Statistical Analysis Plan

Longitudinal Surveillance Registry of ACUITY Spiral

LSR of ACUITY Spiral

C1362

Approved electronically on 02-Jul-2013

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Revision History

Initial Version 1.0 Released August 2009, on study drive

Revision Number	Section	Change	Reason for Change
AA	ALL	Updated to current template	Initial Routing in PDM
	5.3	Added additional FDA analysis	New analysis added mid-study as requested by FDA
	Multiple	Updated references from ERC to CEC, added reference to CEC charter	ERC was re-vamped and changed to a CEC
	4.2 of Version 1.0	Removed table with censoring scenarios	Most involved LATITUDE use which is now optional
	1	Added additional protocol information	Helps clarify study and analyses needed
	3	Added more detail to Statistical Analysis methods	Adds clarity to the SAP

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1 PROTOCOL SUMMARY

The LSR of ACUITY Spiral Study is a prospective, non-randomized, multi-center registry of patients implanted with ACUITY Spiral Lead. The LSR of ACUITY Spiral is designed to collect product status information, any related adverse events and withdrawal data. Patient and device data from the enrollment/implant will be collected on the enrollment form. Patients will have an in-clinic full device evaluation done one month (15 to 29 days) post implant. Thereafter, it is recommended that the patient is seen for a full device evaluation at least once every six months and required at least once every 9 months. Patients may be optionally followed via the LATITUDE® remote monitoring system to facilitate ease of data collection. Upon activation in LATITUDE, data stored in the device including the latest in-clinic lead measurements will be collected via remote interrogation using the LATITUDE Patient Management system. Patients will be followed until they have completed five years of follow-up from implant or until death, withdrawal, or closure of the registry. ACUITY Spiral Leads (Models 4591, 4592, 4593) as well as other components of the implanted system are included in this registry.

2 INTRODUCTION

The primary purpose of the LSR of ACUITY Spiral is to evaluate and report on the long-term reliability and clinical performance of BSC's ACUITY Spiral Lead. Additionally system related information will be collected in this registry.

3 ENDPOINT ANALYSIS

3.1 Primary Endpoint

The ACUITY Spiral Lead will be evaluated by the chronic LV lead-related complication-free rate over a five year follow-up period. The primary endpoint analysis will include confirmed chronic LV lead related complications that result in permanent loss of therapy, invasive intervention, injury or death, and are deemed attributable to a structural lead failure by an independent Clinical Events Committee (CEC).

3.1.1 Hypotheses

H_o : The five (5) year chronic lead-related complication-free rate $\leq$ 92.5%

H_a : The five (5) year chronic lead-related complication-free rate > 92.5%

The null hypothesis will be rejected if the lower one-sided 95% confidence bound for the chronic lead-related complication-free rate is greater than 92.5%.

3.1.2 Sample Size

Based on the calculations below, the sample size for this registry is approximately 1700 patients implanted with the ACUITY Spiral Lead with a successful LATITUDE data transmission. An exact binomial calculation with the parameters in Table 3-1: **Sample Size Parameters and Justification** was used to determine the approximate sample size necessary to detect a clinically meaningful change with 80% power and a one-sided α-level of 0.05. An annual attrition rate of 10% is assumed over the five-year follow-up.

Table 3-1: Sample Size Parameters and Justification

Primary Endpoint	**N**	**P**	**Δ**	**95% Confidence Boundary**	**Justification**
Chronic LV lead-related complications	1000	94.5%	2.0	92.5%	Prospectively defined based on predicate data from EASYTRAK lead*. 95% confidence boundary is clinically acceptable.

*The EASYTRAK lead was studied as part of the CONTAK CD/EASYTRAK Post Approval Study (PMA P010012). Mean implant duration was 26±13 months, with a cumulative implant duration of over 25,000 patient months. The 3 year chronic lead-related complication free rate was 97.9% using Kaplan-Meier methods. Assuming a continued 1.7% annual rate (consistent with observed year to year changes in rates from previous pre-market LV lead studies) from years 3 to 5 would result in an estimated 94.5% chronic complication free-rate at 5 years for the EASYTRAK LV lead.

3.1.3 Statistical Methods

3.1.3.1 Overview

When the final study subject reaches five (5) years of follow-up, the primary analysis will be performed based on the Kaplan-Meier method for the estimation of the five (5) year chronic lead-related complication-free rate, including the lower one-sided 95% confidence interval. The censoring mechanism of the Kaplan-Meier analysis incorporates all available data on study subjects, including those that withdrew or were lost-to-follow-up.

3.1.3.2 Subjects included in Endpoint Analysis

The Kaplan-Meier analysis will begin at 45 days post-implant for each patient. All patients that are successfully implanted with the ACUITY Spiral Lead and still actively followed in the study at 45 days post implant will be included in the analysis.

3.1.3.3 Adverse Events Included in Endpoint

The determination for inclusion of adverse events in the endpoint analysis will be made by an independent Clinical Events Committee (CEC). The adverse event will count against the endpoint if a consensus of CEC members agrees the event meets the definition

of inclusion into the endpoint. Refer to the CEC Charter (CDM00060021) for more information.

LV lead-related adverse events within 45 days following invasive cardiac surgery (device implant, PG change-out, cardiac catheterization, etc.) need to be reported, but will be omitted from the endpoint analysis. In addition, the following events will be collected, but will be excluded from the endpoint analysis unless determined by the Clinical Events Committee (See Protocol Section 4.2.2) to be attributed to a structural lead failure:

- Inability to place the LV lead
- Implant procedure related complications such as CS dissection, CS perforation,
- pneumothorax, arrhythmias, cardiac tamponade, hematoma
- LV Lead-related thrombosis
- In-patient damage to LV lead (e.g., accidental cut to lead body during pocket revision, device replacement, etc.)
- LV Lead dislodgments up to 180 days post implant procedure
- Twiddler's syndrome leading to LV lead dislodgment
- High LV pacing threshold, intermittent LV capture, no capture of LV lead
- Diaphragmatic/pectoral stimulation
- Infection
- Atrial lead, ICD lead, or generator adverse events requiring additional interventions
- Non-LV lead-related hospitalizations
- Non-LV lead-related death
- Lead revisions to optimize therapy
- Exit block
- Physiologic oversensing or undersensing

3.1.3.4 Tests to be performed

The primary endpoint will evaluate the 5-year chronic lead-related complication-free rate, calculated using Kaplan-Meier (product-limit) methods. The Kaplan-Meier analysis will begin at the time of implant for each study subject. The null hypothesis will be rejected in favor of the alternative if the lower one-sided 95% confidence limit for the chronic lead-related complication-free rate is greater than 92.5%. This analysis will be performed after the last subject has completed 5 years of follow-up. The 5-year survival estimate will be calculated using product-limit survival estimates as follows:

Let $t_1 < t_2 < ... < t_D$ represent the distinct event times. For each $i = 1,..., D,$ let n_i be the number of surviving units (the size of the risk set) just prior to t_i. Let d_i be the number of units that fail at t_i, and let $s_i = n_i - d_i$.

The Kaplan-Meier (product-limit) estimate of the survivor function at t_i is the cumulative product $\hat{S}(t_i) = \prod_{j=1}^{i}\left(1 - \frac{d_j}{n_j}\right)$

All the estimators are defined to be right continuous. The corresponding estimate of the standard error is computed using Greenwood's formula (Kalbfleisch and Prentice; 1980) as

$$\hat{\sigma}\left(\hat{S}(t_i)\right) = \hat{S}(t_i)\sqrt{\sum_{j=1}^{i}\frac{d_j}{n_j s_l}}$$

The lower 95% confidence bound at t_i is calculated in SAS as follows:

$$100 * \left(\hat{S}(t_i) - probit(0.95) * \hat{\sigma}\left(\hat{S}(t_i)\right)\right)$$

3.1.3.5 Assumptions for statistical test

The Kaplan-Meier analysis method assumes that censored individuals have the same prospect of survival as those who continue to be followed. Additionally, it is assumed that survival prospects are the same for early as for late recruits to the study.

4 GENERAL STATISTICAL METHODS

4.1 Analysis Sets

All patients that are successfully implanted with the ACUITY Spiral Lead and still actively followed in the study at 45 days post implant will be included in the Primary endpoint analysis. Subjects without an endpoint event who die/withdraw prior to completing 5 years of follow-up will be censored at the death or withdrawal date.

All subjects with an attempted or implanted ACUITY Spiral Lead will be included in the modified analysis as requested by FDA (see section 5.3 for details of this additional analysis).

4.2 Control of Systematic Error/Bias

The LSR of ACUITY Spiral Study is a post-approval clinical study and as such study subjects will essentially include "all-comers" who meet enrollment criteria. Study Investigators are expected to approach all potentially eligible study subjects who have been (within 29 calendar days post implant window), or will be, implanted with the ACUITY Spiral Lead at the investigational center for enrollment into this study until the enrollment ceiling is reached.

5 ADDITIONAL DATA ANALYSES

5.1 Progress Reports

Progress reports to the FDA will be provided by the sponsor every six months. Data for these reports will come from two sources defined as 'Database' and 'ADAM'. The Database is the data repository for the data entered into the electronic data capture system (eDC). ADAM is the data repository that stores data from the LATITUDE remote monitoring system. With protocol revision AC, the use of the LATITUDE remote monitoring system is optional. For those subjects that are on LATITUDE, data from the in-clinic visits will automatically be transferred to BSC and retrieved for analysis via ADAM. For subjects not on LATITUDE (or for whom LATITUDE is not working properly), data from in-clinic visits will be entered into eDC and retrieved for analysis via the Database.

Data in the 6-month progress reports includes, but is not limited to:

- Summary of enrollment and lead status
- Kaplan-Meier plot of time to first endpoint defined chronic ACUITY Spiral Lead-related complication
- Summary of trend analysis (not provided by Biostatistician)
- Summary of LV-lead related adverse events

5.2 Interim Analyses

While the primary endpoint will be analyzed at 5 years, in order to monitor the safety of the study during the enrollment and follow-up phases, BSC has agreed to provide an estimate of the chronic complication-free rate to the FDA in each bi-annual (every 6 months) progress reports. This will include a Kaplan-Meier plot and a table of all adverse events and whether they were adjudicated as counting towards the endpoint or not.

Currently no formal interim analyses are planned for the purpose of stopping this study early for futility, as this is an FDA mandated post market study. However, we will be monitoring the attrition rate and enrollment rates to be able to adequately report to FDA when we believe the study will be completed.

5.3 FDA Requested Modified Complication-Free Rate

Per FDA feedback received on the 30-month Interim Study Status Report (P010012/R028) and subsequent amendment (A001), an additional Kaplan-Meier curve and table will be presented in each 6-month report. This analysis provides data in the form of a modified composite endpoint identical to the analyses provided for the primary endpoint with the following modifications:

a) Chronic events occurring 30 days or greater post-implant

b) Dislodgements occurring 30 or more days post-implant that result in permanent loss of therapy, invasive intervention, injury, or death

c) Elevated LV pacing threshold, intermittent LV capture, and no capture of LV lead occurring 30 or more days post-implant that result in permanent loss of therapy, invasive intervention, injury, or death

d) Diaphragmatic/muscle stimulation occurring 30 or more days post-implant that result in permanent loss of therapy, invasive intervention, injury, or death

e) All LV lead-related perforations

Prior to each 6-month report, the study team will meet to review all new/changed adverse events since the last report to determine inclusion into the modified analysis. The study Biostatistician is responsible for keeping a spreadsheet with all adverse events and the status of inclusion into the modified endpoint.

5.4 Pooling Analysis

If required, center-to-center heterogeneity will be assessed for the primary endpoint by performing a random effects logistic regression analysis. Centers will be deemed to be heterogeneous if the variance of the random center effect is found to significantly differ from zero. A significance level of 10% will be used for this test.

5.5 Changes to Planned Analyses

Any changes to the planned statistical analyses made prior to performing the 5-year analyses will be documented in a Statistical Analysis Plan approved prior to performing the analyses. Changes from the planned statistical methods after the 5-year primary endpoint analysis will be documented in the clinical study report along with a reason for the deviation.

6 VALIDATION

All clinical data reports generated per this plan will be validated per 90702587, Global WI: Clinical Data Reporting Validation.

7 PROGRAMMING CONSIDERATIONS

All endpoint analyses will be performed in SAS, version 9.2 or later. In the event an analysis is required that is better suited for a statistical package other than SAS, this other package (e.g. R) will be used.