documents
  - Records of any adverse device effect, including supporting documentation
  - Records pertaining to subject deaths during the study
  - Documentation and rationale for any deviations from the clinical protocol
  - Any other records required by BIOTRONIK

## 14.2 INVESTIGATOR REPORTS

Investigators are required to prepare and submit to BIOTRONIK the following complete, accurate and timely reports on this study, when necessary:

- Notification of a subject death during the study
- Any unanticipated adverse device effects
- Notification of the withdrawal of IRB approval
- Annual progress reports prepared for the IRB notifying of any deviations from the study plan
- Notification that an informed consent was not obtained from the subject
- Final summary report prepared for the IRB
- Any other information upon the request of an IRB, FDA, or BIOTRONIK

The table below outlines the responsibilities, including time constraints, for submitting the above reports. For further detailed description of the content and nature of these reports, please refer to the IDE regulations 21CFR, Part 812.150.

**Table 6: Investigator Reports**

| Type of Report | Prepared by Investigator for: | Time Constraints of Notification |
|---|---|---|
| Subject death during study | BIOTRONIK, IRB | As soon as possible and as required by reviewing IRB |
| Unanticipated adverse device effect | BIOTRONIK, IRB | Within 10 working days after notification of effect |
| Serious or life-threatening unanticipated adverse device effect | BIOTRONIK, IRB | Within 2 working days after notification of effect |
| Subject withdrawal | BIOTRONIK | Within 5 working days |
| Withdrawal of IRB approval | BIOTRONIK | Within 5 working days of receipt of notice of withdrawal of approval |
| Progress report | BIOTRONIK, IRB | Submitted not less than yearly |
| Significant deviations from study plan | BIOTRONIK, IRB | Within 5 working days after emergency to protect life or physical well-being of subject, otherwise prior approval by BIOTRONIK 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 study |

## 14.3 Sponsor Records

BIOTRONIK will maintain the following records:

- All correspondence pertaining to the study with the investigator(s), IRBs and FDA
- Investigational device shipment and inventory reconciliation reports
- Investigator agreements, financial disclosures, and current curriculum vitae
- Name and address of each investigator and each IRB involved with the study
- Adverse events and complaints
- Adverse device effects (whether anticipated or unanticipated)
- Electronic Case Report Form data
- Confirmation of completed subject informed consent forms
- Clinical study plan and report of prior studies
- Pre-screening reports
- Monitoring reports
- Clinical progress reports

- Statement of the extent to which the good manufacturing practice regulation Part 21 CFR 820 will be followed in manufacturing the Siello lead

## 14.4 SPONSOR REPORTS

BIOTRONIK is responsible for preparing the following reports, when necessary:

**Table 7: Sponsor Reports**

| Type of Report | Prepared by BIOTRONIK for: | Time Constraints of Notification |
|---|---|---|
| Unanticipated adverse device effect | FDA, all reviewing IRBs and participating investigators | Within 10 working days after notification of effect |
| 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 | Within 5 working days |
| Current investigator list | FDA | Names and addresses of participating investigators at 6 month intervals (starting at 6 months after FDA approval) |
| Progress report | FDA, all reviewing IRBs | Submitted not less than yearly |
| Recall and disposition | FDA, all reviewing IRBs | Within 30 working days and will include reasons for request that an investigator return, repair or otherwise dispose of any investigational leads |
| Final report | FDA, all reviewing IRBs and participating investigators | Within 30 working days of completion or termination of study. A final report will be submitted within 6 months after completion or termination of study. |
| Informed consent not obtained | FDA | Within 5 working days of notification of use |

# APPENDIX A: DEFINITION OF TERMS

**AE** (Adverse Event) - An unwanted effect detected in participants either procedure-related, pulse generator-related, or lead-related. The term is used whether or not the effect can be attributed to the leads in the study. For the purposes of this study, BIOTRONIK classifies an AE as either related to the Siello 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 Siello 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 Siello 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.

**Chronic Threshold –** Chronic threshold is defined as the pacing threshold determined at the subject's 3 month follow-up visit.

**eCRF** – Electronic Case Report Form

**EDC** – Electronic Data Capture system

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

**Explantation of a Lead** – Surgical removal of a lead during the acute implant stage, whereby the lead has not been chronically implanted and can be easily removed by simple traction.

**Extracardiac Stimulation –** Clinical observation of inadvertent nerve/muscle stimulation other than cardiac muscle, such as the diaphragm or pectoral muscles.

**Extraction of a Lead** - Surgical removal of a chronically implanted 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 -** One of the following definitions must be met:

1. At implant thresholds for the Siello S lead that are greater than 3.0 Volts at 0.4ms or 0.5ms., or

2. At follow-up, pacing thresholds for the Siello S lead that are greater than 3.5V at 0.4ms or 0.5ms.

**IDE** – Investigational Device Exemption

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

**Intermittent Capture -** Ineffective and inconsistent cardiac stimulation at irregular intervals in response to cardiac pacing delivered outside of the cardiac refractory period with a pacing output that exceeds the safety margin (which is 2 times the measured pacing threshold).

**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–** Complete failure to sense any intrinsic events that occur outside the programmed refractory periods at programmed sensitivity settings.

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

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

**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 Siello lead through a break in the conductor, insulation or connector pin leading to loss of pacing/sensing.

**RV/RA lead** – Right Ventricular/ Right Atrial Lead

**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** – Siello 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.

**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 subject unwittingly rotating the subcutaneous pulse generator.

**Undersensing–** Intermittent failure to sense any intrinsic events that occur outside the programmed refractory periods at programmed sensitivity settings.

# APPENDIX B: TIMELINE

Study Timeline

The timeline of the Pre-Market Study is dependent on the IDE approval date, September 12, 2012.
Additionally, BIOTRONIK made the following assumptions:

- Ability to recruit sufficient number of interested centers (75) and enroll subjects with 556 ventricular and 430 atrial leads within 12 months
- 70% local IRB, 30% central IRB

| Estimated Timeline | Date |
|---|---|
| Siello S IDE approval | IDE date |
| First IRB Approval of Pre-Market Study Clinical Site | IDE date +4 months |
| First Subject Enrolled | IDE date +6 months |
| 5 Clinical Sites open, 25 ventricular leads enrolled | IDE date +7 months |
| 25 Sites open, 200 ventricular leads enrolled | IDE date +12 months |
| 12 Month Interim Pre-Market Study Report submitted | IDE date +12 months |
| 50-75 Sites open, 556 ventricular and 430 atrial leads enrolled | IDE date +19 months |
| 50-75 Sites open, 800 ventricular leads enrolled | IDE date +24 months |
| 24 Month Interim Pre-Market Study Report submitted | IDE date +24 months |
| Last 12 month follow-up on first 500 ventricular and 387 atrial leads | IDE date +31 months |
| Pre-Market Approval Report submitted | IDE date +33 months |
| 50-75 Sites open, 1400 ventricular leads enrolled | IDE date +36 months |
| FDA Approval | IDE date +38 months |
| Up to 75 Sites open, 2124 leads enrolled (minimum 1694 RV leads) | IDE date +42 months |
| 6 Month Interim Post-Approval Registry Status Report submitted | IDE date +44 months |
| 12 Month Interim Post-Approval Registry Status Report submitted | IDE date +50 months |
| 18 Month Interim Post-Approval Registry Status Report submitted | IDE date +56 months |
| 24 Month Interim Post-Approval Registry Status Report submitted | IDE date +62 months |
| 30 Month Interim Post-Approval Registry Status Report submitted | IDE date +68 months |
| 36 Month Interim Post-Approval Registry Status Report submitted | IDE date +74 months |
| 42 Month Interim Post-Approval Registry Status Report submitted | IDE date +80 months |
| 48 Month Interim Post-Approval Registry Status Report submitted | IDE date +86 months |
| 54 Month Interim Post-Approval Registry Status Report submitted | IDE date +92 months |
| 60 Month Interim Post-Approval Registry Status Report submitted | IDE date +98 months |
| Last follow-up on last enrolled subject | IDE date +102 months |
| Final Post-Approval Registry Status Report submitted | IDE date +105 months |