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Aveir™ DR i2i Study
Aveir Dual-Chamber Leadless i2i IDE Study
Study Document No: ABT-CIP-10428
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Sponsor

Abbott Medical
Cardiac Rhythm Management
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Sylmar, CA 91342

[redacted]
Template

[redacted]

Statistical Analysis Plan

ABT-CIP-10428/ Ver B
CRD 1023

Aveir™ DR i2i Study

Aveir Dual Chamber Leadless i2i IDE study

Statistical Analysis Plan (SAP)

(For Europe)

Version B

September 22, 2022

[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 CE mark approval based on ABT-CIP-10428 (CRD 1023), the Aveir DR i2i Study clinical investigation for Europe. This plan is based on the version B of the Clinical Investigation Plan (CIP).

1.2 Clinical Investigation Objectives

Primary Objectives
The primary objectives of this study are to evaluate the safety and effectiveness of the Aveir™ Dual-Chamber (DR) Leadless Pacemaker (LP) system through 12-months post-implant in a subject population indicated for a DDD(R) pacemaker system.

Secondary Objectives
The secondary objectives of this study are to evaluate the safety and effectiveness of the Aveir atrial LP through 12-months post-implant in a subject population indicated for a DDD(R) pacemaker system to support an indication for AAI(R) pacing.

1.3 Clinical Investigation Design

This is a prospective, multi-center, international, single-arm, pivotal investigational study designed to evaluate the safety and effectiveness of the Aveir DR LP system in a subject population indicated for a DDD(R) pacemaker.

The clinical investigation will enroll up to 550 subjects from up to 85 participating centers from the United States, Canada, Europe, and Asia Pacific. The Sponsor may approach centers in other countries for participation in the clinical investigation as needed.

Subjects participating in the clinical investigation will be followed through at least 12 months with data collected at baseline, implant procedure, pre (hospital) discharge, and follow-up at 1 month, 3 months, 6 months, 12 months and every 6 months thereafter until study completion. [redacted]

[redacted]

1.4 Endpoints

The primary and secondary endpoint analyses will be based on newly enrolled (*de novo*) subjects in the investigation who have an attempted implant. *De novo* subjects are defined as subjects that do not have an implanted pacemaker on the date of consent through the date of the Aveir LP implant.

The Aveir DR i2i Study for Europe will include the following endpoints.

1.4.1 Primary Safety Endpoint

The primary safety endpoint evaluates the 12-month Aveir DR LP system Complication Free Rate (CFR) in *de novo* subjects based on CEC adjudication of adverse events.

1.4.2 Primary Effectiveness Endpoint #1

The primary effectiveness endpoint #1 evaluates the 12-month composite success rate evaluating acceptable atrial pacing thresholds and P-wave amplitudes in *de novo* subjects.

1.4.3 Primary Effectiveness Endpoint #2

The primary effectiveness endpoint #2 evaluates the 3-month AV synchrony success rate at rest while seated in *de novo* subjects.

1.4.4 Secondary Safety Endpoint

The secondary safety endpoint evaluates the 12-month Atrial LP CFR in *de novo* subjects based on CEC adjudication of adverse events.

1.4.5 Secondary Effectiveness Endpoint

The secondary effectiveness endpoint evaluates the appropriate and proportional rate response of the atrial LP in de novo subjects during graded exercise testing (CAEP protocol).

1.5 Randomization

Not Applicable.

1.6 Blinding

Not Applicable.

2.0 ANALYSIS CONSIDERATIONS

2.1 Analysis Populations

The analysis populations include:

2.1.1 Full Analysis Population

Full Analysis population includes all subjects who have an attempted implant. An implant is considered attempted when the Aveir Introducer Sheath or Aveir dilator is inserted through the skin of the access site.

[redacted]

2.2 Statistical Methods

For the primary and secondary endpoints, 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, and standard deviations, with quartiles, minimums, maximums, and 95% confidence intervals for the means as per the table mockups.

2.2.2 Descriptive Statistics for Categorical Variables

For categorical variables (e.g. gender, cardiac disease history, etc.), results will be summarized with subject counts and percentages/rates, and where specified in the table mockups, with exact 95% Clopper-Pearson confidence intervals.

2.2.3 Survival Analyses

For time-to-event variables, Kaplan-Meier analysis will be conducted. Subjects without events will be censored at their last known event-free time point, and for 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 primary and secondary endpoint analysis will be based on the newly enrolled (de novo) subjects in the study.

2.3.1 Primary Safety Endpoint Analysis

The primary safety endpoint evaluates the 12-month Aveir DR LP system CFR based on CEC adjudication of adverse events. A complication is defined as a device-or procedure-related serious adverse event (SADE), including those that prevent initial implantation (includes both Atrial LP and Ventricular LP complications and implant procedure-related complications).

The primary safety endpoint hypothesis is:

H_0: CFR ≤ 76.5% vs. H_1: CFR > 76.5%

where 76.5% is the performance goal (PG).

The CFR at 12 months will be estimated using the Kaplan-Meier survival analysis. The associated one-sided lower 97.5% confidence interval will also be provided (using the Greenwood variance estimates). The null hypothesis is rejected at the 2.5% significance level if the LCB exceeds the PG of 76.5%. The p-value from the one-sided Z-test will be calculated and compared to the 2.5% significance level.

The primary analysis population for the primary safety endpoint analysis will be based on subjects in the full analysis population. [redacted]

[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 from the primary 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.

2.3.2 Primary Effectiveness Endpoint #1 Analysis

The primary effectiveness endpoint #1 evaluates the 12-month composite success rate ($Rate_{EP}$) evaluating acceptable atrial pacing thresholds and P-wave amplitudes in de novo subjects.

The primary effectiveness endpoint #1 hypothesis is:

H_0: $Rate_{EP} \leq 80\%$ vs. H_1: $Rate_{EP} > 80\%$

where 80% is the performance goal. The $Rate_{EP}$ is the proportion of subjects who have met success criteria in the primary effectiveness endpoint #1. The acceptable ranges for sensing and pacing which define success criteria are shown in the table below:

Parameter	Acceptable values
Pacing voltage	Pacing threshold ≤ 3.0 V at 0.4 ms
P Sensitivity	P-wave amplitude ≥ 1.0 mV

Success Criteria: A subject will be considered to have met the primary effectiveness #1 endpoint if: pacing threshold voltage ≤ 3.0 V at 0.4 ms at 12-month visit and sensed P-wave amplitude is ≥ 1.0 mV at the 12-month visit.

For subjects that do not have P-wave amplitude measured due to active atrial fibrillation or atrial tachyarrhythmias or any other heart rhythm conditions or procedures which prevent sensing amplitude from being measured, success will be determined from pacing threshold only. For subjects that do not have pacing threshold measured, due to active atrial fibrillation or atrial tachyarrhythmias or any other heart rhythm conditions or procedures which prevent sensing amplitude from being measured, success will be determined from P-wave amplitude only. Subjects that do not have P-wave amplitude and pacing voltage, both of which are unobtainable due to active atrial fibrillation or atrial tachyarrhythmias or any other heart rhythm conditions or procedures which prevent sensing amplitude from being measured, will be excluded from analysis.

The $Rate_{EP}$ will be estimated as a binomial proportion and the 97.5% lower confidence bound of the $Rate_{EP}$ will be calculated using the normal approximation. The null hypothesis is rejected at the 2.5% significance level if the LCB exceeds the PG of 80%. The p-value for the one-sided Z-test will be calculated and compared to the 2.5% significance level.

The primary analysis for the primary effectiveness endpoint #1 will be based on subjects in the full analysis population. Subjects with unsuccessful implants due to reasons other than atrial pacing/sensing (e.g. cardiac anatomy) will be excluded from the analysis. Subjects who don't meet pacing/sensing success criteria at 12-months or subjects with unsuccessful implant solely due to inadequate atrial LP pacing or sensing will be counted as failures. Additionally, subjects with missing 12-month pacing threshold or P-wave amplitude data, multiple imputation will be used to impute success or failure.

[redacted]

2.3.3 Primary Effectiveness Endpoint #2 Analysis

The primary effectiveness endpoint #2 evaluates the 3-month AV synchrony success rate ($Rate_{AV}$) at rest while sitting using a Holter monitor in-clinic.

AV synchrony success is defined as subjects with a paced or sensed ventricular beat within 300 ms following a paced or sensed atrial beat for at least 70% of evaluable cardiac cycles.

The primary effectiveness endpoint #2 hypothesis is:

H_0: $Rate_{AV} \leq 83\%$ vs. H_1: $Rate_{AV} > 83\%$

where 83% is the performance goal. The $Rate_{AV}$ is the proportion of subjects who met success criteria in the primary effectiveness endpoint #2.

The $Rate_{AV}$ will be estimated as a binomial proportion and the 97.5% LCB of the $Rate_{AV}$ will be calculated using the normal approximation. The null hypothesis is rejected at the 2.5% significance level if the LCB exceeds the PG of 83%. The p-value for the one-sided Z-test will be calculated and compared to the 2.5% significance level.

The primary analysis for the primary effectiveness endpoint #2 will be based on subjects in the full analysis population. Subjects with unsuccessful implant solely due to a failure to establish i2i communication at end of implant procedure will be included and imputed as failures. Subjects with unsuccessful implants due to reasons other than AV synchrony (e.g., cardiac anatomy) will be excluded from this analysis.

Additionally, among the implanted population only the AV synchrony data available for evaluation will be used. [redacted]

[redacted]

2.3.4 Secondary Safety Endpoint Analysis

The secondary safety endpoint evaluates the 12-month Aveir atrial LP related CFR_A based on the CEC adjudication of adverse events. The secondary safety endpoint will be tested if all the primary endpoints are met.

An atrial LP complication is defined as an atrial device- or procedure-related SADE, including those that prevent initial LP implantation. Complications that are exclusively related to the ventricular LP or its delivery/retrieval will not be considered atrial LP complications and will be excluded from this evaluation. Complications that cannot be exclusively determined to be related to the ventricular or atrial LP will be considered atrial LP complications (e.g. femoral access complications, embolism, etc.). The secondary safety endpoint hypothesis is:

H_0: $CFR_A \leq 82\%$ vs. H_1: $CFR_A > 82\%$

where 82% is the PG.

The CFR_A at 12 months will be calculated using the Kaplan-Meier survival analysis. The associated one-sided lower 97.5% confidence interval will also be provided (using the Greenwood variance estimates). The null hypothesis is rejected at the 2.5% significance level if the LCB exceeds the PG of 82%. The p-value from the one-sided Z-test will be calculated and compared to the 2.5% significance level.

The secondary safety endpoint analysis will be based on the subjects in the full analysis population. [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. Subjects who have these events will be censored at the time of the event. Additional analysis with these events included will also be provided.

2.3.5 Secondary Effectiveness Endpoint Analysis

The secondary effectiveness endpoint includes evaluation of CAEP exercise protocol for atrial LP. The secondary effectiveness endpoint will be tested if all the primary endpoints are met and the secondary Safety endpoint is also met.

The secondary effectiveness CAEP endpoint hypothesis is:

H_0: Mean Slope < 0.65 or Mean Slope > 1.35
H_1: 0.65 ≤ Mean Slope ≤ 1.35.

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. Subjects will undergo the CAEP exercise test any time after the beginning of their 3-month visit window and before the end of 6-month visit window. Each subject will undergo this test at a single visit.

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. Any CAEP assessments performed which substantially deviate from the CAEP exercise protocol or where insufficient data is available will be excluded from the analysis. The results of subjects who did not meet the analysis criteria will still be reported.

A mixed effects model for repeated measures will be used to estimate the mean slope (through origin) and standard error of mean slope across N subjects. [redacted] A 95% confidence interval for the mean slope will be provided and if this interval falls within the equivalence bounds of [0.65,1.35], the null hypothesis is rejected. [redacted]

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[redacted]

Up to thirty subjects will provide data contributing to this analysis. [redacted]

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2.4 Sample Size Calculations

[redacted]

Sample size calculation for the primary safety endpoint at 12 months (CFR):
[redacted] 300 subjects [redacted] will provide [redacted] to meet a performance goal of 76.5% and reject the null hypothesis at a 2.5% one-sided significance level. [redacted]

Power calculation for the primary effectiveness endpoint #1 at 12 months ($Rate_{EP}$)
[redacted] 240 subjects [redacted] to meet a performance goal of 80% and reject the null hypothesis at a 2.5% one-sided significance level. [redacted]

Power calculation for the primary effectiveness endpoint #2 at 3 months ($Rate_{AV}$)
[redacted] 267 evaluable subjects [redacted] to meet a performance goal of 83% and reject the null hypothesis at a 2.5% one-sided significance level. [redacted]

Power calculation for the secondary safety endpoint at 12 months (CFR_A)
[redacted] 300 subjects [redacted] to meet a performance goal of 82% and reject the null hypothesis at a 2.5% one-sided significance level. [redacted]

Additional sample size for the study
[redacted] up to 200 additional de novo subjects will be enrolled [redacted]. Up to 50 subjects will also be enrolled to assess the upgradeability to a Aveir DR LP system in subjects previously implanted with the Aveir VR LP single chamber analysis.

[redacted]

2.5 Interim Analysis

[redacted]

[redacted]

2.6 Timing of Analysis

[redacted]

2.7 Study/Trial Success

[redacted]

2.8 Handling of Missing Data

A subject may discontinue from the study prior to the 12-month visit. If this situation occurs, reasons for missing data will be summarized to assess the plausibility if the missing data could affect subject's endpoint results.

In addition, sensitivity analyses will be performed to evaluate the potential impact of missing data on the primary safety and effectiveness endpoints.

Sensitivity Analyses for Primary Safety Endpoint
For the primary safety endpoint, tipping point sensitivity analysis will be conducted on all the subjects in the full analysis population.

The tipping point analysis will be performed to assess the impact of the missing data. [redacted]

Sensitivity Analyses for Primary Effectiveness Endpoint #1
The following sensitivity analysis will be conducted for the primary effectiveness endpoint #1.

1. Complete Case: Complete case sensitivity analysis will be conducted for subjects in the full analysis population [redacted]

2. Tipping Point: Tipping Point sensitivity analysis will be conducted for subjects in the full analysis population [redacted]

Sensitivity Analyses for Primary Effectiveness Endpoint #2

For the primary effectiveness endpoint #2, tipping point sensitivity analyses will be conducted for subjects in the full analysis population, excluding those that had an unsuccessful implant due to reasons other than AV synchrony (e.g., cardiac anatomy). For the tipping point analysis, subjects with missing data for the primary effectiveness endpoint #2 will be evaluated with respect to the success rate among these subjects. Subjects with unsuccessful implant solely due to a failure to establish i2i communication at end of implant procedure will be included and imputed as failures. Tipping point is at which the study conclusion will be altered.

2.9 Poolability Issue (if applicable)

Poolability of the primary safety endpoint and the two primary effectiveness endpoints on subjects in the full analysis population will be evaluated by region and across sites. Analysis will be performed based on available data.

The study will be conducted in up to 85 sites in the United States, Canada, Europe and Asia Pacific. The study will be conducted following the same investigational plan, monitoring plan and training plan in all regions. The consistency of results for the primary safety and effectiveness endpoints will be evaluated across regions i.e. US and OUS (outside the US) if there is a sufficient sample size in each region, and across sites with the following site categories:

Large sites: # of subjects enrolled ≥10
Medium sites: 4≤ # of subjects enrolled ≤9
Small sites: # of subjects enrolled ≤3

Descriptive summaries for the primary safety and the two primary effectiveness endpoints will be presented across (1) Regions: US or OUS (outside the US) and (2) Site Categories (Large, Medium or Small). Consistency of results will be examined using Fisher's exact test and assessed at a significance level of 0.15. [redacted]

[redacted]

2.10 Multiplicity Issues

[redacted]

[redacted]

2.11 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 may not be collected and hence data from some European countries may 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 by treatment arms at all scheduled visits.

3.4 Protocol Deviation

Protocol deviations will be summarized by major and minor categories for subjects in whom a protocol deviation was reported.

3.5 Additional Data

The following additional data will be recorded and reported descriptively:

- Comparisons of demographics between the study population to the existing dual-chamber pacemaker population by region
- All adverse events, and whether or not each is device-related or procedure-related
- Implant success rate and reasons for unsuccessful implant

- Device handling characteristics at implant
- Number of device repositioning at time of implantation
- Implant duration, fluoroscopy duration, and time from implant to hospital discharge
- Pre-procedure (i.e. MRI, CT, X-ray) and procedural imaging (i.e. ICE) measures to evaluate the right atrium and/or the atrial LP based on any imaging data provided to the Sponsor
- Final location of LP placement
- Demographics: gender, age, ethnicity, race, indication for pacemaker implant
- Medical history
- Use of beta blocker, ACE, ARB, anti-coagulation, anti-arrhythmic, and anti-platelet medications
- 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 base rate, impedance, pulse amplitude, pulse duration and percentage pacing will also be reported for all visits
- Hospitalizations
- Mortality
- Upgradeability of the Aveir ventricular LP (VR) into the Aveir DR LP system summarized by:
    - Success rate of VR to DR upgrades and reasons for unsuccessful upgrades.
    - Summary of adverse events related to upgrades
    - Summary of device measurements for subjects with an upgrade
- AV synchrony (at various positions and activity levels)
- EQ-5D Health-Related Quality of Life Analysis

[redacted]

3.6 24-Hour Holter Monitor Data Analysis

All capable *de novo* subjects will be asked to wear a 24-hour Holter monitor and complete a symptom diary, until 50 subjects provide data contributing to the analysis. The test may be performed any time after the beginning of the 3-month visit window. The preferred window to perform the 24- hour Holter test is between the 3-month and 6-month visit. These data will be examined for appropriate sensing, pacing, AV Synchrony during the activities of daily living for each subject. In addition, these data will be evaluated for any correlation between any subject symptoms with losses of AV synchrony, if present.
The Sponsor will provide a 24-hour Holter summary report to the respective in-country regulatory agency, which includes the following for each subject:

- Minimum, maximum, and average heart rate
- Percent atrial pacing
- A telemetry strip of the minimum heart rate and a telemetry strip during pacing (the pacing strip may be the same as the minimum heart rate strip but is not required).
- Number of pauses seen (defined as RR interval greater than or equal to 2 sec or < 30 bpm)
- All telemetry strips of a pause greater than the programmed lower rate limit after accounting for any hysteresis programming
- All telemetry strips showing evidence of atrial oversensing, undersensing, or loss of capture

- Programmed parameters (which are necessary to assess if the pauses or minimum heart rate seen on Holter are appropriate or not)
- AV Synchrony
- Appropriate Automatic Mode Switching (AMS) due to atrial arrhythmias
- Reported adverse events and/or subject symptoms with diary entry that is timed and dated to correlate Holter findings with events and/or symptoms.

4.0 DOCUMENTATION AND OTHER 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
AV	Atrioventricular
SAS	Statistical Analysis System
SAP	Statistical Analysis Plan

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6.0 REFERENCES

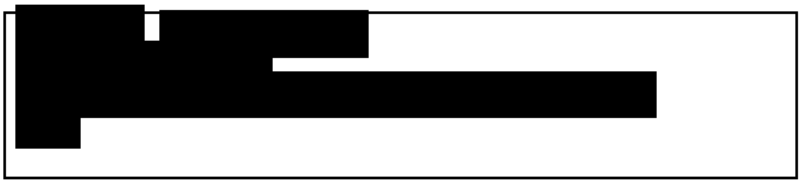
- ABT-CIP-10428/ Rev B, the CIP for Aveir DR i2i study for Europe
- CRD_1023 Aveir DR Case Report Form

7.0 [redacted]

[redacted]

[redacted]

[redacted]



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