ABT-CIP-10355 Ver. C CRD-701
NCT Number: NCT04559945

The Leadless II Study-Phase 2

A safety and effectiveness trial for a leadless pacemaker system

Statistical Analysis Plan (SAP)

(For Europe)

Version C

October 3, 2021

[redacted]

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 submission for CE Mark approval based on The LEADLESS II Study – Phase 2 (A safety and effectiveness trial for a leadless pacemaker system), the ABT-CIP-10355 (CRD-701) clinical investigation. This plan is based on the ABT-CIP-10355 Ver. C, September 24, 2021 Clinical Investigation Plan (CIP).

1.2 Clinical Investigation Objectives

The primary objectives of Phase 2 are to confirm the safety and effectiveness of the Aveir™ Leadless Pacemaker System device from implant through 12-months in a subject population indicated for a VVI(R) pacemaker.

1.3 Clinical Investigation Design

The Leadless II study- Phase 2 is a prospective, non-randomized, multi-center, international clinical study 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 12-month complication-free rate based on CEC adjudication of adverse events.

1.4.2 Confirmatory Effectiveness Endpoint

The confirmatory effectiveness endpoint evaluates pacing thresholds and R-wave amplitudes within the therapeutic range through 12 months post-implant.

1.4.3 Confirmatory Secondary Endpoint

The confirmatory secondary endpoint evaluates an appropriate and proportional rate response during graded exercise testing (CAEP protocol).

[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 CE mark submission of The Leadless II Study- Phase 2 and its clinical report(s).

2.1 Analysis Populations

The following analysis populations are defined for the study.

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 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.

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

[redacted]

subjects with events the time to the first event will be used for the analysis. Survival estimates of the data and associated 95% confidence interval will be presented using cumulative survival and its estimated standard error (Greenwood's formula).

2.3 Endpoint Analysis

The confirmatory endpoint analyses will be based on the 210 newly enrolled subjects in the Phase 2 study only. Subjects who are replaced with the Aveir LP are not included in the confirmatory endpoint analysis.

2.3.1 Confirmatory Safety Endpoint

The confirmatory safety endpoint evaluates the 12-month 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 at 12 months timepoint is:

H_0: CFR ≤ 83% vs. H_1: CFR > 83 %

where 83% is the performance goal.

[redacted]

SADE events that occur on or before the 12-month follow-up visit (360 days) will be included in the confirmatory safety endpoint analysis.

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 from the confirmatory safety endpoint analysis. Subjects who have these events will be censored at the time of the event. 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 2.8.

[redacted]

2.3.2 Confirmatory Effectiveness Endpoint

The confirmatory effectiveness endpoint is a 12-month composite success rate (Rate) evaluating pacing thresholds and R-wave amplitudes.

The confirmatory effectiveness hypothesis is:

H_0: Rate ≤ 80% vs. H_1: Rate > 80%

Where 80.0% 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 12-month visit **and** the sensed R-wave amplitude is either ≥ 5.0 mV at the 12-month visit or ≥ the value at implant.

[redacted]

An additional analysis for confirmatory effectiveness endpoint will also be conducted for subjects in the successful implant population who complete the 12-month visit with evaluable device measurements available. [redacted]

[redacted]

threshold only. These conditions/procedures result in infrequent or absent intrinsic R-waves and may include pacer dependence, complete heart block, or AV node/AV junctional ablation.

[redacted]

Additional sensitivity analysis will be performed on the successful implant subjects to assess the impact of missing data and they are described in Section 2.8.

2.3.3 Confirmatory Secondary Endpoint

The confirmatory secondary endpoint 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]

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 Handling of Missing Data

[redacted]

[redacted]

2.9 Poolability Issue

Poolability of the confirmatory safety endpoint on the enrolled subjects and confirmatory 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]

[redacted]

[redacted]

2.10 [redacted]

[redacted]

2.11 [redacted]

[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 Descriptive Endpoints or 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.
Subjects with a Nanostim SR device who are replaced with the Aveir LP device will not be in the confirmatory endpoint analysis population. For these 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.

4.0 DOCUMENTATION AND OHER CONSIDERATIONS

All analyses will be performed using SAS® for Windows, version 9.2 or higher.

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
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

Acronym or Abbreviation	Complete Phrase or Definition
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

- ABT-CIP-10355 Rev. C, September 24, 2021, the CIP for The Leadless II Study- Phase 2
- CRD_701 Leadless II Case Report Form

7.0 [redacted]