SJM-CIP-10226/Rev P
NCT Number: NCT04559945

The LEADLESS II Study

A safety and effectiveness trial for a leadless pacemaker system (Phase 2)

Statistical Analysis Plan (SAP) (Phase 2)

Version F

July 28, 2021

[redacted]

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Statistical Analysis Plan

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1.0 SYNOPSIS OF STUDY DESIGN

1.1 Purpose of the Statistical Analysis Plan

This statistical analysis plan (SAP) is intended to provide a detailed and comprehensive description of the planned methodology and analysis to be used for Phase 2 of The LEADLESS II Study (A safety and effectiveness trial for a leadless pacemaker system), the SJM-CIP-10226/Rev P (CRD-701) clinical investigation. This plan is based on the SJM-CIP-10226 Rev P, July 28, 2021 Clinical Investigation Plan (CIP).

1.2 Clinical Investigation Objectives

The primary objectives of Phase 2 of this clinical investigation are to confirm the safety and effectiveness of the Aveir™ Leadless Pacemaker System from implant through 6-weeks in a subject population indicated for a VVI(R) pacemaker.

1.3 Clinical Investigation Design

Phase 2 of this prospective, non-randomized, multi-center, international clinical study is designed to **confirm** the safety and effectiveness of the Aveir LP System in a subject population indicated for a VVI(R) pacemaker.

Sponsor will conduct the study at up to 80 centers worldwide [redacted]

1.4 Endpoints

The Phase 2 of the study will include the following confirmatory endpoints.

1.4.1 Confirmatory Safety Endpoint

The confirmatory safety endpoint evaluates a 6-week complication-free rate based on CEC adjudication of the adverse event.

1.4.2 Confirmatory Effectiveness Endpoint

The confirmatory effectiveness endpoint evaluates pacing thresholds and R-wave amplitudes within the therapeutic range through 6 weeks post-implant.

1.4.3 Secondary Endpoints

1. Confirmatory secondary endpoint #1 evaluates an appropriate and proportional rate response during graded exercise testing (CAEP protocol).

2. Secondary endpoint #2 estimates the 2-year survival rate of patients implanted with the Nanostim™ Leadless Pacemaker.

[redacted]

[redacted]

1.5 Randomization

Not applicable

1.6 Blinding

Not applicable

2.0 ANALYSIS CONSIDERATIONS

The summary and analysis described in this SAP will apply to **Phase 2** of the study and its clinical report(s).

2.1 Analysis Populations

The analysis populations include:

2.1.1 Enrolled Population

The Enrolled population includes all subjects who are enrolled in Phase 2 of the study. Subjects who sign an IRB/EC-approved informed consent and have an attempted implant will be considered enrolled in the study.

An attempted implant is defined as the point of skin incision for the insertion of the Aveir Introducer (LSN25301 or LSN25501) for the implant procedure.

2.1.2 Successful Implant Population

The Successful Implant population includes all subjects who are enrolled in Phase 2 of the study with a successful implant of the Aveir LP device.

2.2 Statistical Methods

For the confirmatory endpoints for Phase 2 of the study, hypothesis tests will be performed. In addition, a set of additional data will be summarized by descriptive statistics or Kaplan-Meier analysis.

2.2.1 Descriptive Statistics for Continuous Variables

For continuous variables (e.g. age, etc.), results will be summarized with the numbers of observations, means, standard deviations, minimums and maximums. Two-sided 95% confidence intervals for the means may be presented as appropriate.

2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables (e.g. gender, cardiac disease history, etc.), results will be summarized with subject or observation counts and percentages/rates, etc. Two-sided exact 95% Clopper-Pearson confidence intervals may be presented as appropriate.

[redacted]

2.2.3 Kaplan-Meier Analysis for Time-to-event Variables

[redacted]

2.3 Endpoint Analysis

The confirmatory endpoint analyses will be based on the 200 newly enrolled subjects in the Phase 2 study only. Any subjects enrolled in the continued access phase (CAP), including those subjects who had their Nanostim LP replaced with Aveir LP device, are not included in the confirmatory endpoint analysis.

2.3.1 Confirmatory Safety Endpoint Analysis

The confirmatory safety endpoint evaluates the 6-week complication-free rate (CFR) based on CEC adjudication of the adverse event. Complication is defined as a device-or-procedure-related serious adverse event, including those that prevent initial implantation. This definition of complication is equivalent to the term SADE (Serious Adverse Device Effect) throughout this SAP. The CEC will make the final determination regarding whether an adverse event meets the criteria for the confirmatory endpoint analysis.

The confirmatory safety hypothesis is:

H_0: CFR ≤ 86% vs. H_1: CFR > 86%

where 86% is the performance goal.

[redacted]

To eliminate the possible impact of Covid-19 on the confirmatory safety endpoint analysis, CEC adjudicated primary safety events (SADEs) that are related or possibly related to Covid-19 will be excluded. Additional analysis with these events included will also be provided.

Additional sensitivity analysis based on all the enrolled subjects to assess the impact of missing data on the confirmatory safety endpoint will be performed and they are described in Section 2.9.

[redacted]

2.3.2 Confirmatory Effectiveness Endpoint Analysis

The confirmatory effectiveness endpoint is a 6-week composite success rate (Rate) evaluating pacing thresholds and R-wave amplitudes.

The confirmatory effectiveness hypothesis is:

H_0: Rate ≤ 85% vs. H_1: Rate > 85%

where 85.0% is the effectiveness performance goal. The Rate is the proportion of subjects who have met success criteria in the confirmatory effectiveness endpoint. The acceptable ranges for sensing and pacing which define success criteria are shown in the table below:

Parameter	Acceptable values
Pacing voltage	Pacing threshold ≤ 2.0 V at 0.4 ms
R Sensitivity	R-wave amplitude ≥ 5.0 mV or ≥ value at implant

Success Criteria: A subject will be considered to have met the confirmatory effectiveness endpoint if: pacing threshold voltage ≤ 2.0 V at 0.4 ms at 6-week visit **and** sensed R-wave amplitude is either ≥ 5.0 mV at the 6-week visit or ≥ value at implant.

For subjects, that do not have R-wave amplitude measured due to pacer dependence or AV node ablation, success will be determined from pacing threshold only.

[redacted]

Additional sensitivity analysis will be performed to assess the impact of missing data and they are described in Section 2.9.

2.3.3 CMS Effectiveness Analysis

The CMS effectiveness analysis is a 6-week composite success rate (Rate) evaluating pacing thresholds and R-wave amplitudes.

The CMS effectiveness hypothesis is:

[redacted]

H_0: Rate ≤ 81% vs. H_1: Rate > 81%

where 81.0% is the effectiveness performance goal. The Rate is the proportion of subjects who have met success criteria in the confirmatory effectiveness endpoint. The acceptable ranges for sensing and pacing which define success criteria are shown in the table below:

Parameter	Acceptable values
Pacing voltage	Pacing threshold ≤ 2.0 V at 0.4 ms
R Sensitivity	R-wave amplitude ≥ 5.0 mV or ≥ value at implant

Success Criteria: A subject will be considered to have met the confirmatory effectiveness endpoint if: pacing threshold voltage ≤ 2.0 V at 0.4 ms at 6-week visit **and** sensed R-wave amplitude is either ≥ 5.0 mV at the 6-week visit or ≥ value at implant.

For subjects, that do not have R-wave amplitude measured due to pacer dependence or AV node ablation, success will be determined from pacing threshold only.

[redacted]

2.3.4 Secondary Endpoints Analysis

2.3.4.1 Confirmatory Secondary Endpoint #1 Analysis

The confirmatory secondary endpoint #1 includes evaluation of CAEP exercise protocol. If both the confirmatory safety and confirmatory effectiveness endpoints are met, the following hypothesis will be hierarchically evaluated.

The confirmatory secondary CAEP endpoint hypothesis is:

H_0: Mean Slope is Not Equivalent to 100%

$| \text{Slope} - 100\% | \geq \delta$

H_1: Mean Slope is Equivalent to 100%

$| \text{Slope} - 100\% | < \delta$

Where, δ = equivalence margin, equal to 35%

CAEP exercise protocol

All capable subjects who have completed the 6-minute walk test (6MWT) will be asked to perform a maximal effort CAEP exercise protocol to demonstrate an appropriate and proportional response of sensor-indicated rate in graded exercise tests.

Data from subjects who have completed the 6MWT and have completed at least stage 3 of the CAEP exercise protocol, or 3.6 metabolic equivalent of task (METs), will be included in the analysis. The results of subjects who did not meet the analysis criteria will still be reported.

The analysis of these exercise test data will provide an estimate of the slope of the normalized increase in sensor-indicated rate versus normalized CAEP workload for each subject. [redacted]

[redacted]

2.3.4.2 **Secondary Endpoint #2 Analysis**

The secondary endpoint #2 is the 2-year survival of patients implanted with the Nanostim leadless pacemaker. Kaplan-Meier method of all-cause mortality will be used to estimate the survival rate and the corresponding 95% confidence intervals will be provided. [redacted]

[redacted]

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[redacted]

[redacted]

References:

[redacted]

1. [redacted]

An additional Kaplan-Meier analysis that includes patients implanted with either the Nanostim or the Aveir leadless pacemaker will be provided. [redacted]

2.4 Sample Size Calculations

[redacted]

2.5 Interim Analysis

[redacted]

2.6 Timing of Analysis

[redacted]

2.7 Study/Trial Success

[redacted]

2.8 Subgroups for Analysis

Subgroup analysis will be conducted for the confirmatory safety endpoint (on enrolled population) and effectiveness endpoint (on successful implanted population) to assess consistency by gender on the following data:

-Gender: Male and Female

[redacted]

Other subgroup analyses by age (< median and >=median) and comorbidities (e.g. coronary artery disease) will also be performed using the same method as the subgroup analysis by gender.

2.9 Handling of Missing Data

[redacted]

[redacted]

2.10 Poolability Issue

Poolability of the confirmatory safety endpoint on the enrolled subjects and effectiveness endpoint on the successful implant subjects by region and across sites will be evaluated. Analysis will be performed based on available data.

The Phase 2 study will be conducted in up to 80 sites in the United States, Europe, Canada, and Australia. The study will be conducted following the same investigational plan, monitoring plan and training plan in all regions.

[redacted]

2.11 Multiplicity Issues

[redacted]

2.12 Adjustments for Covariates

[redacted]

3.0 DESCRIPTIVE ENDPOINTS AND ADDITIONAL DATA

3.1 Baseline and Demographic Characteristics

The following baseline, demographic, medical history and medication variables will be summarized descriptively for the subjects in the enrolled population: gender, age, ethnicity, race, history of smoking; key cardiovascular history, prior cardiac interventions, arrhythmia history, primary indication for study device implant, use of beta blocker, ACE, ARB, anti-coagulation, anti-arrhythmic, and anti-platelet medications, etc. and as needed. For subjects enrolled from European sites, race and ethnicity are not collected and hence will not be included in race/ethnicity summary of the demographics table.

3.2 Adverse Events

All reported adverse events (AE), serious adverse events (SAE), adverse device effects (ADE), serious adverse device effects (SADE), unanticipated adverse device effect (UADE) or unanticipated serious adverse device effect (USADE) will be summarized for all enrolled subjects using the number of events, the number of subjects with events and the percentage of subjects with events. All CEC adjudicated events will also be summarized for all enrolled subjects with the number of events, the number of subjects with events and the percentage of subjects with events. An AE listing which includes all adverse events and whether or not each event is device-related or procedure-related will be provided.

3.3 Subject Early Termination

Subject early termination reasons including deaths, withdrawals, lost-to-follow-up, etc. will be summarized descriptively for subjects terminated in the enrolled population.

3.4 Protocol Deviation

Protocol deviations will be summarized descriptively for all subjects in the enrolled population in whom a protocol deviation was reported.

3.5 Additional Data

The following additional data will be recorded and reported descriptively:

- Implant success rate and reasons for unsuccessful implant
- Device handling characteristics at implant
- Number of device repositioning at time of implantation
- Implant duration, fluoro duration, and time from implant to hospital discharge
- Final LP placement

[redacted]

- Remaining device longevity at the six-month visit, as displayed by the programmer based on delivered therapy, programmed settings, percent pacing, and measured pacing impedance.
- Average pacing rate, impedance, pulse amplitude, pulse duration and percentage pacing will also be reported for all visits.
- Hospitalizations
- Mortality

These additional data will be summarized descriptively using the methodology as outlined in Section 2.2 Statistical Methods in the SAP, based on subjects in the enrolled and/or successful implant population with available data as appropriate. No hypothesis tests will be performed.

For the 6-month follow-up data, analysis similar to the confirmatory safety and effectiveness endpoint analysis will be performed and reported. However, the 6-month follow-up data will not be hypothesis tested.

A 6-month CFR will be estimated as a binomial proportion and 97.5% lower confidence bound (LCB) of the CFR will be calculated using the Clopper-Pearson exact method. A 6-month composite success rate (Rate) evaluating pacing threshold and R-wave amplitudes will be estimated as a binomial proportion and the 97.5% lower confidence bound (LCB) of the Rate will be calculated using the Clopper-Pearson exact method.

In addition, the 6-month follow-up complication (CEC adjudicated SADEs) will be summarized and presented with the number of events and number of subjects with events. For time-to-event complication data, freedom from complications (CEC adjudicated SADEs) through 6 months will be analyzed using a Kaplan-Meier analysis (Refer to Section 2.2).

The Phase 1 subjects who are replaced with the Aveir LP device will not be in the confirmatory endpoint analysis population. For these Phase 1 subjects, LP device replacement success rates, data summaries and/or listings for all adverse events and device measurements, from the time of LP replacement through their last available follow-up, will be provided within the PMA amendment containing the confirmatory endpoint analysis. These data through 6-months will also be included within the 6-month follow-up summary report for the confirmatory cohort.

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

[redacted]

5.0 ACRONYMS AND ABBREVIATIONS

Acronym or Abbreviation	Complete Phrase or Definition
CEC	Clinical Events Committee
IRB	Independent or institutional review board
EC	Ethics Committee

[redacted]

Acronym or Abbreviation	Complete Phrase or Definition
CIP	Clinical Investigation Plan
CRF	Case Report Form
AE	Adverse Event (Non-Serious Adverse Event)
SAE	Serious Adverse Event
ADE	Adverse Device Effect (Non-Serious Adverse Device Effect)
SADE	Serious Adverse Device Effect
UADE	Unanticipated Adverse Device Effect
USADE	Unanticipated Serious Adverse Device Effect
ACE	angiotensin-converting enzyme
ARB	angiotensin II receptor blocker
CFR	Complication-free rate
6MWT	Six-minute walk test
CAEP	Chronotropic Assessment Exercise Protocol
MET	Metabolic Equivalent of Task
LCB	Lower Confidence Bound
LP	The modified St. Jude Medical's Aveir LP system consisting of a modified Aveir LP, model LSP112V and its supporting accessories, herein referred to as the Aveir LP system.
SR	St. Jude Medical's original Nanostim LP system consisting of LP Model S1DLCP and its supporting accessories, herein referred to as the Nanostim SR system.
SAS	Statistical Analysis System
SAP	Statistical Analysis Plan

6.0 REFERENCES

- SJM-CIP-10226/Rev P, July 28, 2021, the CIP for Leadless II (CRD_701) study
- CRD_701 Leadless II Case Report Form

7.0 APPENDICES

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