Abbott	Clinical Investigation Plan Cover Page

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LEADLESS II IDE – Phase 2
The Leadless II Study – Phase 2: A Safety and Effectiveness Trial for a Leadless Pacemaker System
Study Document No: SJM-CIP-10226
Version P
Date: 28-JUL-2021

Sponsor

Abbott Medical (formerly St. Jude Medical)
Cardiac Rhythm Management Division
15900 Valley View Court
Sylmar, CA 91342
USA

INVESTIGATION PLAN

The LEADLESS II Study

A safety and effectiveness trial for a leadless pacemaker system

Study Document No: SJM-CIP-10226/Rev P
July 28, 2021

IDE Number: G130138

Clinical Investigation Plan

Compliance Statement:

This clinical investigation will be conducted in accordance with this Clinical Investigation Plan, the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., US 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 812, 21 CFR Part 54, 21 CFR Part 11, and OUS ISO 14155:2011) and the appropriate local legislation(s). The most stringent requirements, guidelines or regulations must always be followed. The conduct of the clinical investigation will be approved by the appropriate Institutional Review Board (IRB)/Ethics Committee (EC) of the respective investigational site and by the applicable regulatory authorities (e.g., FDA, TGA, Health Canada, and applicable competent authorities, etc.).

[redacted]

Clinical Investigation Plan

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

I have read and agree to adhere to the clinical investigation plan and all regulatory requirements applicable in conducting this clinical investigation.

Site Principal Investigator

Printed name:
Signature:
Date:

[redacted]

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[redacted]

[redacted]

Clinical Investigation Plan

1.0 Introduction

Sponsor, St. Jude Medical (now Abbott), has developed a Leadless Pacemaker (LP) system to eliminate leads, pockets, and connectors required by conventional pacemakers and to eliminate associated complications. This concept could improve patient comfort by replacing a surgical procedure with a percutaneous one, eliminating the visible lump and scar at a conventional pacemaker's pectoral implant site, and removing the need for activity restrictions to prevent dislodgement after implantation of a conventional lead. Finally, the concept could permit pacemaker patients to undergo magnetic resonance imaging (MRI) with specified machines, although this is not being evaluated under this protocol.

St. Jude Medical's LP system consists of a pacemaker and its accessories: a programmer, introducer, delivery catheter, and retrieval catheters. The accessories are not intended for use alone or with any device other than the LP. The pacemaker and all accessories, except the programmer, are single-use devices and are supplied sterile.

This clinical investigation will be conducted in accordance with this CIP. All investigators involved in the conduct of the clinical investigation will be qualified by education, training, or experience to perform their tasks and this training will be documented appropriately.

2.0 Purpose / Background

The clinical investigational plan for this IDE study consists of two phases to support the evaluation of the safety and effectiveness of the St. Jude Medical LP system for treatment of bradycardia.

Phase 1 of this clinical investigation (ClinicalTrials.gov identifier: NCT02030418) includes the evaluation of St. Jude Medical's original Nanostim™ Leadless Pacemaker system consisting of LP Model S1DLCP and its supporting accessories. As of this protocol version, Phase 1 has completed the primary safety and effectiveness endpoint analyses, submitted the PMA application, and is currently under the Continued Access Phase (CAP). Due to device malfunctions related to the battery and docking button, the Nanostim system was discontinued and will not be market-released. Study subjects who remain implanted with the Nanostim LP will continue follow-up according to Phase 1 protocol requirements, which are the same as the Phase 2 requirements. For more details about the Phase 1 clinical investigation, please see Appendix VII: Clinical Protocol – Phase 1 and Appendix VIII: CIP Summary (Synopsis) – Phase 1.

Phase 2 of this clinical investigation includes the confirmatory evaluation of the modified St. Jude Medical LP system consisting of a modified LP, model LSP112V and

its supporting accessories, herein referred to as the **Aveir™ Leadless Pacemaker System**. Study subjects who are newly implanted (de novo) with the Aveir LP will contribute to the confirmatory endpoints and follow Phase 2 protocol requirements. In addition, Phase 1 study subjects may have their original Nanostim LP replaced with the Aveir LP according to the system replacement procedures outlined in this protocol. Although these subjects have already been enrolled in this study, subject re-consent will be required prior to the replacement procedure with the Aveir system. These subjects will continue follow-up according to Phase 2 requirements while resuming their original follow-up schedule. European subjects enrolled in the Leadless Observational Study who need replacement of their Nanostim LP with the Aveir LP may be enrolled in this IDE **only after** the confirmatory enrollments have been completed for Phase 2 (i.e. during the CAP for Phase 2). Since these subjects are newly enrolled in this IDE, they will follow all the Phase 2 protocol requirements.

2.1 Overall Study Objectives and Endpoints

The overall primary objectives for this IDE study are to evaluate the safety and effectiveness of the St. Jude Medical LP system in an acute period post-implant in a subject population indicated for a VVI(R) pacemaker. The safety endpoint evaluates a complication free rate based on CEC adjudication of adverse events. The effectiveness endpoint evaluates pacing thresholds and R-wave amplitudes within the therapeutic range. The evaluation time points for these endpoints for Phase 1 and Phase 2 are specified in Sections 25.2 and 3.2, respectively.

3.0 Clinical Protocol – Phase 2

3.1 Study Design and Scope

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 that contributed enrollments to Phase 1 of this IDE study or contributed enrollments in the Leadless Observational Study in Europe. The Sponsor expects to enroll up to 200 newly implanted (de novo) subjects in 6 months, accounting for attrition over the 6-week follow-up period for the confirmatory analysis. [redacted]

Enrollment in Phase 2 of the LEADLESS II clinical study is expected to take approximately 6 months. Sponsor anticipates the duration of study participation to

[redacted]

be approximately 15 months. All eligible subjects will undergo implant attempt with an Aveir LP.

All subjects will consent to continue annual follow-ups each year until 9 years after implant, in a long-term post-approval study.

The following study evaluations will occur after implant:

- Pre-discharge assessment
- 2-week follow-up visit (in-office or clinic)
- 6-week follow-up visit (in-office or clinic)
- 3-month follow-up visit (in-office or clinic)
- 6-month follow-up visit (in-office or clinic)
- Every 6 months thereafter until study completion

Follow-up schedules will be calculated from the date of successful implant.

The clinical investigation has been designed to involve as little pain, discomfort, fear, and any other foreseeable risk as possible for subjects. Refer to the Risks Analysis section of this clinical investigation plan for details.

3.2 Study Objective and Endpoints

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

Confirmatory Safety Endpoint
The confirmatory safety endpoint evaluates a 6-week complication-free rate based on CEC adjudication of adverse events.

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

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]

3.2.1 Confirmatory Endpoints

3.2.1.1 Confirmatory Safety Endpoint

The goal of the confirmatory safety endpoint evaluation is to demonstrate an acceptable complication-free rate (CFR); including any complication that prevents initial implantation. [redacted]

Confirmatory Safety Endpoint Evaluation at 6 weeks:

H_0: CFR $\leq$ 86% vs. H_1: CFR > 86%

[redacted]

3.2.1.2 Confirmatory Effectiveness Endpoint

The composite confirmatory effectiveness endpoint will be used to evaluate pacing thresholds and R-wave amplitudes at the 6-week visit and to document the percentage of subjects with acceptable sensing and pacing performance. Acceptable ranges for sensing and pacing are shown in the table below.

Acceptable Ranges for Sensing and Pacing

Parameter	Acceptable test values
Pacing voltage	Pacing threshold $\leq$ 2.0 V at 0.4 ms
R Sensitivity	R-wave amplitude $\geq$ 5.0 mV or $\geq$ value at implant

[redacted]

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

[redacted]

The inability to sense or pace within the programmable range available in the Aveir device, resulting in device repositioning, replacement, or removal will be captured in the associated safety endpoints.

Confirmatory Effectiveness Endpoint Evaluation at 6 Weeks:

H_0: Rate ≤ 85.0% vs. H_1: Rate > 85.0%

[redacted]

3.2.1.3 Data Analysis of Confirmatory Safety and Effectiveness Endpoints

The analysis population for the Confirmatory Safety Endpoint will be all enrolled subjects who sign an IRB/EC-approved informed consent and who have an attempted implant.

The analysis population for the Confirmatory Effectiveness Endpoint will be all enrolled subjects with a successful implant. For subjects with missing 6-week pacing threshold or R-wave amplitude data, the last observation carried forward will be used in the analysis.

The confirmatory endpoint analyses will be based on the 200 (de novo) enrolled subjects in the Phase 2 study only. Any subjects enrolled in the CAP, including those subjects who need a replacement of their Nanostim LP with the Aveir LP, are not included in the confirmatory endpoint analysis.

The confirmatory safety and effectiveness endpoints must be met at the 6-week evaluations for the study to be considered an appropriate basis for PMA approval.

Both confirmatory safety and effectiveness endpoints will be tested against the pre-specified performance goals at 6 weeks with one-sided exact tests for binomial proportion.

[redacted]

Detailed statistical analyses for Phase 2 will be specified in the Statistical Analysis Plan.

3.2.2 Confirmatory Secondary Endpoint #1

The confirmatory secondary endpoint #1 includes evaluation of a Chronotropic Assessment Exercise Protocol (CAEP) exercise protocol. If both the Confirmatory Safety and Confirmatory Effectiveness Endpoints are met, then the following hypothesis will be hierarchically evaluated:

Confirmatory Secondary CAEP Endpoint

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%

6 Minute Walk Test (6MWT)

All capable subjects will be asked to perform a minimal effort six-minute walk test (6MWT) simulating daily walking activity to identify the appropriate sensor parameters for each subject prior to conducting the CAEP exercise protocol. After completion of the 6MWT, the appropriate sensor parameters will be programmed into the Aveir device and used for the subsequent CAEP protocol.

CAEP exercise protocol

All capable subjects who have completed the 6MWT protocol 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.

[redacted] Approximately 30 subjects among the confirmatory analysis population with a successful implant will provide data contributing to the analysis.

[redacted]

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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] To ensure that a robust cross-section of subjects is evaluated, approximately 30 subjects will undergo this assessment.

[redacted]

[redacted]

[redacted]

The 6MWT will be performed any time after the beginning of the 2-week visit window. The CAEP protocol will be performed after completion of the 6MWT protocol and any time after the beginning of the 6-week visit window. [redacted]

3.2.3 Secondary Endpoint #2

The secondary endpoint #2 estimates the 2-year survival rate of patients implanted with the Nanostim leadless pacemaker using the Kaplan-Meier method of all-cause mortality. The survival probability estimate and upper and lower 95% confidence intervals will be reported. [redacted]

[redacted]

[redacted]

separate analysis specifically for each type of pacemaker will be performed and reported.

3.2.4 Additional data

The following additional data will be recorded and reported:

- 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, fluoro duration, and time from implant to hospital discharge
- Final 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 at implant
- 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
- Summary of adverse events, replacement success rate, and device measurements for subjects previously implanted with the Nanostim device that were replaced with the Aveir device in Phase 2

3.3 Description of Device

3.3.1 Identification of the device: proprietary and code names

The Aveir Leadless Pacemaker System consists of these items:

Device Name	Description	Device Model	Serial/Lot Controlled	Legal Manufacturer	Region/ Country	Regulatory Status
Aveir™ Leadless Pacemaker, Right Ventricular	Modified Aveir LP Pacemaker with new battery and fixed-post docking button,	LSP112V	Serial number	St. Jude Medical	U.S. Canada Australia Europe (including U.K.)	Investigational

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Device Name	Description	Device Model	Serial/Lot Controlled	Legal Manufacturer	Region/ Country	Regulatory Status
	packaged with a loading tool.					
Aveir™ Delivery Catheter	Delivery Catheter for implanting a Aveir LP	LSCD111	Lot number	St. Jude Medical	U.S. Canada Australia Europe (including U.K.)	Investigational
Aveir™ Retrieval Catheter	Triple Loop Retrieval Catheter for retrieving a Aveir LP	LSCR111	Lot number	St. Jude Medical	U.S. Canada Australia Europe (including U.K.)	Investigational
Aveir™ Introducer, 30 cm	25F Introducer, 30 cm for providing a conduit into the venous system	LSN25301	Lot number	St. Jude Medical	U.S. Canada Australia Europe (including U.K.)	Investigational
Aveir™ Introducer, 50 cm	25F Introducer, 50 cm for providing a conduit into the venous system	LSN25501	Lot number	St. Jude Medical	U.S. Canada Australia Europe (including U.K.)	Investigational
Aveir™ Link Module	Programmer Link and Accessories for interrogating and programming the Aveir LP after implant	LSL02	Serial Number	St. Jude Medical	U.S. Canada Australia Europe (including U.K.)	Investigational

[redacted]

Device Name	Description	Device Model	Serial/Lot Controlled	Legal Manufacturer	Region/ Country	Regulatory Status
Aveir™ Programmer Software Application	Leadless application software which resides in the SJM Merlin Programmer	3330	N/A	St. Jude Medical	U.S. Canada Australia Europe (including U.K.)	Investigational

3.3.2 Indication for Use

The Aveir™ Leadless Pacemaker system is indicated for management of these conditions:

- Sinus bradycardia with infrequent pauses or unexplained syncope with EP findings
- Chronic atrial fibrillation with 2 or 3° AV or bifascicular bundle branch block (BBB)
- Normal sinus rhythm with 2 or 3° AV or BBB block and a low level of physical activity or short expected lifespan

3.3.3 Description of the device and its intended application

The Aveir LP system consists of the Aveir LP device and its associated accessories listed in 3.3.1. The Aveir LP system is a leadless pacemaker system deployable into the heart's right ventricle and capable of single-chamber (VVIR) functionality. The pacemaker and all its accessories (except for the Link Module) are single-procedure devices and are furnished sterile.

The devices in the Aveir LP system achieve their intended purposes as described in the subsections below.

3.3.3.1 Aveir LP

Intended Use: The Aveir™ Leadless Pacemaker is intended to provide bradycardia pacing as a pulse generator with built-in battery and electrodes for implantation in the right ventricle. The LP is intended to provide sensing of intrinsic cardiac signals and delivery of cardiac pacing therapy to the target treatment group.

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As a *leadless* pacemaker, the Aveir LP does not need a connector, pacing lead, or pulse generator pocket. The LP is delivered percutaneously via the femoral vein through an Aveir™ Introducer and Delivery Catheter.

A distal non-retractable, helix affixes the LP to the endocardium. Three additional short suture segments on the outside of the LP nosecone (or helix mount) provide secondary fixation securement. Sensing and pacing occur between a distal tip electrode near the helix and the external can (or case) of the LP.

The distal tip electrode is a titanium-nitride coated platinum-iridium disc located at the center of the fixation helix, with an approximate geometric surface area of 2 mm^2. The tip electrode includes a single dose of dexamethasone sodium phosphate (DSP), intended to reduce inflammation. The ring electrode is the uncoated part (no parylene) of the titanium pacemaker case, with a geometric surface area $\geq$127 mm^2. The inter-electrode distance is $\geq$ 24 mm. The LP's proximal end has a feature for docking to delivery and retrieval catheters, which provides for repositioning capability.

The LP communicates bi-directionally with the external Aveir™ Link Module in conjunction with a Merlin PCS Model 3650 programmer to interrogate and program the LP and to monitor ECG waveforms for observing LP function.

The Link Module provides an interface between the Merlin Programmer and standard ECG electrodes placed on the subject's torso, for two-way communication with the implanted LP(s) and acquisition of the surface ECG. The Programmer transmits signals to an implanted LP via conducted communication with sub-threshold electrical pulses applied via skin electrodes.

Consequently, the LP transmits signals using circuits and electrodes already provided for pacing, with data encoded in pulses delivered during the heart's refractory period. This conducted communication allows data to be communicated between the LP and surface electrodes at a low current that does not affect pacing or sensing functions. The LP also has a commanded EGM (CEGM) for Current of Injury (COI) assessment. An EGM shows the heart's electrical activity as sense by the pacing system. The COI is a measure intended to assess implant integrity during the implant procedure, like conventional transvenous leads.

The LP also senses right-ventricular blood temperature to provide an increase in pacing rate with increased metabolic demand.

Otherwise, the Aveir LP has the same operating principles as a conventional cardiac pacemaker. For further information, refer to the Instructions for Use for the Aveir Leadless Pacemaker.

[redacted]

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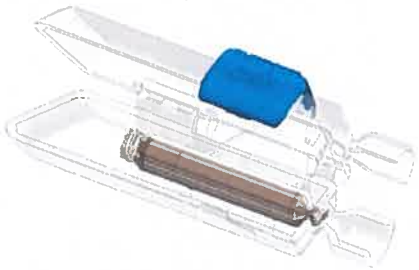
The Aveir LP is provided preloaded in the Loading Tool. The Loading Tool is used to facilitate the attachment of the LP onto the Delivery Catheter in a sterile field prior to implantation into the patient. The Loading Tool does not have direct patient contact. The illustrations below show the Loading Tool and features of the Aveir LP.

LP packaged in Loading Tool



Aveir LP

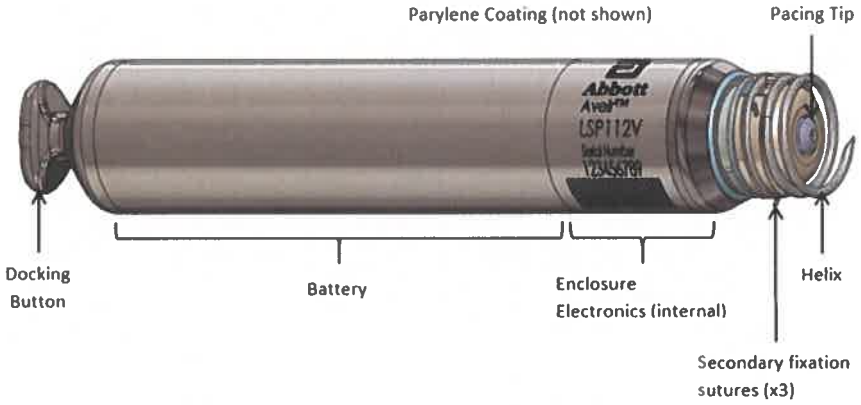


Table 1: LP Features

Model	LSP112V
Length	38.0 mm (1.50 in)
Diameter	6.5 mm (0.26 in)
Volume	1.1 cm^3
Mass	2.4 grams
Fixation Mechanism	Distal non-retractable helix
Fixation Depth	Approximately 1.63 mm
Electrode Tip	Semispherical
Electrode spacing	≥ 24 mm

Ring electrode surface are	≥ 127 mm^2

Please refer to the Aveir LP Instructions for Use for a complete listing of the LP materials in contact with blood or tissue and other technical specifications.

3.3.3.2 Aveir™ Delivery Catheter

Intended use: The Aveir™ Delivery Catheter is intended to be used in the peripheral vasculature and the cardiovascular system to deliver and manipulate an Aveir™ Leadless Pacemaker (LP). Delivery and manipulation includes implanting an LP within the target chamber of the heart.

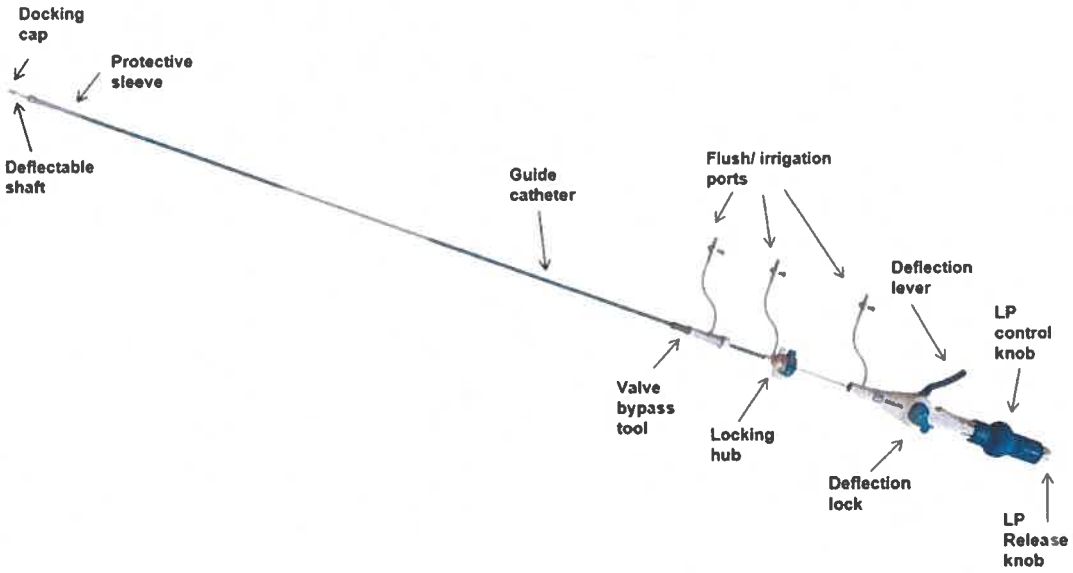
The delivery catheter system provides a means to perform these actions:

- Attach and dock a separate LP pre-loaded in the loading tool
- Position the protective sleeve over the LP helix and lock the sleeve into place
- Advance the Aveir LP from an access site in the groin (utilizing minimally invasive techniques) through the femoral vein into the right ventricle
- Hand inject contrast solution through the guide catheter flush port to its distal tip
- Pull back the protective sleeve to expose the flexible section of the delivery catheter system
- Map the endocardium with the docked LP to assess appropriateness of implant site
- Position the LP and rotate it to affix the LP helix to the endocardium
- Undock the LP from the delivery catheter system leaving the LP tethered to the delivery catheter system to measure thresholds with minimal force transmission from the delivery catheter system
- Re-dock to the delivery catheter system, unscrew and reposition the LP if necessary to acceptable thresholds
- Disconnect the LP from the tethers of the delivery catheter system, leaving the LP implanted in the endocardium

Apart from the docking mechanism, the delivery catheter and its control system (handle) have the same operating principle as a conventional steerable catheter and control system. The Aveir™ Delivery Catheter (delivery catheter system) includes a steerable delivery catheter, an integrated guiding catheter with a protective sleeve designed to protect an attached LP's fixation helix and electrode, and a valve bypass tool to dilate the 25 Fr inner diameter (ID) introducer sheath hemostasis valve and advance the system into the femoral vein.

The delivery catheter has an effective length of 105 cm (41.3 inches).

The illustration below shows mechanical characteristics of the delivery catheter:



3.3.3.3 Aveir™ Link Module and Programmer Software

Intended Use: The Aveir™ Link Module is intended for use in conjunction with a Merlin™ PCS Model 3650 programmer[1] to interrogate and program an Aveir™ Leadless Pacemaker (LP) and to monitor LP function. It is intended for use by trained healthcare professionals in a hospital or healthcare setting. It is not intended for use in domestic establishments.

The Aveir™ Link Module, model LSL02 communicates with an implanted Aveir™ LP via conducted communication through the St. Jude Medical™ Patient Cable and skin electrodes. Safe, high frequency electrical pulses are sent between the LP and programmer system to program and interrogate the LP. The Link Module also uses the Patient Cable and skin electrodes to acquire a patient's ECG waveform. The Link Module is powered via a St. Jude Medical™ Merlin™ PCS Model 3650's USB port.

[1]The Aveir™ Link module is used with a St. Jude Medical™ Merlin™ Patient Care System (Merlin PCS) Model 3650. Merlin PCS Model 3650 is a portable, dedicated programming system designed to interrogate, program, display data, and test St. Jude Medical™ implantable devices, but which can alternatively perform similar functions for an Aveir™ Leadless Pacemaker when used with the Link Module as described herein. Refer to the Merlin™ Patient Care System User's Manual for further information.

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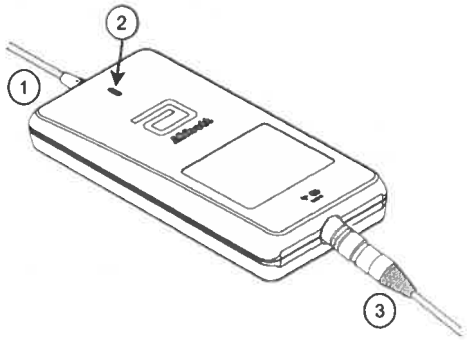
The Aveir™ Link Module connected to a Merlin™ PCS (Model 3650, P030054/S8) enables non-invasive communication with the implanted medical device allowing the user to retrieve device diagnostics and customize the device parameters to meet the patient needs without requiring additional surgery. The Aveir™ Programmer Software Application will reside on Merlin™ PCS, and not on the Link Module.

The Aveir™ Programmer Software interfaces with the Aveir™ Link Module and Merlin Patient Care System Programmer (PCS) to provide a communication link to an LP implanted in a patient. The Programmer Software, model number 3330 is used to configure the LP with appropriate features and pacing characteristics. The Programmer Software also retrieves saved diagnostic information from the LP.

For further information refer to the Instructions for use for the Aveir™ Link Module.

The illustration below shows the mechanical characteristics of the Link Module:

Aveir Link Module



1. USB cable: Connects to the Merlin PCS programmer
2. LED light illuminates when the Link Module is receiving appropriate power
3. Patient connector: connects to the patient using the Patient Cable and skin electrodes

Table 2 -Link Features

Model	LSL02
Dimensions	4.4 inches x 8.8 inches x 1.5 inches
Weight	One (1) pound
Rated Power	5 Watts
Rated Current	1 Amp
Rated Voltage	5 VDC
Projected Service Life	7 years
Patient Cable Model	3625 or 3626

3.3.3.4 Aveir™ Introducer

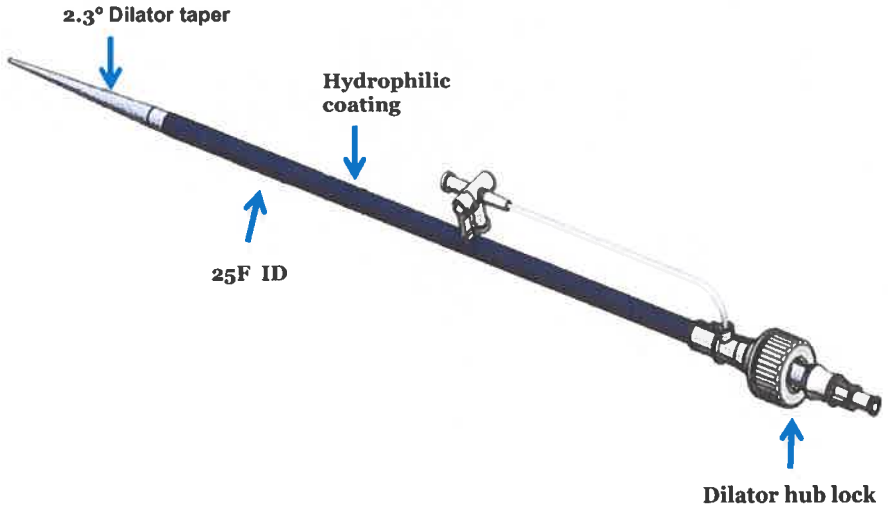
Intended Use: The Aveir™ Introducer is intended to provide a conduit into the venous system for insertion of diagnostic and other interventional devices.

The Introducer is designed to perform as a guiding sheath for introduction of diagnostic or interventional devices. The Aveir™ Introducer is compatible with the Aveir™ Delivery and Aveir™ Retrieval Catheters.

The Introducer is comprised an introducer sheath with a flush port and three-way stopcock and a dilator. The Aveir™ Introducer has a 25F inner diameter and comes in two lengths, measured by introducer sheath length – 30 cm (Model LSN25301) and 50 cm (Model LSN25501).

The introducer sheath is coated with a hydrophilic lubricious coating. The introducer sheath is fitted with a hemostasis valve to minimize air introduction during introducer insertion and/or exchange, a sideport with a three-way stopcock for fluid infusion, and a suture loop. The introducer features a radiopaque tip marker incorporated within the sheath material to identify the location of the distal tip of the sheath. For further information, refer to the device instructions for use.

The illustration below shows the mechanical characteristics of the 25F introducer:



Introducer Sheath

Model	LSN25301	LSN25501
Length	30 cm (11.8 inches)	50 cm (19.7 inches)
Inner diameter (ID)	8.0 mm (25 Fr) (0.316 inches)	8.0 mm (25 Fr) (0.316 inches)

Dilator

Model	LSN25301	LSN25501
Length	46.5 cm (18.3 inches)	66.5 cm (26.2 inches)
Inner diameter (ID)	0.9 mm (0.0382 inches)	0.9 mm (0.0382 inches)

3.3.3.5 Aveir™ Retrieval Catheter

Intended Use: The Aveir™ Retrieval Catheter is intended to be used in the peripheral vasculature and the cardiovascular system to retrieve and manipulate an Aveir™ Leadless Pacemaker (LP). Retrieval and manipulation includes removing the LP from the heart or peripheral vasculature.

The Retrieval Catheter uses a triple-loop snare to grasp the docking feature on the proximal end of an Aveir LP, mate the LP to the retrieval catheter, unscrew the LP, and retrieve the LP.

The retrieval catheter is intended to be manipulated by a single operator and allows the operator to:

- Advance the snare from an access site in the groin (utilizing minimally invasive techniques) through the femoral vein into the heart
- Steer and position the snare toward the docking button of the Aveir LP
- Snare the docking button of the Aveir LP
- Dock the retrieval catheter to the Aveir LP
- Rotate the Aveir LP to unscrew the LP helix from the endocardium
- Protect the Aveir LP helix and electrode during retrieval
- Extract the Aveir LP through the access site in the groin

Apart from the docking mechanism, the retrieval catheter and its control system (handle) have the same operating principle as a conventional steerable catheter and

control system. The system includes a valve bypass tool, a steerable retrieval catheter, an integrated guiding catheter with a protective sleeve with a protective sleeve, and a tri-loop snare. For additional information, refer to the Retrieval Catheter Instructions for Use.

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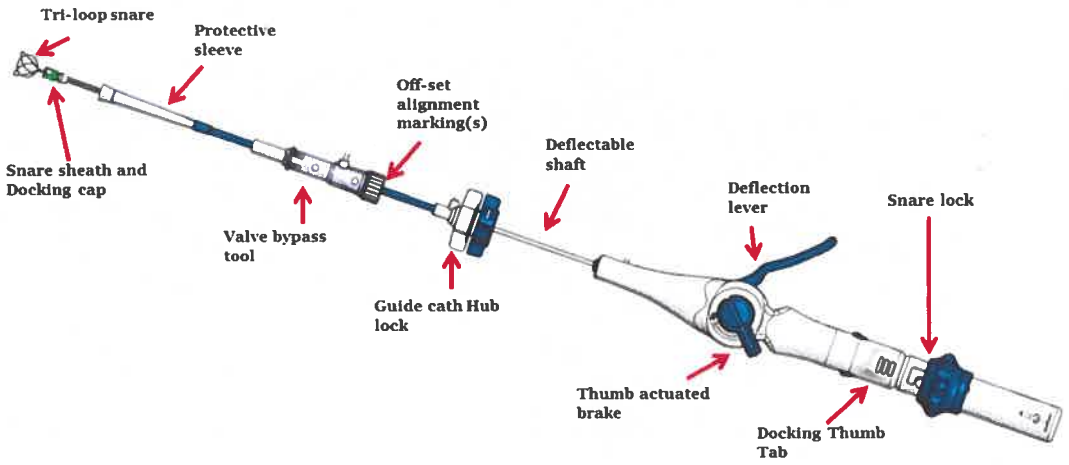
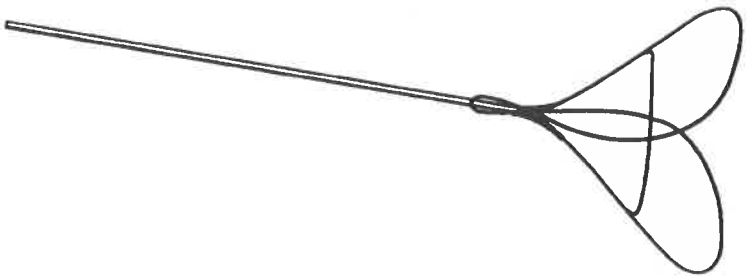
The illustration below shows the mechanical characteristics of the Retrieval Catheter.



Catheter effective length = 105 cm (41.3 inches)



Snare loop inner diameter = 20 mm (0.787 inch)

3.3.4 Configurations and Variants

In this clinical investigation, St. Jude Medical includes one configuration each of the leadless pacemaker, delivery catheter, and retrieval catheter. St. Jude Medical may incorporate a validated change to the Aveir LP implant and/or programmer software,

when necessary, to correct observed non-conformance with intended device operation.

3.4 Subject Selection

The inclusion and exclusion criteria are consistent with recommendations of the European Society of Cardiology,[1] American College of Cardiology, American Heart Association, and the Heart Rhythm Society.[2] Additionally, sponsor has included investigator input.

Eligibility for implant is based on conformance to all prospectively defined inclusion and exclusion criteria.

3.4.1 Inclusion Criteria

Eligible subjects will meet **all** of the following.

1. Subject must have one of the clinical indications before device implant in adherence with Medicare, ACC/AHA/HRS/ESC single chamber pacing guidelines including:

   - ☐ Chronic and/or permanent atrial fibrillation with 2° or 3° AV or bifascicular bundle branch block (BBB block), including slow ventricular rates (with or without medication) associated with atrial fibrillation; or
   - ☐ Normal sinus rhythm with 2° or 3° AV or BBB block and a low level of physical activity or short expected lifespan (but at least one year); or
   - ☐ Sinus bradycardia with infrequent pauses or unexplained syncope with EP findings; and

2. Subject is ≥18 years of age; and
3. Subject has a life expectancy of at least one year; and
4. *Subject is not enrolled in another clinical investigation; and
5. Subject is willing to comply with clinical investigation procedures and agrees to return for all required follow-up visits, tests, and exams; and
6. Subject has been informed of the nature of the study, agrees to its provisions and has provided a signed written informed consent, approved by the IRB/EC; and
7. Subject is not pregnant and does not plan to get pregnant during the course of the study.

3.4.2 Exclusion Criteria

Subjects will be excluded if they meet **any** of the following.

1. Subject has known pacemaker syndrome, has retrograde VA conduction, or suffers a drop in arterial blood pressure with the onset of ventricular pacing; or
2. Subject is allergic or hypersensitive to < 1 mg of dexamethasone sodium phosphate (DSP);
3. Subject has a mechanical tricuspid valve prosthesis; or
4. Subject has a pre-existing endocardial pacing or defibrillation leads; or
5. Subject has current implantation of either conventional or subcutaneous implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) device; or
6. Subject has an implanted vena cava filter; or
7. Subject has evidence of thrombosis in one of the veins used for access during the procedure; or
8. **Subject had recent cardiovascular or peripheral vascular surgery within 30 days of enrollment; or
9. *Subject has an implanted leadless cardiac pacemaker; or
10. † Subject is implanted with an electrically-active implantable medical device with stimulation capabilities (such as neurological or cardiac stimulators).

* Except for subjects who are enrolled in the Leadless Observational Study and need their existing Nanostim LP replaced with the Aveir LP. These subjects may only be enrolled in this IDE during the CAP study of Phase 2.
† Does not apply to a medical device known to not be impacted by the Aveir™ Link Module telemetry signals or to a medical device than can be temporarily turned off during interrogation/programming of an Aveir™ LP.
**Recent cardiovascular or peripheral vascular surgery within 30 days of enrollment is defined as the following:

[redacted]

[redacted]

3.5 Study Procedures

This section provides a description of all the clinical-investigation-related procedures that subjects undergo during the clinical investigation. **Figure 1** illustrates study flow and **Table 3** lists a summary of scheduled assessments. Refer to **Figure 1** and **Table 3** for an overview of the required study procedures at each interval or study visit.

The clinical-investigation-related procedures do not require additional radiation compared to a traditional VVIR lead implant and conform to standard of care for pacemaker patient management with the exception of the following:

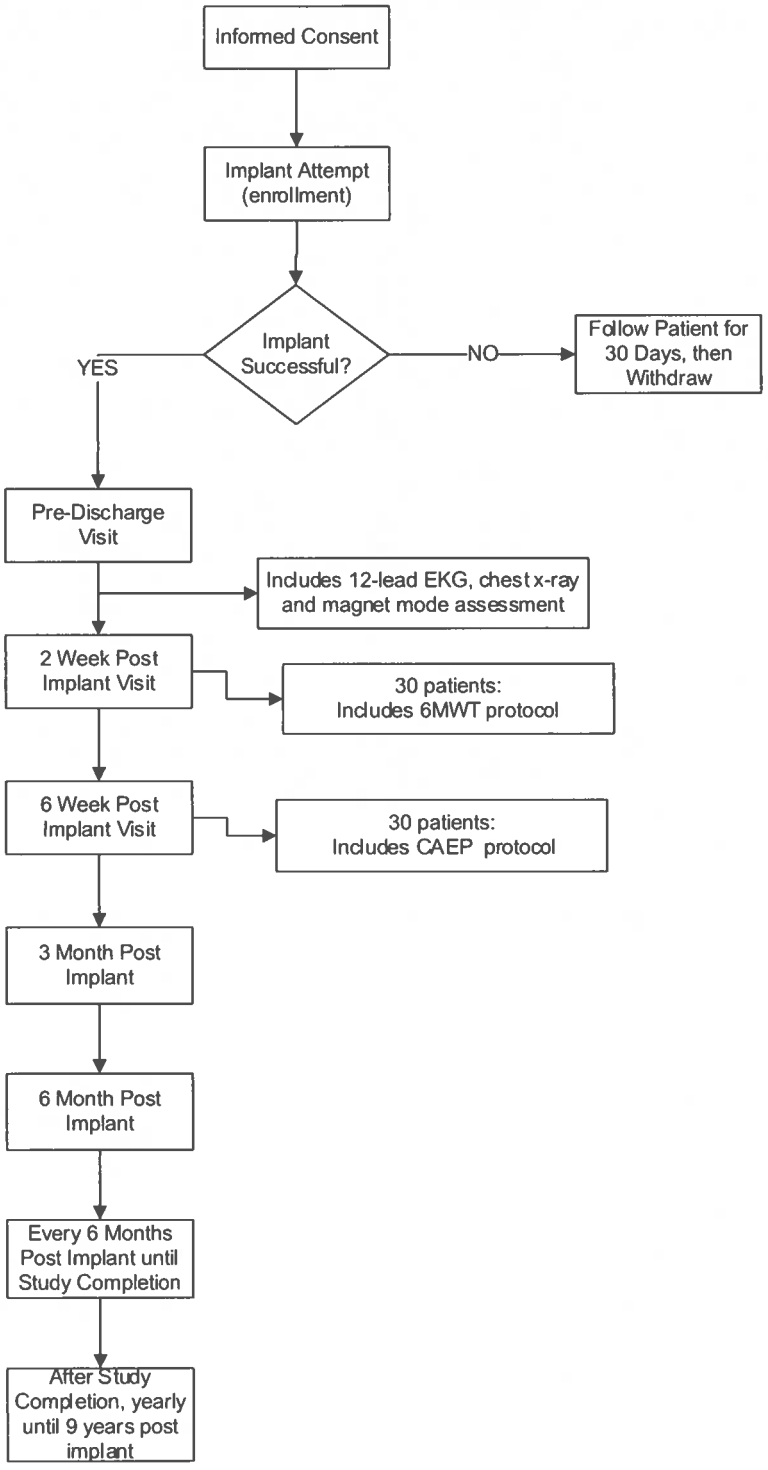
- Femoral vein access instead of subclavian vein access
- Addition of 6-minute walk and treadmill tests for rate response feature evaluation
- EQ-5D Quality of Life patient survey

Sponsor representatives may assist the investigator in assessing pacemaker effectiveness (for example pacing, sensing, and rate response effectiveness), downloading diagnostic information and programming pacemaker parameters. Sponsor representatives may also assist the team in equipment setup prior to and during a procedure.

[redacted]

Clinical Investigation Plan

Figure 1: Study Flow Diagram



Clinical Investigation Plan

Table 1: Schedule of Assessments – Phase 2

	Pre-procedure Assessments		Procedure Assessment	Post-procedure Assessments						
Activity	*Screen & Enroll*	*Baseline*	*Implant*	*Pre-Discharge Assessment*	*2-week Follow-up Visit[1]*	*6-week Follow-up Visit[1]*	*3-month Follow-up Visit[2]*	*6-month [2]*	*Every 6-months until study completion[3]*	*Additional Visits*
Inclusion Exclusion	✓									
Informed Consent	✓									
Pregnancy Assessment/Test	✓									
Medical History/Patient Status		✓								
Baseline Assessment		✓								
Procedure			✓							
Post-procedure Pre-discharge				✓						
Aveir LP Assessment and Programming			✓	✓	✓	✓	✓	✓	✓	✓
12-lead ECG		✓		✓						
X-ray of a pacemaker				✓						
Follow-up Visit					✓	✓	✓	✓	✓	✓
Sensor Optimization exercise test 6MWT [4]					(✓)	(✓)	(✓)	(✓)	(✓)	(✓)
Graded exercise test CAEP Protocol [5]						(✓)	(✓)	(✓)	(✓)	(✓)
EQ-5D patient survey		✓		✓	✓	✓	✓	✓		
Additional CRFs (when applicable)										
Adverse Event			✓	✓	✓	✓	✓	✓	✓	✓
Device Deficiency			✓	✓	✓	✓	✓	✓	✓	✓
Deviation		✓	✓	✓	✓	✓	✓	✓	✓	
Study Withdrawal			✓	✓	✓	✓	✓	✓	✓	✓
Product Out of Service			✓	✓	✓	✓	✓	✓	✓	✓
System Revision				✓	✓	✓	✓	✓	✓	✓
Death			✓	✓	✓	✓	✓	✓	✓	✓
COVID-19 Assessment Log			✓	✓	✓	✓	✓	✓	✓	✓
Healthcare Utilization				✓	✓	✓	✓	✓	✓	✓

1 ±7 days

[redacted]

2 ±30 days
3 ±45 days
4 All capable subjects are asked to perform a 6-minute walk test (6MWT) until approximately 30 subjects provide data contributing to the analysis. The preferred time period to perform the 6MWT is anytime from the beginning of the 2-week visit. The parenthesis indicates that this test is not required for all subjects and is not required for each visit.
5 All capable subjects are asked to perform a CAEP treadmill test until approximately 30 subjects provide data contributing to the analysis. The preferred time period to perform the CAEP treadmill test is anytime from the beginning of the 6-week visit. The parenthesis indicates that this test is not required for all subjects and is not required for each visit.

[redacted]

3.5.1 Enrollment Requirements

3.5.1.1 Recruitment and Enrollment

Candidates for this clinical investigation include patients indicated for a VVI(R) pacemaker. Pre-enrollment records will include evidence of diagnosis indicating need for VVI(R) pacemaker. For the Leadless II study, it is the sponsor's intention that the enrolled subject population be as representative as possible of the eligible population. Physician investigators are strongly encouraged to evaluate all consecutive eligible subjects for participation in the study and, if inclusion and exclusion criteria are met, to approach all eligible subjects, regardless of gender.

[redacted]

Screen subjects as outlined by the inclusion/exclusion criteria. Obtain informed consent from the subject. Investigator will not start any study-specific procedures or alterations of patient care until the informed consent process has been completed and investigator obtains a signed Informed Consent Form.

Collect data on the subject, including gender, age, ethnicity, race, cardiac disease history, cardiac medications (beta blockers, ACE, ARB, anti-platelets, anti-arrhythmics, anti-coagulants), arrhythmia history, patient status, and indication for pacemaker implant. Subjects who sign an IRB/EC-approved informed consent and have an attempted implant will be considered enrolled in the study.

Once eligibility screening is completed, subject provides informed consent, and the investigator implants the Aveir device—or attempts to implant—complete and submit the forms listed under the Implant Procedures to sponsor.

3.5.1.2 Subject Numbering

An identification (ID) number will identify enrolled subjects. [redacted]

[redacted]

3.5.1.3 Enrollment of Medicare Beneficiaries (US only)

This clinical trial will enroll appropriate Medicare beneficiaries that qualify based on the inclusion and exclusion criteria set forth in the trial. This IDE clinical trial adheres to all standards of Medicare coverage requirements set forth by the Coverage with Evidence Development (CED) for National Coverage Determination (NCD) 20.8.4, Leadless Pacemakers and clinical trial coverage policies of the Center for Medicare and Medicaid Services (CMS). Section 10, Risks Analysis section, describes how all enrolled subjects, including Medicare beneficiaries, may be affected by the device under investigation.

Subjects enrolled in the clinical investigation are expected to be consistent with the Medicare population based on age range, demographic characteristics and cardiovascular risk factors representative of the Medicare patient population, so as such, the clinical investigation results are expected to be generalizable to the Medicare population.

3.5.1.4 Historically Under-Represented Demographic Subgroups

The Sponsor intends to implement FDA's guidance on sex-specific data in medical device clinical investigations to ensure adequate representation of women and other traditionally under-represented demographic subgroups in this clinical investigation. As noted in the guidance, some barriers to participation of women and ethnic minorities in clinical investigations have traditionally been:

- Lack of understanding about main obstacles to participation of such subgroups in clinical research
- Inclusion/exclusion criteria potentially not needed to define the clinical investigation population may unintentionally exclude specific subgroups
- Under diagnosis of disease etiologies and pathophysiology leading to under referral of demographic subgroups
- Avoidance of specific subgroups by investigators and Sponsors due to the perception that it takes more time and resources to recruit them
- Fear of fetal consequences (for female participants)
- Family responsibilities limiting women's ability to commit time for follow-up requirements

[redacted]

[2] Vivek Y. Reddy, et al. Percutaneous Implantation of an Entirely Intracardiac Leadless Pacemaker. NEJM. 2015; 373:1125-1135.

[redacted]

The Sponsor will take the following steps to ensure adequate representation of women and racial or ethnic minorities in this clinical investigation:

- The Sponsor will provide training to investigational site personnel to ensure adequate representation of these demographic subgroups
- The Sponsor will regularly review enrollment data to investigate whether there is under-representation of these demographic subgroups
- The Sponsor will regularly review withdrawal rates for under-represented subgroups and compare these rates with that in the overall clinical investigation population
- As appropriate and necessary, the Sponsor will retrain sites on the importance of recruiting and retaining subjects in the clinical investigation
- The Sponsor will approach sites without bias or consideration for specific demographic subgroups
- The Sponsor will have informed consent materials in alternative languages and will work with sites and IRBs/ECs on recruitment materials

3.5.2 Baseline Assessment

Investigator will record subject's medical history on the Enrollment Form. Investigator will record the subject's baseline EQ-5D survey responses prior to implant on the EQ-5D Form. Investigator will record specific cardiac medications (beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics) given to the subject during the same hospital stay as the procedure, as well as during the follow-up period. All subjects will undergo standard laboratory assessment per site's standard of care. For female subjects of childbearing age, investigator will document a pregnancy assessment, which may include obtaining a blood sample for conducting a pregnancy test.

3.5.2.1 Medications

Investigator will administer all medications per hospital standard of care for pacemaker implant and femoral venous catheterization procedures. Use of anticoagulation medications is not required with the implantation of the Aveir

device. Investigator will record beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics given during procedure.

3.5.3 Implant Procedure

3.5.3.1 Femoral Vein Assessment and Access

Turi (2005, 2008), Abu-Fadel *et al* (2009), Seto *et al* (2010), and Fitts *et al* (2008) have shown that physicians can minimize access-site complications by using ultrasound guidance or fluoroscopic guidance when accessing vessels in the groin.[3-7] Although sponsor supports using either technique for assessing femoral vein access-site location, size and presence of disease, investigator will use medical judgment and follow institutional standard of care when accessing the femoral vein during catheter-based procedures.

The ideal puncture site should be located **below the inguinal ligament and above the bifurcation** (Refer to Figure 2).[5,8-10] Penetrate the skin and puncture the femoral vein using the Seldinger technique. Due to the introducer sheath size, investigator may need to "nick and spread" the tissue at the access-site location to allow for easier transition of the introducer sheath through the tissue tract.

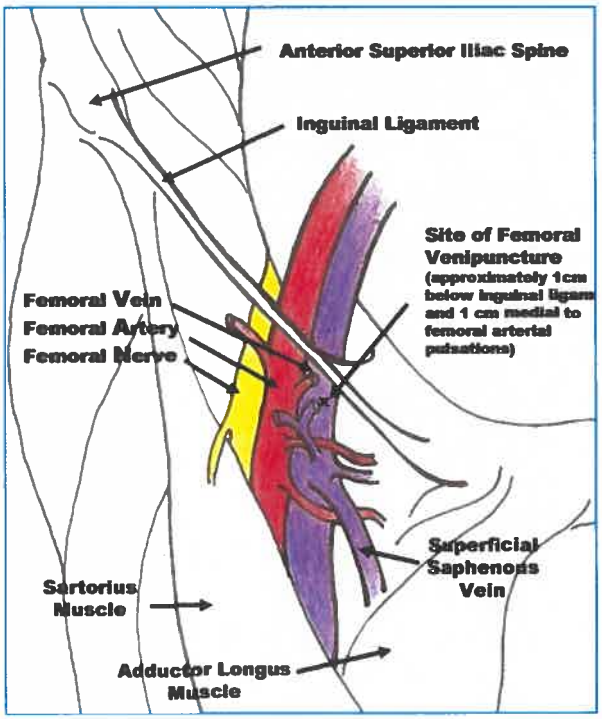


Figure 2. Location of femoral vein in relation to femoral artery, inguinal ligament and femoral head

3.5.3.2 LP Preparation and Implant

Investigator will prepare and implant the Aveir device in accordance with the manufacturer's instructions for use (IFU). Consult the IFU for implantation guidelines and general handling information. Only approved investigators will be responsible for performing the implant procedure, including placement of the Aveir device. Investigator will follow standard institutional catheter-based and pacemaker-lead implantation procedures, guidelines, and precautions.

3.5.3.3 LP Assessment and Programming

Investigator and/or sponsor will interrogate the Aveir LP using the market-approved St. Jude Medical™ Merlin™ Patient Care System (Model 3650) with the Leadless Link Module (Model LSL02). Investigator will measure and record the following parameters.

- Capture threshold at (0.4 ms)*
- Impedance
- R-wave amplitude*
- Battery voltage and remaining capacity to RRT
- Device Longevity

* *R-wave amplitude measurements are not required if the subject's intrinsic rate has been established to be below 30 beats per minute. Capture thresholds are not required if a high ventricular rate is present. Confirm at least three consecutive beats have capture before recording the capture threshold results.*

To avoid potential complications associated with under-sensing, Investigator shall program a sensing margin of at least two times the intrinsic cardiac amplitude (e.g., for an intrinsic R-wave of 4 mV, program the R-sensitivity ≤2 mV).

To avoid potential complications associated with loss of pacing capture, Investigator shall maintain pulse amplitude margin of at least two times the pacing threshold (e.g., for a pacing threshold of 0.5V, program the pulse amplitude ≥1.0V).

3.5.3.4 LP Repositioning and/or Release

Once the investigator implants the Aveir device and successfully demonstrates acute effectiveness, the investigator may release the Aveir device. Investigator may reposition Aveir LP, if necessary. For release and repositioning procedures, refer to the IFU. Once the Aveir LP has been released, investigator will use a retrieval catheter for removal, if needed (Refer to Retrieval Catheter IFU). Once the LP has been removed, investigator may attempt to implant another Aveir LP, or instead, choose to implant a market-approved pacemaker or ICD. When the investigator has released the Aveir LP, s/he will use fluoroscopy to assess positioning of the implanted LP.

3.5.3.5 Unsuccessful Implant

Investigators will follow subjects who have an unsuccessful implant for a period of 30 days to evaluate for adverse events. At the end of the 30 days, the investigator will withdraw the subject. The investigator must document the nature of the unsuccessful implant on the Implant Form. Subjects who have an unsuccessful implant will not be eligible for re-implantation attempts with the investigational device at a later date.

Data Submission

Once information has been collected and required testing has been completed at the implant visit, complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Enrollment Form (includes medications)
- Patient Status Form

- EQ-5D patient survey (baseline assessment prior to implant)
- Implant Form (includes medications)
- Aveir LP Assessment and Programming Form
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- Death Form, if applicable
- Product Out of Service Form, if applicable
- COVID-19 Assessment Log, if applicable

3.5.4 Aveir LP Retrievals and Replacement

When considering Aveir LP retrieval and replacement, investigators will refer to the respective IFUs.

In the event an Aveir LP must be removed during the clinical study follow-up period, investigators may opt to replace the Aveir LP in the following ways:

- Retrieve the first Aveir device and implant a new Aveir device,
- Deactivate the first Aveir device and implant a second Aveir device in close proximity to the first one, or
- Deactivate the first Aveir device and implant a traditional pacemaker or ICD with a lead.

Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- System Revision Form
- Healthcare Utilization Form
- Aveir LP Assessment and Programming Form, if applicable
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- Death Form, if applicable
- Study Withdrawal Form, if applicable
- Product out of Service Form, if applicable

- COVID-19 Assessment Log, if applicable

*If the subject has the Aveir LP removed at any time during the study, and the subject **will not** receive a replacement Aveir LP, follow the subject for 30 days, and withdraw the subject from the study. Complete and submit the following case report forms to St. Jude Medical, Sylmar, CA using the EDC system.*

- Study Withdrawal Form
- Product Out of Service Form
- Aveir LP Assessment and Programming Form, if applicable
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- Death Form, if applicable
- COVID-19 Assessment Log, if applicable

3.5.5 Post-procedure Assessments

The follow-up period is sufficient to demonstrate safety and effectiveness. Additionally, during this follow-up period, sponsor will identify any residual risks and complications.

Subjects will be seen at the following intervals:

- Pre-discharge assessment
- 2-week follow-up visit (in-office or clinic)
- 6-week follow-up visit (in-office or clinic)
- 3-months follow-up visit (in-office or clinic)
- 6-months follow-up visit (in-office or clinic)
- After completing the 6-month follow-up assessment, subjects will return every 6 months until study completion
- Subjects consent to continue in post-approval studies and will have follow-ups at least annually, until nine years after implant

Table 2: Follow-up Assessment Windows

Post Implant (Pre-Discharge)	**2-week follow-up**	**6-week follow-up**
0-2days	14 ± 7 days	42 ± 7 days
3-month follow-up	**6-month follow-up**	
90 ± 30 days	180 ± 30 days	
Every 6 months post 6-month visit until study completion		
Every 180 ± 45 days		

3.5.5.1 Access-site Management During Hospital Stay

Investigator will manage vascular-access sites per standard of care. Investigator will assess and document any post-procedural access-site bleeding event based on the following grading system.

ACCESS-SITE OOZING: Superficial bleeding of a cutaneous or subcutaneous origin characterized by diffuse localized bleeding and controlled with minimal care (e.g., application of manual pressure, application of sandbag).

ACCESS-SITE HEMATOMA: A localized collection of extravasated blood in subcutaneous tissue at the access site that does not require intervention. A metric ruler should be used to measure the widest portion of the hematoma.

ACCESS-SITE HEMATOMA REQUIRING INTERVENTION: A localized collection of extravasated blood in subcutaneous tissue at the access site that is considered life threatening and requires emergency wound exploration (e.g., acutely expanding hematoma, acute leg pain/numbness/swelling) and/or prolongation of hospital stay.

ACCESS-SITE RE-BLEEDING: Localized bleeding at the access site that occurs after hospital discharge. These bleeds are typically associated with an event (e.g., fall, attempted suture removal, physical activity).

3.5.5.2 Pre-Discharge Assessment

Investigator will assess all subjects at the implant center prior to hospital discharge, or within 2-days post implant, whichever is shorter. Investigation team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics;
- Measure and record Aveir LP performance, as described in 3.5.3.3 LP Assessment and Programming;
- Assess magnet mode;
- Program Aveir LP per physician discretion;
- Obtain a 12-lead electrocardiogram (ECG) with pacing ON;
- Obtain a posterior/anterior (P/A) and lateral view chest x-ray to assess final LP position;
- Investigator will use medical judgment and provide institutional standard of care for post-pacemaker-implant monitoring.
- Collect medical billing information for implant

Data Submission

Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Pre-Discharge Form (includes medication changes)
- Aveir LP Assessment and Programming Form
- Healthcare Utilization Form
- EQ-5D patient survey
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable
- COVID-19 Assessment Log, if applicable

3.5.5.3 2-week and 6-week follow-up visits

All subjects will return to the investigation site for a 14-day and 42-day (±7 days) follow-up visit. During this visit, investigation team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics;
- Measure and record LP performance, as described in 3.5.3.3 LP Assessment and Programming;
- Program Aveir LP and adjust programmable parameters of LP, as needed.
- 6 Minute Walk Test (6MWT)[3]
  - Administer 6MWT with rate-response feature in **VVIR ON** using the Rate Response Optimization function of the programmer (Refer to the 6 Minute Walk Test Protocol).
  - After completing 6MWT, use the Rate Response Optimization function of the programmer to model the response of the algorithm to the 6MWT protocol so that a peak sensor rate of approximately 100 beats/min is achieved. The results of this Rate Response Optimization are then used to adjust programmable sensor parameters of Aveir LP in preparation for the subsequent CAEP protocol.
- CAEP Protocol[4]
  - If the 6MWT is conducted the same day as the CAEP protocol, wait at least 1 hour after the 6MWT has been completed prior to starting the CAEP protocol.
  - The optimized sensor parameters resulting from the 6MWT are advised for the CAEP protocol, however, the physician has discretion to alter these parameters. Administer CAEP protocol with rate-response feature in **VVIR ON** mode (refer to CAEP protocol).
  - After completing the CAEP protocol, program Aveir LP and adjust programmable parameters of LP, as needed.

Data Submission

Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Follow-up Visit Form (includes medication changes)
- Aveir LP Assessment and Programming Form
- EQ-5D patient survey

[3] Administration of the 6MWT can be done any time between the 2-week and 6-week follow-up visit, (until 30 subjects contribute to the analysis).
[4] Administration of the CAEP protocol can be done any time between the 6-week and 3- month follow-up visit, (until 30 subjects contribute to the analysis).

- 6MWT Exercise Test Form, if applicable
- CAEP Exercise Test Form, if applicable
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable
- Healthcare Utilization Form, if applicable
- COVID-19 Assessment Log, if applicable

3.5.5.4 3-Month Visit

All subjects will return to the investigation site for a 90-day (±30 days) follow-up visit. During this visit, investigation team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics;
- Measure and record Aveir LP performance, as described in 3.5.3.3 LP Assessment and Programming;
- Program Aveir LP and adjust programmable parameters of LP, as needed;

Data Submission

Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Follow-up Visit Form (includes medication changes)
- Aveir LP Assessment and Programming Form
- EQ-5D patient survey
- Medications, if any changes
- 6MWT Exercise Test Form, if applicable
- CAEP Exercise Test Form, if applicable
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable

- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable
- Healthcare Utilization Form, if applicable
- COVID-19 Assessment Log, if applicable

3.5.5.5 6-Month Follow-up Visit

All subjects will return to the investigation site for a 180-day (±30 days) follow-up visit. During this visit, investigation team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics;
- Measure and record Aveir LP performance, as described in 3.5.3.3 LP Assessment and Programming.

Data Submission

Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Follow-up Visit Form (includes medication changes)
- Aveir LP Assessment and Programming Form
- EQ-5D patient survey
- 6MWT Exercise Test Form, if applicable
- CAEP Exercise Test Form, if applicable
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable
- Healthcare Utilization Form, if applicable

- COVID-19 Assessment Log, if applicable

3.5.5.6 Follow-up Visit Every Subsequent 6-Months until Study Completion

All subjects will return to the investigation site every 180-days (±45 days) follow-up visit. During this visit, investigation team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics;
- Measure and record Aveir LP performance, as described in 3.5.3.3 LP Assessment and Programming;
- Program Aveir LP and adjust programmable parameters of LP, as needed.

Data Submission

Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Follow-up Visit Form (includes medication changes)
- Aveir LP Assessment and Programming Form
- 6MWT Exercise Test Form, if applicable
- CAEP Exercise Test Form, if applicable
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable
- Healthcare Utilization Form, if applicable
- COVID-19 Assessment Log, if applicable

3.5.5.7 Unscheduled Follow-up Visits

If a subject returns to the investigational site for a visit that is related to the device or implant procedure, the research team will:

- Assess for adverse events and deviations from investigation plan;

- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics;
- As applicable, measure and record Aveir LP performance, as described in 4.5.3.3 LP Assessment and Programming;
- Program Aveir LP and adjust programmable parameters of LP, as needed.

Data Submission

Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Follow-up Visit Form (includes medication changes)
- Aveir LP Assessment and Programming Form
- 6MWT Exercise Test Form, if applicable
- CAEP Exercise Test Form, if applicable
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable
- Healthcare Utilization Form, if applicable
- COVID-19 Assessment Log, if applicable

4.0 Hospitalizations

All hospitalizations, outpatient services, emergency room and urgent care visits that are related to heart failure, cardiac/ non-cardiac reasons and LP implant/retrieval/replacement procedure(s) must be reported to St. Jude Medical via a Healthcare Utilization Form within 10 working days of the center becoming aware of the subject's admission to the hospital. The investigation team will submit the Healthcare Utilization Form and supporting documentation (i.e., Admission/Discharge Summary) to St. Jude Medical, Sylmar, CA using the EDC system.

5.0 Protocol Deviations

Investigators are required to adhere to the investigation plan, signed Investigator's Agreement, applicable federal or state/local, laws and regulations, and any conditions required by the IRB/EC, or FDA/other country regulatory agencies.

A protocol deviation is used to describe situations in which the investigation plan was not followed. Investigator must report all deviations from the investigational to sponsor per 21 CFR §812.150. In addition, investigator must report all deviations to the reviewing IRB/EC per the IRB's/EC's reporting requirements.

Investigator must notify sponsor and the reviewing IRB/EC of any deviation from the investigation plan to protect the life or physical well-being of a subject in an emergency as soon as possible, but not later than 5-working days after the deviation has occurred, or no later than 5-working days after the investigator becomes aware of the deviation.

6.0 Adverse Events

To comply with worldwide standards and guidelines on clinical investigation adverse event reporting, the Sponsor has adopted uniform and worldwide applicable standard definitions and reporting timelines to be used and adhered to by the investigators.

A Clinical Events Committee (CEC) will review and adjudicate all Adverse Events. The CEC will base their final adjudication on the information provided on the case report forms, medical records, and their clinical knowledge and experience.

Investigator will document all AEs on the Adverse Event Form, including (at a minimum) a description of the event, date of onset, relationship to the investigational device, required interventions, duration, and outcome. Investigator will monitor all AEs until they are resolved, determined to be a chronic condition or the subject is lost to follow-up. Investigator will report all AEs regardless of whether it is anticipated or unanticipated and regardless of classification, seriousness, outcome or causality. Investigator will document AE relatedness to COVID-19 on the Adverse Event Form and may provide the assessments from any COVID-19 diagnoses/tests on the COVID-19 Assessment Log, as applicable.

Should an AE occur, complete an Adverse Event Form and submit to sponsor. If an adverse event occurs between scheduled visits, report the event as soon as possible without waiting until the next scheduled visit. Report the adverse event to the IRB/EC per the IRB/EC policy. Investigator will return any retrieved devices to sponsor for analysis.

Serious Adverse Event (SAE) Reporting
The investigator should report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	SAEs must be reported to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined herein.

The date the site staff became aware of the event that met the criteria of an SAE, it must be recorded in the source document. The Investigator will further report the SAE to the local IRB/EC according to the institution's IRB/EC reporting requirements.

Unavoidable AEs are not reportable unless the condition worsens or continues beyond the time frame listed below. Unavoidable AEs, listed below, do not need to be reported if they are resolved within the time frame specified.

Table 3: Unavoidable AEs related to the Implant Procedure

Event	Time Frame post-Implant
Anesthesia related nausea/vomiting	<24 hours
Low-grade fever (<100 degree Fahrenheit fever or < 37.8 degree Celsius	< 48 hours
Percutaneous access pain	< 72 hours
Mild to moderate bruising/ecchymosis at percutaneous access site	< 72 hours
Sleep problems (insomnia)	< 72 hours
Back pain related to laying on the table	< 72 hours

If an **UNANTICIPATED (SERIOUS) ADVERSE DEVICE EFFECT** occurs, Sponsor requires the investigator to report any UADE/USADE to the Sponsor as soon as possible [21 CFR 812.150 (a) (1)], but within 3 calendar days [Sponsor's requirement] of the investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB/ECs per IRB/EC requirements. Sponsor will take any steps necessary to investigate the event and will be responsible for notifying FDA and all other participating IRBs/ECs and investigators.

Should sponsor determine, either through physician reports or in-house testing, that an unanticipated adverse event presents an unreasonable risk to participating subjects, sponsor will suspend the clinical investigation and notify all participating investigators, IRBs/ECs and FDA.

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Table 4: List of foreseeable adverse events and anticipated adverse device effects

*Access site bleeding event	
Air embolism	Intermittent capture
Angina pectoris	Interruption of desired pacemaker function due to electrical interference, either electromyogenic or electromagnetic
Arterial puncture	Keloid formation
AV fistula	Loss of normal device function due to battery failure or component malfunction
Bladder puncture	Muscle and nerve stimulation
Blood transfusion	Myocardial damage
Blunted or poor sensor response	Myocardial infarction
Body rejection phenomena	Myocardial irritability
Bowel penetration	Oversensing
Cardiac arrhythmias	Pacemaker syndrome
Cardiac dissection	Palpitations
Cardiac perforation	Pericardial effusion or rub
Cardiac tamponade	Pericarditis
Chronic nerve damage	Phrenic nerve/diaphragmatic stimulation
Damage to vessels	Pneumothorax/Hemothorax
Death	Premature battery depletion
Device dislodgment	Programmer/software anomaly
Dizziness	Pseudoaneurysm formation
Dyspnea	Psoas abscess
Embolism	Reaction to contrast
Endocarditis	Septic arthritis
Excessive Bleeding	Seroma
Exit block	Syncope
Failure to capture/loss of capture	Threshold elevation
Femoral nerve injury with resulting paresthesias	Thromboemboli
Heart Failure	Thrombosis
Hematoma formation, including retroperitoneal hematoma/hemorrhage	Undersensing
High impedance	Valve damage
Inability to interrogate or program due to programmer or device malfunction	Venous occlusion

Inability to disengage snare from docking button	
Induced ventricular ectopy or arrhythmias	Venous perforation
Infection, local at access site, or systemic	Ventricular ectopy
Insufficient cardiac output	Ventricular tachycardia

***Access site bleeding event is defined in sections 3.5.5.1.**

A right ventriculogram carries risk, most notably, allergic reaction to contrast media.

6.1 Device Deficiencies/Malfunctions

Sites should report all device deficiencies/malfunctions on the appropriate CRF form.

The investigator must report all device deficiencies/malfunctions to the Sponsor as soon as possible but no later than outlined below.

Clinical Sites	Reporting timelines
All Sites	Sites must report device deficiencies/malfunctions to the Sponsor no later than 3 calendar days from the day the site personnel became aware of the event or as per the investigative site's local requirements, if the requirement is more stringent than those outlined.

Sites must report device deficiencies/malfunctions to the IRB/EC per the investigative site's local requirements.

Sites should return the device, if not implanted or not remaining in the subject, to the Sponsor.

6.2 Adverse Event Reporting to Country Regulatory Authorities by the Sponsor

The Sponsor will report SAEs and reportable device deficiencies/malfunctions to the country regulatory authority, per local requirements.

Note: Reportable device deficiencies/malfunctions include device deficiencies/malfunctions that might have led to an SAE if a) suitable action had not been taken or b) intervention had not been made or c) if circumstances had been less fortunate. These are handled under the SAE reporting system.

7.0 Deaths

All subject deaths that occur during this study must be reported to St. Jude Medical within 3 calendar days of the center being notified (Refer to SAE Reporting in Section 6.0). Notification of a death should include a detailed statement of the pertinent events and be signed by the investigator in addition to the completion of the appropriate forms (Death form, Withdrawal form, and Product Out of Service form) and submitted to St. Jude Medical, Sylmar, CA using the EDC system. It is the investigator's responsibility to notify the IRB/EC per the IRB/EC policy.

- Date and time of death
- Place death occurred (e.g. hospital, nursing home, subject's home)
- If death was witnessed
- Identification of the rhythm at the time of death, if known (include any available documentation)
- Cause of death
- Any other circumstances surrounding the death
- Approximate time interval to death from the initiating event
- Autopsy report (if performed)
- Whether it was device and/or procedure related
- Whether it was related to the study

If any of the above information is not available, investigator will provide an explanation in the death narrative of what attempts (and how many) were made to obtain the information, and the outcome of those attempts. At a minimum, investigator will place two (2) phone calls, followed by a certified letter, to the subject's next of kin and provide clinical notes and witness statements. If possible, interrogate the pacemaker. Retrieve and print all episode diagnostics, and programmed parameters. If applicable, the pacemaker should then be programmed **OFF.** Attempt to explant the pacemaker and return any explanted devices to sponsor for analysis promptly. Clearly state on Case Report Form the reason the pacemaker is not being returned to sponsor.

8.0 Committees and Core Laboratories

8.1 Data and safety monitoring board (DSMB)

Sponsor will establish an independent DSMB to review safety data. The DSMB will consist of at least 3 members with study-related backgrounds. Members will include at least one statistician and two cardiologists with pacemaker experience. St. Jude Medical will appoint members of the DSMB and the chairperson. St.

Jude Medical may provide administrative support to DSMB meetings, but will not be a voting member and will not be present during closed portions of the meeting. Non-DSMB members are not allowed to be present during DSMB closed meetings. Refer to the DSMB Charter.

Sponsor will provide to FDA/other country regulatory agency within 10 working days of receipt copies of written communication from the DSMB that relates to safety concerns, or changes to the study plan, procedures or informed consent document. Sponsor will provide the DSMB within 10 working days copies of any letter from FDA or other country regulatory agency that relates to safety concerns, or changes to the study plan, procedures or informed consent document.

8.2 Clinical events committee (CEC)

Sponsor will establish an independent CEC to review all adverse events. The CEC's role is to determine relationship of event to device and or procedure. The CEC will consist of at least 3 members with study-related backgrounds. Members will include cardiologists with pacemaker experience. St. Jude Medical will appoint members of the CEC and the chairperson. St. Jude Medical may supply study information and provide administrative support for CEC meetings, but will not be a voting member. Refer to the CEC Charter.

9.0 Withdrawals

Withdrawal is defined as termination of a subject's participation from the clinical trial. All reasonable efforts should be made to retain the subject in the clinical trial until completion of the clinical trial. All reasons for withdrawal will be documented. Reasons for withdrawal include, but are not limited to the following:

- Subject Death
- Subject and/or Family Request representing withdrawal of consent
- Subject Lost to Follow-Up: Subject will be considered "lost to follow-up" after a minimum of 2 documented phone calls by personnel at the investigational center to the subject or emergency contact, a certified letter is sent to the last known address and two consecutive visits pass without the investigator receiving data.
- Subject Participation terminated by investigator based on the best medical interest of the study subject
- LP explanted and not reimplanted
- Unsuccessful Implant
- LP abandoned and Aveir LP not re-implanted

[redacted]

A Withdrawal Form will be completed and submitted to St. Jude Medical, Sylmar, CA using the EDC system.

10.0 Risk Analysis

St. Jude Medical addresses the risk of poor usability of the programmer through a usability engineering process complying with EN 62366:2007.

St. Jude Medical has implemented a risk management process in conformance with EN ISO 14971:2012. The application of this risk management process to the leadless pacemaker system is documented in a risk management file. The risk management file also includes a risk management plan (St. Jude Medical's standard operating procedure for risk management).

This risk management process includes risk analysis, risk evaluation, and risk control. These are documented for the leadless pacemaker system in a top-down system hazard analysis; bottom-up failure mode effects analyses for the pacemaker, catheters, programmer and introducer; software safety analyses for the pacemaker and programmer; annual reviews of post-production information on similar devices; and a system risk management report. These bottom-up analyses provide risk analysis for single component failure as required by EN 45502-1:1997 §19.3.

10.1 Product-related risks

St. Jude Medical conducted system hazard analysis for the LP system. This analysis found that the system employed state of the art therapy and materials. Failure-mode-effects analyses of each device in the system confirmed that the level of risk is as expected for pacing systems. Thus, the risk assessment focused on the potential influence of novel design features: implantation procedure; access site; fixation characteristics; absence of lead, connector, and antenna; device retrieval; and conductive communication with programmer Link. St. Jude Medical's risk assessment identified uncertainties relating to product-specific risks, such as those associated with percutaneous delivery via a femoral vein, and dislodgement or migration. The need for product-specific risk-control measures was identified, such as fixation optimization and warning of risk for subjects with pulmonary arterial hypertension or lung disease.

10.2 Clinical risks

St. Jude Medical's risk assessment following the system hazard analysis concluded that the subject population and delivered therapy are essentially the same as those of existing VVIR therapy. Thus, existing clinical evidence addresses proof of concept of therapy and supports the view that clinical risks should be the same as those seen with comparable existing products.

The follow-up period of 6-12 months is consistent with the follow-up duration of comparable devices in studies for regulatory approval, which in turn was determined by the well-known maturation time of the interface between the electrode and myocardium, which is typically reached by three months[5]. Animal study, human clinical trial results and feedback from physicians indicate that the delivery, implantation and retrieval procedures will not expose the subject, the physician or third parties to radiation in excess to that from implantation of a conventional single chamber pacemaker and lead.

10.3 Anticipated clinical benefits

Implantation of the LP for cardiac pacing could offer certain advantages as compared to a conventional pacemaker. Specifically, the benefits that are associated with the use of the LP could include:

- Precise and repeatable procedure;
- Percutaneous procedure (potential outpatient procedure);
- Eliminates the need for lead (no risk of lead fracture, lowers risk of infection);
- Eliminates the need for a pocket (lowers risk of infection, no need for scar and/or lump);
- Eliminates the need for connectors (eliminates connector complications);
- Eliminates the visible lump and scar at a conventional pacemaker's pectoral implant site;
- Could lessen the need for activity restrictions after implantation;

10.4 Benefit/risk assessment

It is concluded from preclinical data (risk analysis and literature review) that clinical risks are comparable to those associated with currently available therapy. Uncertainty exists in relation to risks associated with novel features (percutaneous delivery via a femoral vein and the possibility dislodgement or migration). These residual risks cannot be estimated with confidence without data from a clinical investigation. Taking into account the nature of the possible harm that could arise from these device-related risks and the assurance provided by pre-clinical data, the risk-benefit balance associated with the use of the LP in a clinical trial is considered to be favourable.

[5] Hayes DL, Friedman PA, Cardiac pacing, defibrillation, and resynchronization: a clinical approach, Wiley 2011,

10.5 Conclusions from pre-clinical risk evaluation

Clinical investigation needs to confirm safety and performance of novel design features. The basis for design of this investigation may be summarized as follows:

- Most design features are equivalent to existing products and will have been verified by pre-clinical evaluation.
- Literature shows that for conventional pacemakers, approximately 96% of subjects are event-free at 6-months.
- Risk analysis indicates novel features should not be associated with significant residual risks or complications.
- It is not possible to design a clinical investigation to investigate low-level or unexpected risks, on the basis of a statistical analysis.
- The objective should be to identify a flaw in the pre-clinical risk analysis, exposing the minimum number of subjects to the risk.

It is concluded that the results of the pre-clinical evaluation justify the design of the clinical investigation to determine whether the LP is suitable for the purpose and the population for which it is intended. The clinical investigation has been designed to ensure that the results obtained have clinical relevance and scientific validity and address the clinical investigation objectives.

11.0 Investigator Information

This clinical investigation will be conducted by investigators with experience and/or willingness to be trained in the use of the device therapy for the treatment of bradyarrhythmias. An investigator should have experience in and/or will be responsible for:

- Conducting the clinical investigation in accordance with the signed agreement with sponsor, the investigation plan, all applicable FDA regulations (21 CFR Parts 50, 54, 56, 812) or other country regulatory agency requirements, GCP guidelines, and any conditions of approval imposed by the IRB/EC
- Providing signed Investigator's Agreement
- Providing signed Financial Disclosure Form
- Providing IRB/EC-approved Informed Consent
- Collection and archiving of data obtained pursuant to the requirements of the investigation plan during the course of the study and after the study has been completed
- Strict adherence to the investigation plan testing requirements
- Screening and selecting appropriate subjects.

It is acceptable for the principal investigator to delegate one or more of the above functions to an associate or co-investigator, however, the principal investigator remains responsible for the proper conduct of the clinical investigation, complying with the investigation plan and collecting all required data. In clinical investigations involving active implantation of an investigational product, the investigation is not transferable to other implant centers attended by the investigator unless prior approval is obtained from sponsor.

The clinical investigation will be financed by the Sponsor. Investigational sites will be compensated by the Sponsor for participation in the clinical investigation per the conditions of agreement between the Sponsor and the Investigational site.

12.0 Monitoring Procedures

St. Jude Medical (now Abbott) will serve as the sponsor of the LEADLESS II clinical investigation. It is the responsibility of St. Jude Medical as the sponsor of the study to ensure proper monitoring of the investigation and to see that all the clinical requirements are met.

Prior to beginning the study, sponsor personnel will contact the investigator or designee to discuss the investigation plan and to review the data requirements in

detail. A monitor will visit the investigator or designee periodically during the study to monitor progress, to assist in gathering the required data and to answer any questions. During these visits, the clinical monitor will review the subject's records to verify that all records and files are up to date, and to assure compliance with all requirements of the protocol and FDA regulations or other regulatory agency regulations.

The investigator will make subject and study records available to the clinical monitor for periodic inspection. Sponsor and/or designee will monitor the clinical investigation over its duration according to the CIP-specific monitoring plan which will include the planned extent of source data verification.

Responsibility for overall study management will be held by the DVP, Global Clinical Affairs, St. Jude Medical.

Clinical Studies Department
St. Jude Medical (now Abbott)
15900 Valley View Court
Sylmar, CA 91342
TEL: +1 (818) 493-3297
FAX: +1 (800) 254-6411

12.1 FDA or Other Country Regulatory Agency Inspections

The investigator and/or designee should contact sponsor within 24 hours upon being notified of an impending FDA or other country regulatory agency inspection. A clinical monitor may assist and review study documentation with the investigator and/or designee to prepare for the audit.

An investigator shall permit authorized FDA or other country regulatory agency employees, at reasonable times and in a reasonable manner, to enter and inspect any establishment where investigational devices are used and to inspect and copy all records relating to an investigation.

An investigator shall permit authorized FDA or other country regulatory agency employees to inspect and copy records that identify subjects, upon notice that FDA or other country regulatory agency has reason to suspect that adequate informed consent was not obtained, or that reports required to be submitted by the investigator to the sponsor or IRB/EC have not been submitted or are incomplete, inaccurate, false, or misleading.

13.0 Labeling

Sponsor will provide all implants and accessories with labels in USA stating, **"CAUTION--Investigational device. "Limited by Federal (or United States) law to investigational use."** Sponsor will also provide implants and accessories for use in other countries with appropriate country-specific labeling.

Sponsor will provide all implants and catheters as sterile units, and the packaging lists the method of sterilization, manufacturing date, manufacturer name and address, use before date, that devices are single use only, model number, and lot or serial number.

The programmer and accessories' labels contain the company name, location and phone number, model number, and lot or serial number.

Software versions are displayed on the programmer screen and in printed or saved reports. Validated changes to implant and programmer software are allowed during the study, when necessary, to correct an observed nonconformance with intended device operation.

Leadless implants, catheters and programmers will be stored in a clean, dry, secure location at room temperature prior to shipment to the clinical site.

14.0 Consent Materials

All subjects will be consented for nine-year follow-up, so that they can additionally contribute to post-approval studies. Refer to sample consent form, Patient Informed Consent.

Failure to obtain informed consent from a subject prior to study enrollment should be reported to sponsor within 5 working days and to the reviewing IRB/EC consistent with the IRB's/EC's reporting requirements.

15.0 IRB/EC Information

IRB/EC approval for the study and informed consent will be required prior to beginning the study. A copy of the IRB/EC approval and corresponding informed consent must be forwarded to sponsor prior to authorization of the institution to begin the study. Any withdrawal of IRB/EC approval should be reported to sponsor within 5 working days of the withdrawal of approval.

Any amendments to the CIP as well as associated ICF changes will be submitted to the IRB/EC and written approval obtained prior to implementation, according to each institution's IRB/EC requirements.

No changes will be made to the CIP or ICF or other written information provided to the patient without appropriate approvals, including IRB/EC, the Sponsor, and the regulatory agencies (if applicable).

A list of IRBs/ECs for Institutions participating in the clinical investigation will be provided upon request.

16.0 Other Institutions

The name and address of each institution, at which a part of the investigation may be conducted, that has not been identified under IRB/EC information, will be provided upon request.

17.0 Records and Reports

Clinical investigators are required to maintain all study records, prepare and submit reports, and permit FDA Bioresearch Monitoring Inspections or other country regulatory agency monitoring inspections relating to the investigator's participation in and conduct of the study, as described in 21 CFR §812.150. Sponsor will provide study data to the FDA on an annual basis or as requested by the FDA. Sponsor will provide study data to other country regulatory agencies at specified intervals or as requested by each regulatory agency.

17.1 Custody

An investigator may withdraw from the responsibility to maintain records for the period required and transfer custody of the records to any other person who will accept responsibility for them as described, including the requirements regarding FDA or other country regulatory agency inspection. Notice of transfer shall be given to sponsor and FDA/other country regulatory agency no later than ten working days after transfer occurs.

17.2 Data Handling

Sponsor and/or its affiliates will maintain documentation of the systems and procedures used in data collection for the duration of the clinical investigation.

CRF data collection will be performed through a secure web portal and only authorized personnel will access the Electronic Data Capture (EDC) system using a unique username and password to enter, review or correct data. Passwords and electronic signatures will be strictly confidential.

The data will be subjected to consistency and validation checks within the EDC system and supplemental review by the Sponsor.

At the conclusion of the clinical investigation, completed CRF images with the date-and-time stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be provided to the investigational sites.

For the duration of the clinical investigation, the Investigator will maintain complete and accurate documentation including, but not limited to, medical records, clinical investigation progress records, laboratory reports, CRFs, signed ICFs, device accountability records, correspondence with the IRB/EC and clinical investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation.

17.3 Protection of Personally Identifiable Information

The Sponsor respects and protects personally identifiable information collected or maintained for this clinical investigation.

The Sponsor implements technical and physical access controls to ensure that Personal Information is accessible only to and processed only on a 'need to know' basis, including periodic review of access rights, and revocation of access when an individual's employment is terminated or the individual transitions to a role that does not require access to Personal Information, and appropriate restrictions on physical access to premises, facilities, equipment, and records containing Personal Information.

The Sponsor requires the investigational sites to transfer into Sponsor's data management systems only pseudonymous Personal Information (key-coded) necessary to conduct the Clinical Investigation, such as the patient's medical condition, treatment, dates of treatment, etc. The Sponsor discloses as part of the clinical investigation informed consent process that some Sponsor representatives still may see Personal Information at the participating sites for technical support of the participating physicians on the device implant or procedures, monitoring and quality control purposes. Confidentiality of Personal Information will be observed by all parties involved at all times throughout the clinical investigation. The privacy of each subject and confidentiality of his/her information will be preserved in reports and when publishing any data.

The Sponsor data management systems and processes were designed, developed, and tested according to industry standards to appropriately safeguard Confidential Information (including any Personal Information) against unauthorized access and/or interference by third parties, intrusion, theft, destruction, loss or alteration. Clinical Investigation data are encrypted in transit and at rest.

The Sponsor maintains a Privacy Incident procedure that complies in all respects with Applicable Law and industry best practices.

17.4 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, and issuing and resolving data discrepancies. If appropriate, the DMP may be updated throughout the duration of the clinical investigation. All revisions will be tracked and document controlled.

17.5 Source Documentation

Regulations and GCP require the Investigator to maintain information in the subject's original medical records that corroborates data collected on the CRFs. In order to comply with these regulatory requirements/GCP, the following information should be included in the subject record at a minimum and if applicable to the clinical investigation:

- Medical history/physical condition of the subject before involvement in the clinical investigation sufficient to verify CIP entry criteria
- Dated and signed notes on the day of entry into the clinical investigation referencing the Sponsor, CIP number, subject ID number and a statement that informed consent was obtained
- Dated and signed notes from each subject visit (for specific results of procedures and exams)
- Adverse events reported and their resolution, including supporting documents, such as discharge summaries, catheterization laboratory reports, ECGs, and lab results including documentation of site awareness of SAEs and of investigator assessment of device relationship for SAEs.
- CIP-required laboratory reports and 12-lead ECGs reviewed and annotated for clinical significance of out of range results (as applicable).
- Notes regarding CIP-required and prescription medications taken during the clinical investigation (including start and stop dates)
- Subject's condition upon completion of or withdrawal from the clinical investigation
- Any other data required to substantiate data entered into the CRF
- Patient reported outcome measures may be completed using CRF worksheets. These serve as the source documentation.

17.6 Case Report Form Completion

Primary data collection based on source-documented hospital and/or clinic chart reviews will be performed clearly and accurately by site personnel trained on the CIP and CRF completion. The investigator will ensure accuracy, completeness, legibility and timeliness of the data reported to the Sponsor on the CRFs and in all

required reports. Data on CRFs will be collected for all subjects that are enrolled into the clinical investigation.

17.7 Retention Period

Investigator is required to maintain records during the investigation and for a period of two years, or as per the applicable regulatory record retention requirements, after the date on which the investigation is terminated or completed. Sponsor will maintain records until they are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

17.8 Investigational Devices Accountability

The Sponsor ships investigational products only to the Principal Investigator (the responsible leader of the investigational site) or his/her legal designee of each site, after sites receive documentation of site activation and shipping authorization is complete.

The Investigator or an authorized designee must maintain adequate records of the receipt and disposition of each investigational device, including part number, batch number, and serial number (if applicable), date used, subject identification, and treating physician.

The Sponsor requires clinical sites to store all investigational products according to the labeling and Instructions for Use in a secure area to prevent unauthorized access or use. Storage locations for the devices at investigational sites must be locked with access restricted only to investigators and authorized personnel.

All investigational devices that are associated with a device failure or device deficiency must be returned immediately to the Sponsor.

18.0 Publications

The data and results from the clinical investigation are the sole property of the Sponsor. The Sponsor shall have the right to access and use all data and results generated during the clinical investigation. The Investigators will not use clinical investigation-related data without the written consent of the Sponsor for any purpose other than for clinical investigation completion or for generation of publication materials, as referenced in the Clinical Trial Agreement. Single-center results are not allowed to be published or presented before the multi-center results. Any proposals for publications or presentations by the investigators must be reviewed and approved by the Sponsor in a timely manner to enable Sponsor review in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement.

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The Sponsor will register this clinical investigation on www.clinicaltrials.gov, in accordance with the International Committee of Medical Journal Editors guidelines, or any other applicable guidelines. Sponsor shall be responsible for any such registration and results posting as required by the ClinicalTrials.gov website. Institution and/or Principal Investigator(s) shall not take any action to register the clinical investigation. A full report of the pre-specified outcomes, regardless of the results, will be made public through the ClinicalTrials.gov website no later than 12 months after clinical investigation completion, as required by section 801 of the FDA Amendments Act. If this clinical investigation is terminated early, the Sponsor will make every effort to hasten the release of the pre-specified outcomes through the ClinicalTrials.gov website.

19.0 Appendix I: Abbreviations and Acronyms

Abbreviation	Definition	Abbreviation	Definition
2°	Second degree	EP	Electrophysiology
3°	Third degree	ESC	European Society of Cardiology
6MWT	Six-minute walk test	ICD	Implantable cardioverter defibrillator
ACC	American College of Cardiology		
ACT	Activated clotting time	IFU	Instructions for use
ADL	Activities of daily living	INR	International normalized ratio
AE	Adverse event	IRB	Independent or institutional review board
AHA	American Heart Association	LP	Leadless pacemaker
		MET	Metabolic Equivalent of Task
AV	Atrioventricular	MRI	Magnetic resonance imaging
BBB	Bifascicular bundle branch	PA	Pulmonary arterial
CAEP	Chronotropic assessment exercise protocol	PtIr	Platinum Iridium
CFR	Complication free rate	RR	Rate response
CIP	Clinical investigation plan (also referred to as clinical protocol)	RV	Right Ventricle
CRF	Case report form	SAE	Serious adverse event
CRT	Cardiac resynchronization therapy	TiN	Titanium nitride
EC	Ethics Committee	UADE	Unanticipated adverse device effect
ECG	Electrocardiogram		
EGM	Electrogram	USADE	Unanticipated serious adverse device effect

20.0 Appendix II: Definitions

Adverse Event: Any unfavorable clinical event which impacts or has the potential to impact the health or safety of a subject caused by or associated with a study device or intervention.

Complication: A device- or procedure-related serious adverse event, including any adverse event that prevents initial implantation.

Cardiac Tamponade: Confirmed or suspected accumulation of fluid in the pericardial space.

Cardiac Perforation: An excursion of the LP through the cardiac muscle. Signs and symptoms of a perforation by LP may include radiographic evidence of excursion of the LP into the pericardial sac, abnormal echocardiography indicative of a perforation, the accumulation of fluid in the pericardium, cardiac tamponade, or subject symptoms such as chest pain and discomfort.

Device deficiency: Any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

Device-malfunction: the failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed.

Diaphragmatic/Phrenic Nerve Stimulation: Electrical activation of the diaphragm muscle by the device output pulse. The abrupt diaphragmatic contraction is noted clinically as hiccups associated with each pacing stimulus. The pacing stimulus may stimulate the diaphragm either directly or indirectly via the phrenic nerve.

Dislodgement: The movement of the LP from its originally implanted position resulting in elevated pacing thresholds or a decrease in sensing.

Elevated Pacing Thresholds: Pacing thresholds > 2.5 V at 0.4 ms at implant. Following lead maturation at 6-8 weeks, an increase in pacing thresholds of 1.2 V at 0.4 ms or greater between visits. This definition is intended to serve as a guideline and it is understood that individual subjects may have unique situations.

Implant procedure duration: Defined as the time from delivery catheter and LP insertion to removal.

Implant success rate: Defined as the number of subjects leaving the implant procedure with an implanted and functioning LP device, divided by the number of subjects in whom implantation is attempted.

Loss of Capture: The inability of the device's output pulse to result in depolarization and contraction of the ventricle. Causes include insufficient stimulus strength, separation of the electrode from the myocardium and placement of the stimulating electrode in contact with a non-responsive portion of the myocardium such as scar tissue. Delivery of an output pulse at a time when the myocardium is physiologically refractory is not loss of capture, since capture is not physiologically feasible.

Loss of Sensing: A condition in which the pulse generator is unable to sense intrinsic cardiac signals.

Oversensing: The detection of inappropriate electrical signals by the pulse generator's sense amplifier. These signals, such as myopotentials, electromagnetic interference, or T waves must be of sufficient duration to interfere with normal device function.

Procedure duration: Defined as the time from femoral introducer insertion to removal.

Serious Adverse Event (SAE): Any untoward medical occurrence that:

a. Led to death,
b. Led to serious deterioration in the health of the subject, that either resulted in
    1. A life-threatening illness or injury, or
    2. A permanent impairment of a body structure or a body function, or
    3. In-patient or prolonged hospitalization, or
    4. Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function, or requires an invasive strategy to remedy, or
c. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

NOTE: Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

Sponsor understands that the following items meet the definition of serious adverse event if they require hospitalization or prolong hospitalization, even though an invasive approach may not be necessary to resolve: AV fistula, pseudoaneurysm, blood transfusions, tricuspid valve damage, pericardial effusion, pulmonary embolus, device dislodgement, right ventricular perforation, thrombus formation on the device, ventricular arrhythmias even if not associated with an invasive strategy to remedy.

Non-invasive means such as device re-programming do not meet the criteria for medical or surgical intervention.

Time to discharge: Defined as the time from introducer sheath removal to discharge.

Unanticipated (serious) adverse device effect (UADE/USADE): 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. [21 CFR 812.3(s)]

Unavoidable adverse event: An unavoidable AE is defined as an adverse event related to the implant procedure that is expected to occur for a projected duration in all subjects.

Undersensing: The failure of the pulse generator to sense R-waves, causing delivery of inappropriately timed, asynchronous or competitive output pulses. Undersensing can sometimes be corrected by programming the device to a more sensitive setting, i.e., decreasing the millivolt value.

21.0 Appendix III: Site Contact Information

Contact information for each participating clinical site is available under separate cover by contacting the Sponsor at:

Clinical Studies Department
St. Jude Medical (now Abbott)
15900 Valley View Court
Sylmar, CA 91342
TEL: +1 (818) 493-3297
FAX: +1 (800) 254-6411

22.0 Appendix IV: Graded Exercise Test (CAEP Protocol)

The Chronotropic Assessment Exercise Protocol (CAEP)

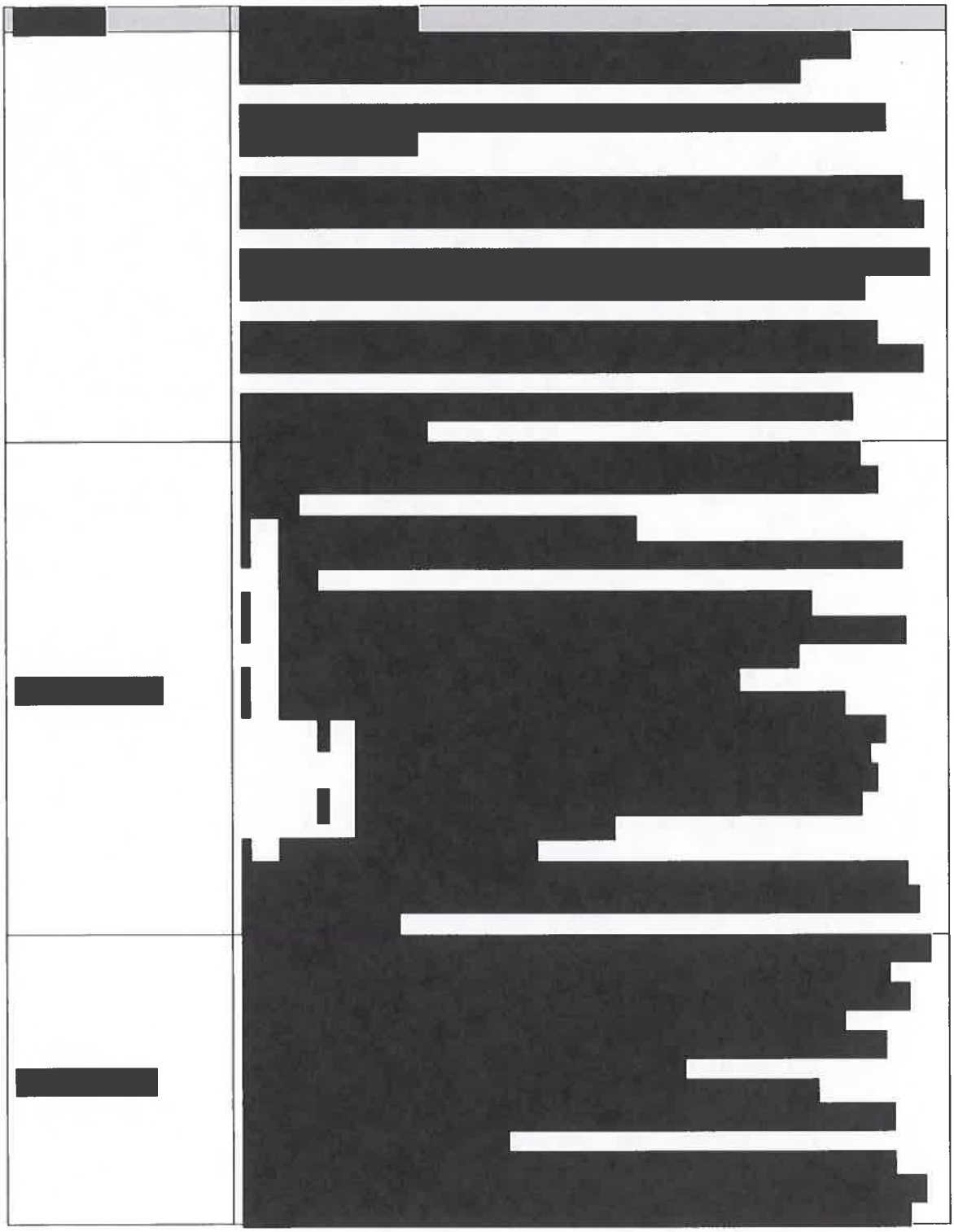
Stage	Speed (MPH)	Speed (KPH)	Grade (%)	Time (min)	Cumulative time	METs
0	1.0	1.6	0	2	2	1.5
1	1.0	1.6	2	2	4	2.0
2	1.5	2.4	3	2	6	2.8
3	2.0	3.2	4	2	8	3.6
4	2.5	4.0	5	2/	10	4.6
5	3.0	4.8	6	2	12	5.8
6	3.5	5.6	8	2	14	7.5
7	4.0	6.4	10	2	16	9.6
8	5.0	8.0	10	2	18	12.1
9	6.0	9.7	10	2	20	14.3
10	7.0	11.3	10	2	22	16.5
11	7.0	11.3	15	2	24	19.0

Source:

Wilkoff, B. L., Corey J., "A Mathematical Model of the Cardiac Chronotropic Response to Exercise", Journal of Electrophysiology, 3(3) June 1989, pages 176-180

23.0 Appendix V: CIP Revision History

Clinical Investigation Plan



Clinical Investigation Plan

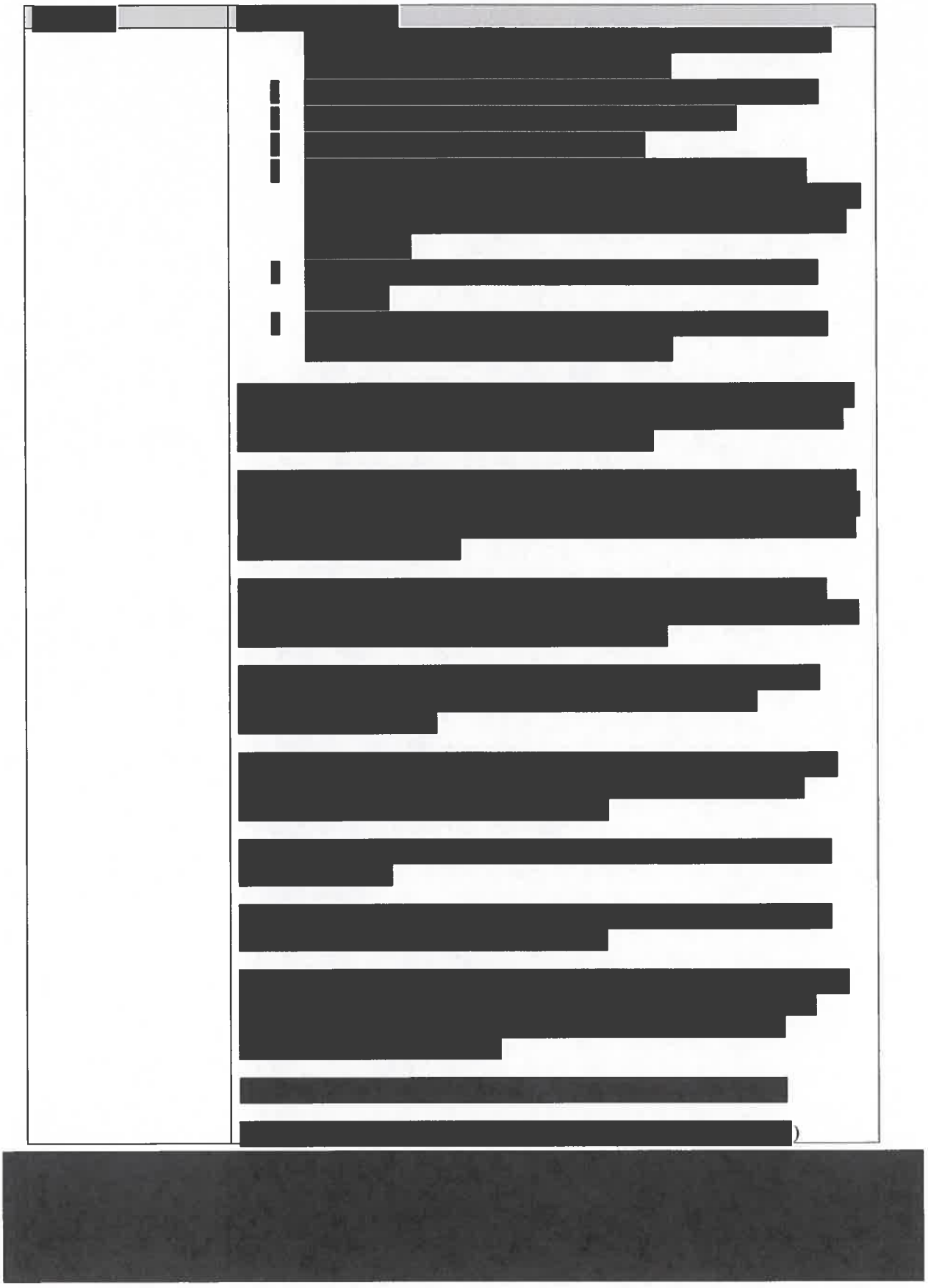
Revision #	Reason for Revision
	severe pulmonary disease producing frequent hospitalizations for respiratory distress or requiring continuous home oxygen)" Revised estimated schedule dates due to the addition of the CAP study: Last subject enrolled: November 2016 Last subject visit: December 2016 IP Section 6.3.2: Removed exclusion #4 to be consistent with the LP/Delivery [redacted]
[redacted]	[redacted]

Clinical Investigation Plan

Revision #	Reason for Revision
[redacted]	[redacted]

[redacted]

Clinical Investigation Plan



Clinical Investigation Plan

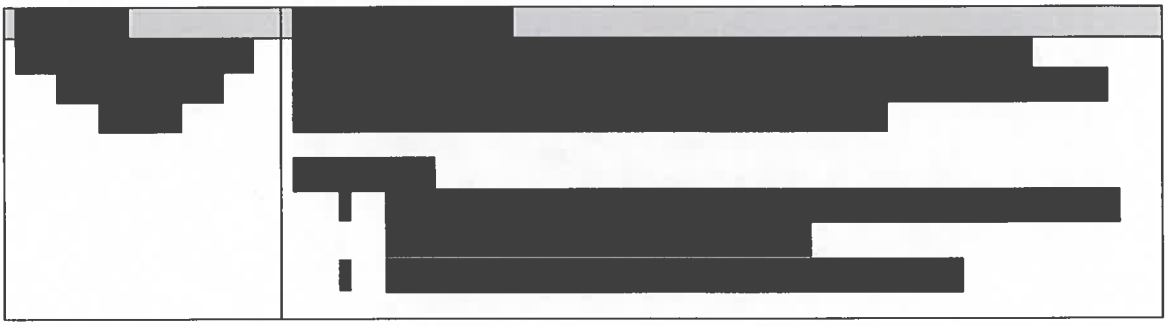
Revision #	Reason for Revision
	[redacted]

[redacted]

Clinical Investigation Plan

Revision #	Reason for Revision
[redacted]	• [redacted] [redacted] [redacted] [redacted]

[redacted]



24.0 Appendix VI: CIP Summary (Synopsis) – Phase 2

CIP Summary (Synopsis) – Phase 2	
Title	A safety and effectiveness trial for a leadless pacemaker system – The LEADLESS II Study
Investigational Device	Aveir Leadless Pacemaker (LP) – Model LSP112V
Regulatory Classification of the Investigational Device	Class III
Number of Institutions	Up to 80 sites worldwide with up to 60 investigation sites in the United States.
Number of Subjects	Up to 200
Trial Population	Subjects who are at least 18 years old, and who are indicated for a VVI(R) pacemaker
Schedule of Assessments	Enrollment, Implant, Pre-Discharge, 2-week, 6-week, 3-month, 6-month follow-up, 12-month follow-up, and every 6 months thereafter until study completion. Subjects consent to continue in post-approval studies and will have follow-ups at one year and each year thereafter until nine years after implant.
Study Design	Prospective, non-randomized, single-arm, international multicenter, clinical safety and effectiveness investigation.
Study Objective	The primary objectives of Phase 2 of this study are to **confirm** the

CIP Summary (Synopsis) – Phase 2	
	clinical safety and effectiveness of the Aveir LP system in subjects who are indicated for VVI(R) pacemaker.
Confirmatory Safety Endpoint	The confirmatory safety endpoint evaluates the 6-week complication-free rate.
Confirmatory Effectiveness Endpoint	The confirmatory effectiveness endpoint evaluates pacing thresholds and R-wave amplitudes within the therapeutic range through 6 weeks post-implant.
Confirmatory Secondary Endpoint #1	The confirmatory secondary endpoint #1 evaluates an appropriate and proportional rate response during graded exercise testing (CAEP protocol), performed after the beginning of the 6-week visit.
Secondary Endpoint #2	The secondary endpoint #2 estimates the 2-year survival rate of patients implanted with the Nanostim™ Leadless Pacemaker.
[redacted]	[redacted]
Study continuation and supplementary analyses after PMA application	Subjects will continue follow-up every six months under the IDE until FDA-approval to close the IDE. All subjects implanted with the Aveir LP system in this IDE study will consent to continue annual follow-ups each year until 9 years after implant, in a long-term post-approval study.
Inclusion Criteria	Eligible subjects will meet **all** of the following: 1. Subject must have one of the clinical indications before device implant in adherence with Medicare, ACC/AHA/HRS/ESC single chamber pacing guidelines including: ☐ Chronic and/or permanent atrial fibrillation with 2 or 3° AV or bifascicular bundle branch block (BBB block), including slow ventricular rates (with or without medication) associated with atrial fibrillation; or ☐ Normal sinus rhythm with 2 or 3° AV or BBB block and a low level of physical activity or short expected lifespan (but at least one year); or

[redacted]

CIP Summary (Synopsis) – Phase 2	
	☐ Sinus bradycardia with infrequent pauses or unexplained syncope with EP findings; and 2. Subject ≥18 years of age; and 3. Subject has life expectancy of at least one year; and 4. *Subject is not enrolled in another clinical investigation; and 5. Subject is willing to comply with clinical investigation procedures and agrees to return for all required follow-up visits, tests, and exams; and 6. Subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent, approved by the IRB/EC; and 7. Subject is not pregnant and does not plan to get pregnant during the course of the study.

Clinical Investigation Plan

CIP Summary (Synopsis) – Phase 2	
Exclusion Criteria	Subjects will be excluded if they meet **any** of the following: 1. Subject has known pacemaker syndrome, has retrograde VA conduction or suffers a drop in arterial blood pressure with the onset of ventricular pacing; or 2. Subject is allergic or hypersensitive to <1 mg of dexamethasone sodium phosphate; or 3. Subject has a mechanical tricuspid valve prosthesis; or 4. Subject has a pre-existing endocardial pacing or defibrillation leads; or 5. Subject has current implantation of either conventional or subcutaneous implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT); or 6. Subject has an implanted vena cava filter; or 7. Subject has evidence of thrombosis in one of the veins used for access during the procedure; or 8. Subject had recent cardiovascular or peripheral vascular surgery within 30 days of enrolment; or 9. *Subject has an implanted leadless cardiac pacemaker; or 10. **Subject is implanted with an electrically-active implantable medical device with stimulation capabilities (such as neurological or cardiac stimulators). * Except for subjects who are enrolled in the Leadless Observational Study and need their existing Nanostim LP replaced with the Aveir LP. These subjects may only be enrolled in this IDE during the CAP study of Phase 2. ** Does not apply to a medical device known to not be impacted by the Aveir™ Link Module telemetry signals or to a medical device than can be temporarily turned off during interrogation/programming of an Aveir™ LP
Enrollment	Subjects who sign an IRB/EC-approved informed consent and have an attempted implant will be considered enrolled in the study.
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Clinical Investigation Plan

CIP Summary (Synopsis) – Phase 2	
	[redacted]
Schedule of Assessments Schedule of Assessments (Cont'd)	Pre-procedure Assessments • Inclusion/exclusion criteria • Informed consent • Pregnancy assessment • 12-lead ECG • Medical history • Medications[6] Implant Assessments • Femoral vein assessment and access • Procedure details • LP implant • LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs Post-procedure Assessments • Access-site assessment • 12-lead ECG • X-ray of pacemaker • LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs 2-week Visit • LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs • Sensor parameter optimization test (6MWT) until approximately 30 subjects provide data contributing to the analysis (optional)

[6] Data are collected for beta blocker, ACE, ARB, anti-arrhythmic, anti-coagulant, and anti-platelet medications, at all visits.

[redacted]

CIP Summary (Synopsis) – Phase 2	
	6-week Visit • LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs • Graded exercise test (CAEP protocol) until approximately 30 subjects provide data contributing to the analysis (optional) 3-month Visit • LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs • 6MWT (optional) • CAEP (optional) 6-month Visit • LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs • 6MWT (optional) • CAEP (optional) Every 6-month Visits • LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs • 6MWT (optional) • CAEP (optional)

25.0 Appendix VII: Clinical Protocol – Phase 1

25.1 Study Design and Scope

Phase 1 of this prospective, non-randomized, multi-center, international clinical study (ClinicalTrials.gov identifier: NCT02030418) is designed to evaluate the safety and effectiveness of the Nanostim™ System in a subject population indicated for a VVI(R) pacemaker.

[redacted]

Enrollment in the LEADLESS II clinical study is expected to take approximately 14 months. Sponsor anticipates the duration of study participation to be approximately 26 months. All eligible subjects will undergo implant attempt with a Nanostim™ LP.

All subjects will consent to continue annual follow-ups each year until 7 years after implant, in a long-term post-approval study.

The following study evaluations will occur after implant:

- Pre-discharge assessment
- 2-week follow-up visit (in-office or clinic)
- 6-week follow-up visit (in-office or clinic)
- 3-month follow-up visit (in-office or clinic)
- 6-month follow-up visit (in-office or clinic)
- Every 6 months thereafter until study completion

Subjects consent to continue in post-approval studies and will have follow-ups at one year and each year thereafter until seven years after implant.

Follow-up schedules will be calculated from the date of successful implant.

[redacted]

25.2 Study Objective and Endpoints

The primary objectives of Phase 1 are to assess the safety and effectiveness of the Nanostim device from implant through 6-months in a subject population indicated for a VVI(R) pacemaker.

Primary Safety Endpoint
The primary safety endpoint evaluates a 6-month complication-free rate based on CEC adjudication of the adverse event.

Primary Effectiveness Endpoint
The primary effectiveness endpoint evaluates pacing thresholds and R-wave amplitudes within the therapeutic range through 6 months post-implant.

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

Supplementary Safety Endpoint
The supplementary safety endpoint evaluates a 1-year complication-free rate based on CEC adjudication of the adverse event.

Supplementary Effectiveness Endpoint
The supplementary effectiveness endpoint evaluates pacing thresholds and R-wave amplitudes within the therapeutic range through 1 year post-implant.

25.2.1 Primary Endpoints

A PMA application will be submitted to FDA upon successful demonstration of the 6-month primary safety and effectiveness endpoints. These 6-month data will be sufficient for FDA to review the PMA and make a determination of the safety and effectiveness of the device and the approvability of the PMA.

25.2.1.1 Primary Safety Endpoint

The goal of the primary safety endpoint evaluation is to demonstrate an acceptable complication-free rate (CFR); including any complication that prevents initial implantation. [redacted]

[redacted]

Subjects whose initial implantation procedure was not successful will not be eligible for re-implantation attempts with the investigational device at a later date.

Subjects who leave the study before their 6-month visit will be censored at the time they leave the study. So, any complications that occur in subjects that leave the study before their 6-month visit will be included in this analysis.

Primary Safety Endpoint Evaluation at 6 Months

H_0: CFR $\leq$ 86% vs. H_1: CFR > 86%

[redacted]

25.2.1.2 Primary Effectiveness Endpoint

The composite primary effectiveness endpoint will be used to evaluate pacing thresholds and R-wave amplitudes at the 6-month visit and to document the percentage of subjects with acceptable sensing and pacing performance. Pacing thresholds and R-wave amplitudes will be collected, tabulated for each visit, and

[redacted]

also displayed as frequency plots. Acceptable ranges for sensing and pacing are shown in the table below.

Table 2: Acceptable Ranges for Sensing and Pacing

Parameter	Acceptable test 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 primary effectiveness endpoint if the pacing threshold voltage is ≤ 2.0 V at 0.4 ms **and** the sensed R-wave amplitude is either ≥ 5.0 mV at the 6-month visit or ≥ the value at implant.

[redacted]

The inability to sense or pace within the programmable range available in the Nanostim™ device, resulting in device repositioning, replacement, or removal will be captured in the associated safety endpoints.

Primary Effectiveness Endpoint Evaluation at 6 Months

H_0: Rate ≤ 85.0% vs. H_1: Rate > 85.0%

[redacted]

25.2.1.3 Data Analysis of Primary Safety and Effectiveness Endpoints

The following analysis populations are defined for the study:

Intent-to-Treat (ITT): Subjects who meet the enrollment criteria, provide signed Informed Consent, and who have an attempted or successful implant are considered enrolled in the study and part of the ITT population.

[redacted]

The primary safety and effectiveness endpoints must be met at the 6-month evaluations for the study to be considered an appropriate basis for PMA approval.

[redacted]

25.2.1.4 Adaptive Sample Size Re-estimation

[redacted]

25.2.1.5 Pooling of Regions and Sites

[redacted]

25.2.1.6 Missing Data

[redacted]

[redacted]

25.2.1.7 Subgroup Analyses

[redacted]

25.2.1.8 Conditional Probability of Meeting 1-Year Primary Endpoints

[redacted]

[redacted]

[redacted]

25.2.2 Secondary Endpoint

The secondary endpoint includes evaluation of a CAEP exercise protocol. [redacted]

Secondary CAEP Endpoint

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 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.

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

25.2.3 Supplementary Endpoints

The following supplementary endpoints will be evaluated at 12 months after implant.

25.2.3.1 Supplementary Safety Endpoint Evaluation at 12 Months

H_0: CFR $\leq$ 84.5% vs. H_1: CFR > 84.5%

[redacted]

25.2.3.2 Supplementary Effectiveness Endpoint Evaluation at 12 Months

H_0: Rate $\leq$ 85.0% vs. H_1: Rate > 85.0%

[redacted]

[redacted]

[redacted]

25.2.4 Additional data

The following additional data will be recorded and reported:

- 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, fluoro duration, and time from implant to hospital discharge
- Final 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
- A table and histogram across all subjects of remaining longevity at the six-month and 1-year visits, 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

Holters

All capable subjects will be asked to wear a 24-hour Holter monitor and complete a diary, until 30 subjects provide data contributing to the analysis. T[redacted]

[redacted]

[redacted]

25.3 Description of Device

25.3.1 Identification of the device: proprietary and code names

The Nanostim™ leadless pacemaker system consists of these items:

System Model#	Device Identifier/Model	Device Name	Description
S1DLCP*	N/A	Nanostim Leadless Pacemaker Nanostim Delivery System Catheter	Includes Nanostim LP built with old battery assembled with Gen 1.5 Delivery System Catheter
N/A	S1RTRI	Nanostim Retrieval System Catheter – Triple Loop Snare	System 1, Triple Loop Retrieval Catheter for retrieving a Nanostim LP
N/A	S1RSIN	Nanostim Retrieval System Catheter – Single Loop Snare	System 1, Single Loop Retrieval Catheter for retrieving a Nanostim LP
N/A	S1S18F	Nanostim Introducer Kit	System 1, 18F Introducer Kit, 30cm for providing a

			conduit into the venous system
N/A	LSN18501	Nanostim Introducer Kit	System 1, 18F Introducer Kit, 50 cm for providing a conduit into the venous system
N/A	S1LINK	Nanostim Programmer Link	System 1, Programmer Link and Accessories for interrogating and programming the Nanostim LP after implant

*Note: the Nanostim Leadless Pacemaker, model S1DLCP is no longer being distributed or implanted. [redacted] This device is now being replaced with Aveir LP model LSP112V evaluated under Phase 2 of this protocol.

25.3.2 Description of the device and its intended application

The Nanostim™ LP system consists of the Nanostim™ LP and its accessories listed in 25.3.1. The intended application of the Nanostim™ LP is implant in the right ventricle, with permanent duration (greater than 30 days). The intended application of the delivery catheter, retrieval catheters, and introducer is external communicating, circulating blood contact, with limited duration (less than 24 hours). The intended application of the communications link is external, with skin contact via an approved cable and ECG electrodes. The devices in the system achieve their intended purposes as described in the subsections below:

25.3.2.1 Nanostim™ LP

The Nanostim™ LP provides bradycardia pacing as a pulse generator with built-in battery and electrodes, for permanent implantation in the right ventricle. As a leadless pacemaker, it does not need a connector, pacing lead, or pulse generator pocket. A distal non-retractable, single-turn helix affixes the Nanostim™ LP to the endocardium. Sensing, pacing and communication with the external programmer occur between a distal electrode near the helix and the external can of the Nanostim™ LP. The tip electrode is a titanium-nitride coated platinum-iridium disc located at the center of the fixation helix, with a geometric surface area of 2 mm^2. The tip electrode includes 0.1 to 0.7 mg of dexamethasone sodium phosphate, intended to reduce inflammation. The ring electrode is the uncoated part of the titanium pacemaker case, with a geometric surface area >500 mm2. The inter-electrode distance is >10 mm. The pacemaker's proximal end has a feature for docking to delivery and retrieval catheters, which provides for repositioning capability.

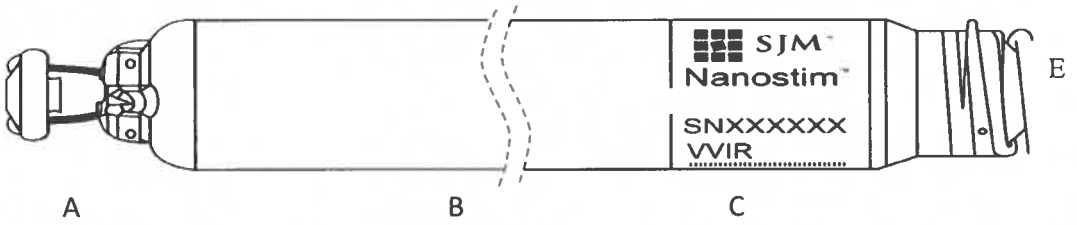
[redacted]

The pacemaker communicates bi-directionally with the programmer via electrical signals conducted between the implanted Nanostim™ LP's electrodes and skin electrodes applied to the patient's chest and connected to the programmer. Consequently the pacemaker transmits signals using circuits and electrodes already provided for pacing, with data encoded in pulses delivered during the heart's refractory period.

The pacemaker senses right-ventricular blood temperature to provide an increase in pacing rate with increased metabolic demand.

Otherwise, the Nanostim™ LP has the same operating principles as a conventional cardiac pacemaker. For further information refer to the Instructions for use of the device.

The drawing below shows mechanical characteristics of the Nanostim LP.



A. Docking Interface button with cables	B. Ring electrode	C. Insulated Nosecone
D. MP35N fixation helix	E. Titanium nitride (TiN) coated platinum-iridium (PtIr) electrode with steroid (proximal to helix).	

Pacemaker length = 42 mm.
Pacemaker outer diameter (max) = 6.15 mm.

25.3.2.2 Nanostim™ Delivery System Catheter

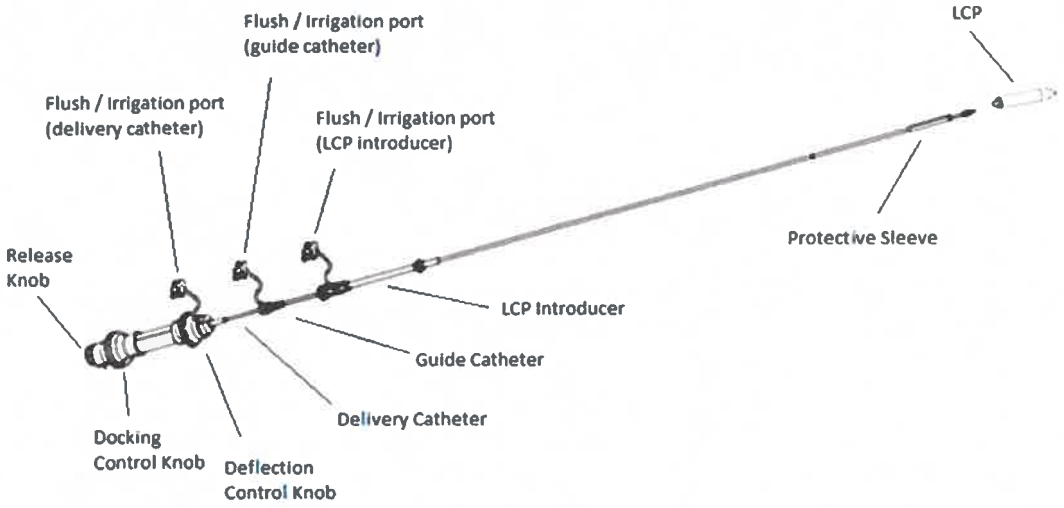
The delivery catheter provides a means for a single operator to:

- Advance the Nanostim™ LP from an access site in the groin (utilizing minimally invasive techniques) through the femoral vein to the apex of the right ventricle,
- Protect the Nanostim™ LP helix and electrode during delivery,
- Position the Nanostim™ LP and rotate it to affix the helix,
- Undock the Nanostim™ LP from the delivery catheter leaving the Nanostim™ LP tethered to the delivery catheter, to measure thresholds without force from the catheter.

- Re-dock to the catheter, unscrew and reposition the Nanostim™ LP if necessary for acceptable thresholds.
- Undock from the Nanostim™ LP, leaving it implanted, and disconnect it from the tether.

Apart from the docking mechanism, the delivery catheter and its control system (handle) have the same operating principle as a conventional steerable catheter and control system. The system includes an introducer, a steerable delivery catheter, and an integrated guiding catheter with a protective sleeve designed to protect the fixation helix and electrode. The catheter has an effective length of 128 cm and the catheter maximum outer diameter is 4.5 mm (0.178 inch). The Gen 1.5 Nanostim Delivery System Catheter contains a 10F steerable delivery catheter.

The drawing below shows mechanical characteristics of the delivery catheter:



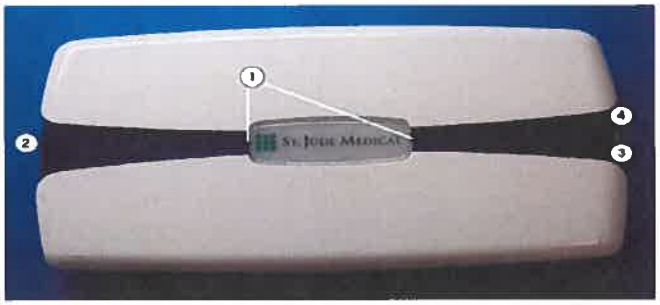
25.3.2.3 Nanostim™ Programmer Link

The programmer displays the patient's electrocardiogram and the status of the implanted Nanostim™ LP, and it sends commands to change Nanostim™ LP parameter settings as directed by a user. The programmer transmits signals to an implanted LCP via conducted communication with subliminal 250 kHz pulses applied to the skin electrodes. Apart from this conducted communication, it has the same operating principle as a conventional pacemaker programmer.

The Nanostim™ Programmer Link uses a St. Jude Medical Merlin Patient Care System Programmer (Model 3650) with a USB interface to an external module

(Nanostim™ Programmer Link). The module uploads St. Jude Medical Nanostim software to the Merlin programmer and provides an interface between the programmer and standard ECG electrodes placed on the subject's torso, for two-way communication with the implanted pacemaker and display of the surface ECG. For further information refer to DC-01471, Instructions for use, S1LINK programmer.

The photographs below show mechanical characteristics of the Nanostim™ Programmer Link:



Top view

1. LED lights will illuminate when the S1LINK is receiving appropriate power
2. Patient connector. Connect to the patient using the patient cable and skin electrodes.
3. USB connector. Connect to the St. Jude Merlin programmer using the USB cable.
4. Auxiliary power connector. Not required in normal use

Bottom view

5. The mating slot in the middle of the S1LINK is designed to slide on top of a mount that is affixed via glue to the back of a St Jude Merlin programmer.
6. The S1LINK is approximately 4.5" x 9.5" x 1.5". Its case is made of plastic. The S1LINK weighs approximately one pound.

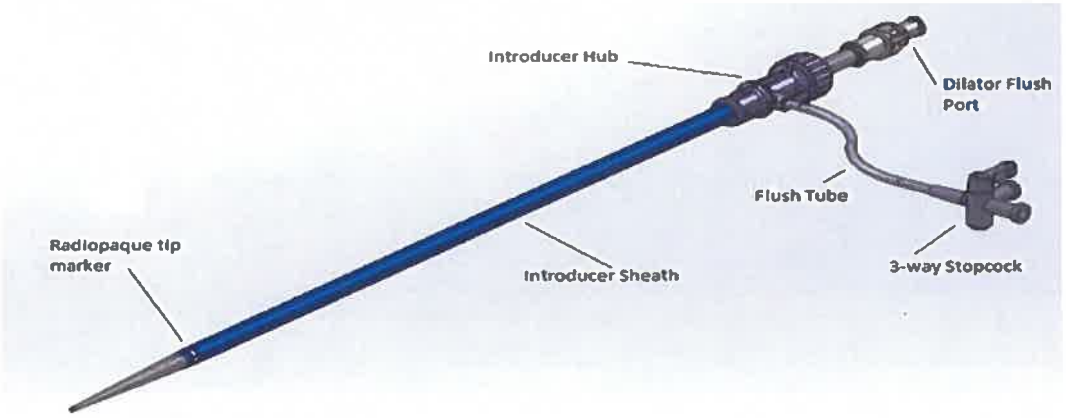
25.3.2.4 Nanostim™ 18F introducer kit

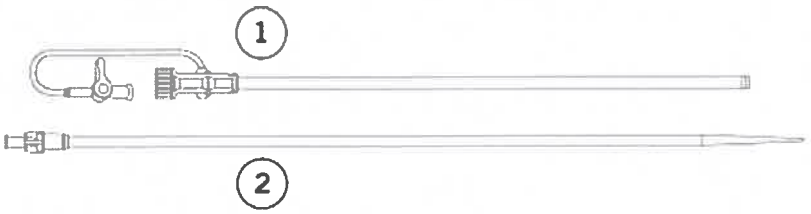
The system includes an 18F introducer kit intended to provide a conduit into the venous system for insertion of diagnostic and other interventional devices. The Introducer Kit is comprised of a dilator and an introducer sheath. The Introducer Kit is compatible with 0.035" and 0.038" guidewires and is available in 18F and two lengths, 30cm (model S1S18F) or 50cm (model LSN18501).

The introducer sheath is fitted with a hemostasis valve to prevent blood loss and minimize air introduction during introducer insertion and/or exchange. A sideport

with a three-way stopcock is provided for fluid infusion. The introducer features a radiopaque tip marker incorporated within the sheath material to identify the location of the distal tip of the sheath. For further information, refer to the device instructions for use.

The drawings below show mechanical characteristics of the 18F introducer kit:





1. Introducer Sheath
2. Dilator

Model	S1S18F	LSN18501
Length	30 cm (11.8 inches)	50 cm (19.7 inches)
Inner Diameter (ID)	6.4 mm (.252 inches)	6.4 mm (.252 inches)

25.3.2.5 Nanostim™ Retrieval System Catheters

The retrieval catheters use a snare to engage the docking feature on the proximal end of the Nanostim™ LP, mate the retrieval catheter with the docking cap, unscrew it, and retrieve it.

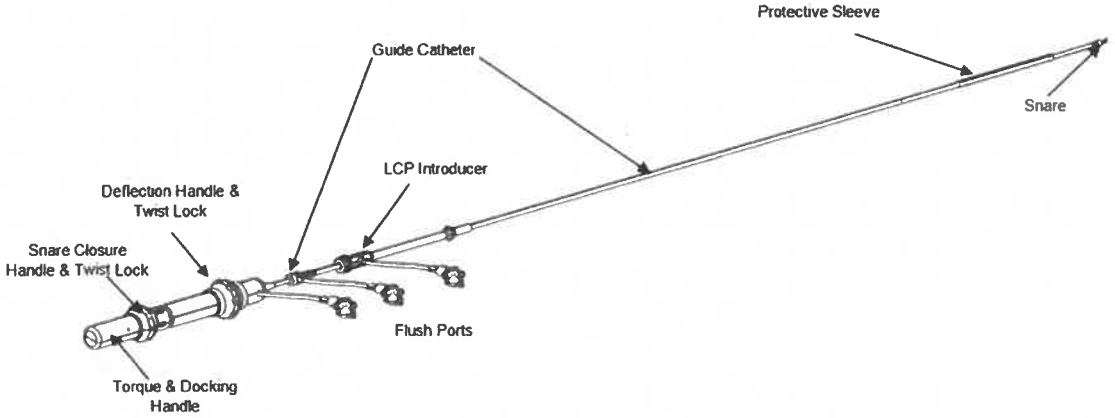
Consequently, the retrieval catheter provides means for a single operator to:

- Mate with the proximal button of the Nanostim™ LP from an access site in the groin through the femoral vein to the right ventricle.
- Dock to the Nanostim™ LP,
- Rotate the Nanostim™ LP to unscrew the helix from the endocardium,

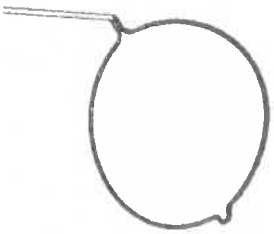
- Protect the Nanostim™ LP helix and electrode during retrieval
- Extract the Nanostim™ LP through the access site in the groin.

Apart from the accessing, and docking features, the retrieval system has the same operating principle as a conventional steerable catheter and control system (handle). For additional information, refer to the device Instructions for use.

The drawings below show mechanical characteristics of the Retrieval catheter system



Catheter effective length = 128 cm, catheter outer diameter (max) = 4.5 mm (0.176 inch).



Single-loop snare for S1RSIN
Loop inner diameter = 19 mm (0.748 inch)

Triple-loop snare for S1RTRI
Loop inner diameter = 20 mm (0.787 inch)

25.3.3 Configurations and Variants

In this clinical investigation, St. Jude Medical includes one variant each of the leadless pacemaker[8] and delivery catheter, and two variants of the retrieval catheter.

[8] Note: the pacemaker, model S1DLCP is no longer being distributed or implanted. However, patients implanted with this device are continued to be followed using this protocol and SJM recommendations outlined in the communication to investigators dated October 28, 2016.

St. Jude Medical may incorporate a validated change to the Nanostim™ LP implant and/or programmer software, when necessary, to correct observed non-conformance with intended device operation.

25.4 Subject Selection

The inclusion and exclusion criteria are consistent with recommendations of the European Society of Cardiology,[1] American College of Cardiology, American Heart Association, and the Heart Rhythm Society.[2] Additionally, sponsor has included investigator input.

Eligibility for implant is based on conformance to all prospectively defined inclusion and exclusion criteria.

25.4.1 Inclusion Criteria

Eligible subjects will meet **all** of the following.

1. Subject must have one of the clinical indications before device implant in adherence with Medicare, ACC/AHA/HRS/ESC single chamber pacing guidelines including:
   - ☐ Chronic and/or permanent atrial fibrillation with 2 or 3° AV or bifascicular bundle branch block (BBB block), including slow ventricular rates (with or without medication) associated with atrial fibrillation; or
   - ☐ Normal sinus rhythm with 2 or 3° AV or BBB block and a low level of physical activity or short expected lifespan (but at least one year); or
   - ☐ Sinus bradycardia with infrequent pauses or unexplained syncope with EP findings; and
2. Subject is ≥18 years of age; and
3. Subject has a life expectancy of at least one year; and
4. Subject is not be enrolled in another clinical investigation; and
5. Subject is willing to comply with clinical investigation procedures and agrees to return for all required follow-up visits, tests, and exams; and
6. Subject has been informed of the nature of the study, agrees to its provisions and has provided a signed written informed consent, approved by the IRB; and
7. Subject is not pregnant and does not plan to get pregnant during the course of the study.

25.4.2 Exclusion Criteria

Subjects will be excluded if they meet **any** of the following.

1. Subject has known pacemaker syndrome, has retrograde VA conduction, or suffers a drop in arterial blood pressure with the onset of ventricular pacing; or
2. Subject is allergic or hypersensitive to < 1 mg of dexamethasone sodium phosphate (DSP);
3. Subject has a mechanical tricuspid valve prosthesis; or
4. Subject has a pre-existing endocardial pacing or defibrillation leads; or
5. Subject has current implantation of either conventional or subcutaneous implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) device; or
6. Subject has an implanted vena cava filter; or
7. Subject has evidence of thrombosis in one of the veins used for access during the procedure; or
8. *Subject had recent cardiovascular or peripheral vascular surgery within 30 days of enrollment; or
9. Subject has an implanted leadless cardiac pacemaker

*Recent cardiovascular or peripheral vascular surgery within 30 days of enrollment is defined as the following:

25.5 Study Procedures

This section provides a description of all the clinical-investigation-related procedures that subjects undergo during the clinical investigation. **Figure 1** illustrates study flow

and **Table 1** lists a summary of scheduled assessments. Refer to **Figure 1** and **Table 1** for an overview of the required study procedures at each interval or study visit.

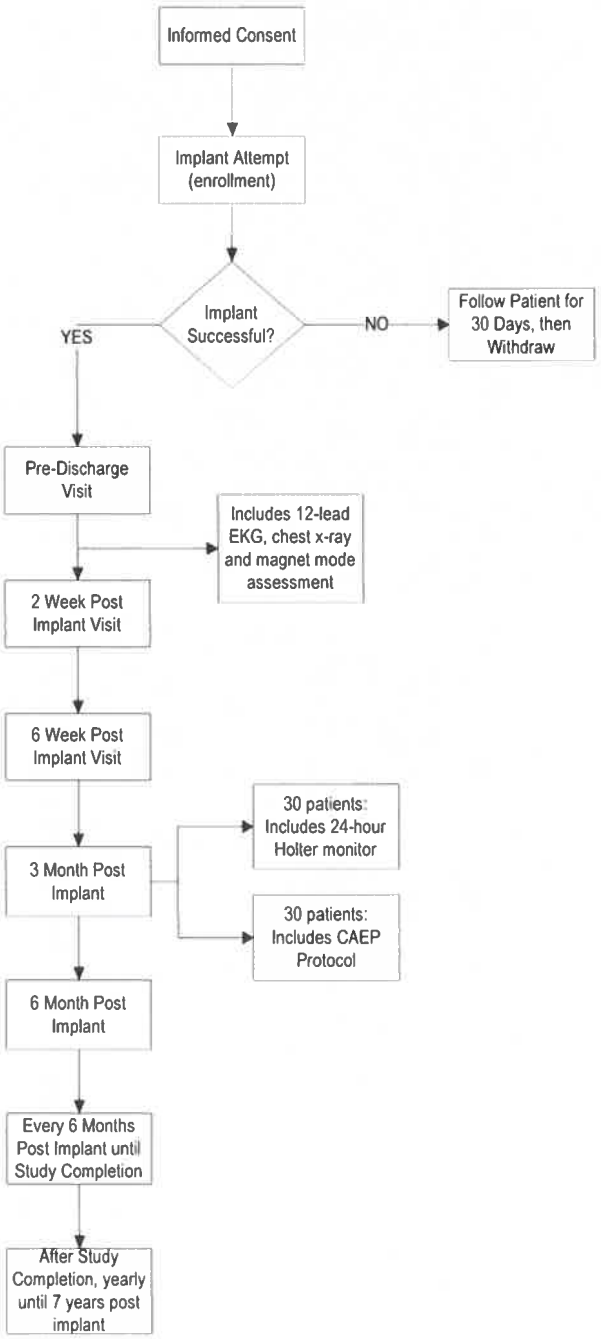
The clinical-investigation-related procedures do not require additional radiation compared to a traditional VVIR lead implant and conform to standard of care for pacemaker patient management with the exception of the following:

- Femoral vein access instead of subclavian vein access
- Addition of Treadmill tests
- Addition of 24 hour Holter monitor

Sponsor representatives may assist the investigator in assessing pacemaker effectiveness (for example pacing, sensing, and rate response effectiveness), downloading diagnostic information and programming pacemaker parameters. Sponsor representatives may also assist the team in equipment setup prior to and during a procedure.

Clinical Investigation Plan

Figure 1: Study Flow Diagram



Clinical Investigation Plan

Table 5: Schedule of Assessments – Phase 1

	Pre-procedure Assessments		*Procedure Assessment*	*Post-procedure Assessments*						
Activity	*Screen & Enroll*	*Baseline*	*Implant*	*Post-procedure Assessment*	*2-week Follow-up Visit[1]*	*6-week Follow-up Visit[1]*	*3-month Follow-up Visit[2]*	*6-month Follow-up Visit[2]*	*Every 6-months until study completion[3]*	*Additional Visits*
Inclusion Exclusion	✓									
Informed Consent	✓									
Pregnancy Assessment/Test	✓									
Medical History		✓								
Baseline Assessment		✓								
Procedure			✓							
Post-procedure Pre-discharge				✓						
Nanostim™ LP Assessment and Programming			✓	✓	✓	✓	✓	✓	✓	✓
12-lead ECG		✓		✓						
X-ray of a pacemaker				✓						
Follow-up Visit					✓	✓	✓	✓	✓	✓
24-hour Holter monitor with diary[4]							✓			
Graded exercise test CAEP Protocol[5]							✓			
EQ-5D patient survey				✓	✓	✓	✓			
Additional CRFs (when applicable)										
Adverse Event			✓	✓	✓	✓	✓	✓	✓	✓
Deviation		✓	✓	✓	✓	✓	✓	✓	✓	
Study Withdrawal				✓	✓	✓	✓	✓	✓	✓
Product Out of Service			✓	✓	✓	✓	✓	✓	✓	✓
System Revision				✓	✓	✓	✓	✓	✓	✓
Death			✓	✓	✓	✓	✓	✓	✓	✓
Healthcare Utilization				✓	✓	✓	✓	✓	✓	✓

1 ±7 days
2 ±30 days
3 ±45 days
4 All capable subjects are asked to wear a 24-hour Holter and complete a diary, until 30 subjects provide data contributing to the analysis. The preferred window to perform the 24 hour Holter test is between the 3-month and 6-month visit.

[redacted]

[redacted]

[redacted]

25.5.1 Enrollment Requirements

25.5.1.1 Recruitment and Enrollment

Candidates for this clinical investigation include patients indicated for a VVI(R) pacemaker. Pre-enrollment records will include evidence of diagnosis indicating need for VVI(R) pacemaker. For the Leadless II study, it is the sponsor's intention that the enrolled subject population be as representative as possible of the eligible population. Physician investigators are strongly encouraged to evaluate all consecutive eligible subjects for participation in the study and, if inclusion and exclusion criteria are met, to approach all eligible subjects, regardless of gender. [redacted]

Screen subjects as outlined by the inclusion/exclusion criteria. Obtain informed consent from the subject. Collect data on the subject, including gender, age, ethnicity, race, cardiac disease history, cardiac medications (beta blockers, ACE, ARB, anti-platelets, anti-arrhythmics, anti-coagulants), arrhythmia history, and indication for pacemaker implant. Subjects who sign an IRB-approved informed consent and have an attempted or successful implant will be considered enrolled in the study.

Once eligibility screening is completed, subject provides informed consent, and the investigator implants the Nanostim™ device—or attempts to implant—complete and submit the forms listed under the Implant Procedures to sponsor.

25.5.1.2 Subject Numbering

An identification (ID) number will identify enrolled subjects. [redacted]

25.5.2 Baseline Assessment

Investigator will record subject's medical history on the Enrollment Form. Investigator will record specific cardiac medications (beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics) given to the subject during the same hospital stay as the procedure, as well as during the follow-up period. All subjects will undergo standard laboratory assessment per site's standard of care. For female subjects of childbearing age, investigator will document a pregnancy assessment, which may include a obtaining a blood sample for conducting a pregnancy test.

[redacted]

Investigator will not start any study-specific procedures or alterations of patient care until the informed consent process has been completed and investigator obtains a signed Informed Consent Form.

25.5.2.1 Medications

Investigator will administer all medications per hospital standard of care for pacemaker implant and femoral venous catheterization procedures. Use of anticoagulation medications is not required with the implantation of the Nanostim™ device. Investigator will record beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics given during procedure.

25.5.3 Implant Procedure

25.5.3.1 Femoral Vein Assessment and Access

Turi (2005, 2008), Abu-Fadel *et al* (2009), Seto *et al* (2010), and Fitts *et al* (2008) have shown that physicians can minimize access-site complications by using ultrasound guidance or fluoroscopic guidance when accessing vessels in the groin.[3-7] Although sponsor supports using either technique for assessing femoral vein access-site location, size and presence of disease, investigator will use medical judgment and follow institutional standard of care when accessing the femoral vein during catheter-based procedures.

The ideal puncture site should be located **below the inguinal ligament and above the bifurcation** (Refer to Figure 2).[5,8-10] Penetrate the skin and puncture the femoral vein using the Seldinger technique. Due to the introducer sheath size, investigator may need to "nick and spread" the tissue at the access-site location to allow for easier transition of the introducer sheath through the tissue tract.

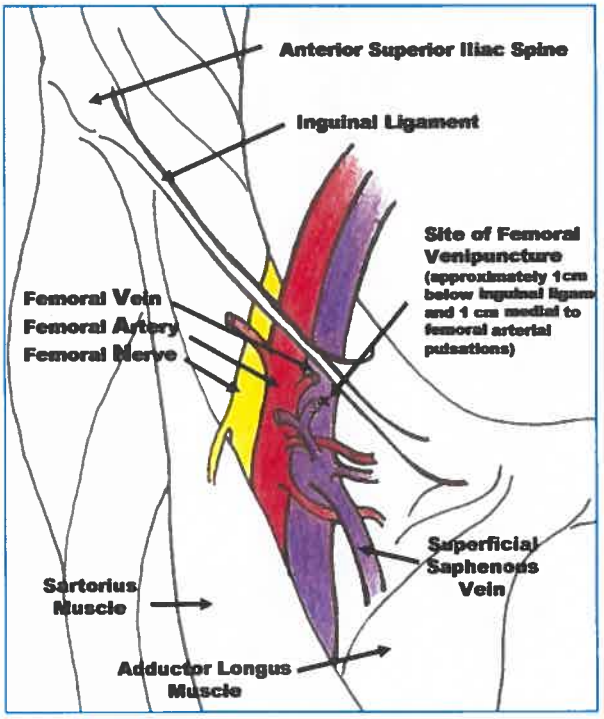


Figure 2. Location of femoral vein in relation to femoral artery, inguinal ligament and femoral head

25.5.3.2 Nanostim™ LP Preparation and Implant

Investigator will prepare and implant the Nanostim™ device in accordance with the manufacturer's instructions for use (IFU). Consult the IFU for implantation guidelines and general handling information. Only approved investigators will be responsible for performing the implant procedure, including placement of the Nanostim™ device. Investigator will follow standard institutional catheter-based and pacemaker-lead implantation procedures, guidelines, and precautions.

25.5.3.3 Nanostim™ LP Assessment and Programming

Investigator and/or sponsor will interrogate the Nanostim™ device using the market-approved St. Jude Medical™ Merlin™ Patient Care System (Model 3650) with the Nanostim™ Programmer Link. Investigator will measure and record the following parameters.

- Capture threshold at (0.4 msec)*
- Impedance*
- R-wave amplitude*
- Battery voltage and Estimated time to RRT
- Cumulative paced and sensed event counters

* *R-wave amplitude measurements are not required if the subject's intrinsic rate has been established to be below 30 beats per minute. Capture thresholds are not required if a high ventricular rate is present. Confirm at least three consecutive beats have capture before recording the capture threshold results.*

* *For subjects implanted with the Nanostim™ LP (Model S1DLCP)-Impedance measurements should not be done because performing this commanded measurement in a device with a high resistance battery can render the device immediately non-functional.*

To avoid potential complications associated with under-sensing, Investigator shall program a sensing margin of at least two times the intrinsic cardiac amplitude (e.g., for an intrinsic R-wave of 4 mV, program the R-sensitivity ≤ 2 mV).

To avoid potential complications associated with loss of pacing capture, Investigator shall maintain pulse amplitude margin of at least two times the pacing threshold (e.g., for a pacing threshold of 0.5V, program the pulse amplitude ≥1.0V).

25.5.3.4 Nanostim™ LP Repositioning and/or Release

Once the investigator implants the Nanostim™ device and successfully demonstrates acute effectiveness, the investigator may release the Nanostim™ device. Investigator may reposition Nanostim™, if necessary. For release and repositioning procedures, refer to the IFU. Once the Nanostim™ has been released, investigator will use a retrieval catheter for removal, if needed (Refer to Retrieval Catheter IFU). Once the Nanostim™ has been removed, investigator may attempt to implant another Nanostim™ , or instead, choose to implant a market-approved pacemaker or ICD. When the investigator has released the Nanostim™, s/he will use fluoroscopy to assess positioning of the implanted Nanostim™.

25.5.3.5 Unsuccessful Implant

Investigators will follow subjects who have an unsuccessful implant for a period of 30 days to evaluate for adverse events. At the end of the 30 days, the investigator will withdraw the subject. The investigator must document the nature of the unsuccessful implant on the Implant Form.

Data Submission

Once information has been collected and required testing has been completed at the implant visit, complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Enrollment Form (includes medications)
- Implant Form (includes medications)
- Nanostim™ LP Assessment and Programming Form
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Death Form, if applicable
- Product Out of Service Form, if applicable

25.5.4 Nanostim™ Retrievals and Replacement

When considering Nanostim™ retrieval and replacement, investigators will refer to the respective IFUs.

In the event a Nanostim™ must be removed during the clinical study follow-up period, investigators may opt to replace the LPs in the following ways:

- Retrieve the first Nanostim™ device and implant a new Aveir device*,
- Deactivate the first Nanostim™ device and implant a second Aveir device* in close proximity to the first one, or
- Deactivate the first Nanostim™ device and implant a traditional pacemaker or ICD with a lead.

If the subject has the Nanostim™ device replaced with an Aveir device, the subject must be re-consented with the current IRB-approved version of the informed consent form **prior to the replacement procedure. After successful replacement with the Aveir device, the subject will continue with his/her original follow-up schedule.*

Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- System Revision Form
- Healthcare Utilization Form
- Nanostim™ LP Assessment and Programming Form, if applicable
- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Death Form, if applicable
- Study Withdrawal Form, if applicable
- Product out of Service Form, if applicable

*If the subject has the Nanostim™ removed at any time during the study, and the subject **will not** receive a replacement Aveir LP, follow the subject for 30 days, and withdraw the subject from the study. Complete and submit the following case report forms to St. Jude Medical, Sylmar, CA using the EDC system.*

- Study Withdrawal Form
- Product Out of Service Form
- Nanostim™ LP Assessment and Programming Form, if applicable
- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Death Form, if applicable

25.5.5 Post-procedure Assessments

The follow-up period is sufficient to demonstrate safety and effectiveness. Additionally, during this 6-month follow-up period, sponsor will identify any residual risks and complications.

Subjects will be seen at the following intervals:

- Pre-discharge assessment
- 2-week follow-up visit (in-office or clinic)
- 6-week follow-up visit (in-office or clinic)
- 3-months follow-up visit (in-office or clinic)
- 6-months follow-up visit (in-office or clinic)
- After completing 6-month follow-up assessment, subjects will return every 6 months until study completion
- Subjects consent to continue in post-approval studies and will have follow-ups at one year and each year thereafter until seven years after implant.

Table 6: Follow-up Assessment Windows

Post Implant (Pre-Discharge)	**2-week follow-up**	**6-week follow-up**
0-2days	14 ± 7 days	42 ± 7 days
3-month follow-up	**6-month follow-up**	
90 ± 30 days	180 ± 30 days	
Every 6 months post 1-year until study completion		
Every 180 ± 45 days		

25.5.5.1 Access-site Management During Hospital Stay

Investigator will manage vascular-access sites per standard of care. Investigator will assess and document any post-procedural access-site bleeding event based on the following grading system.

ACCESS-SITE OOZING: Superficial bleeding of a cutaneous or subcutaneous origin characterized by diffuse localized bleeding and controlled with minimal care (e.g., application of manual pressure, application of sandbag).

ACCESS-SITE HEMATOMA: A localized collection of extravasated blood in subcutaneous tissue at the access site that does not require intervention. A metric ruler should be used to measure the widest portion of the hematoma.

ACCESS-SITE HEMATOMA REQUIRING INTERVENTION: A localized collection of extravasated blood in subcutaneous tissue at the access site that is considered life threatening and requires emergency wound exploration (e.g., acutely expanding hematoma, acute leg pain/numbness/swelling) and/or prolongation of hospital stay.

ACCESS-SITE RE-BLEEDING: Localized bleeding at the access site that occurs after hospital discharge. These bleeds are typically associated with an event (e.g., fall, attempted suture removal, physical activity).

25.5.5.2 Pre-Discharge Assessment

Investigator will assess all subjects at the implant center prior to hospital discharge, or within 2-days post implant, whichever is shorter. Investigation team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics;
- Measure and record Nanostim™ LP performance, as described in 3.5.3.3 Nanostim™ LP Assessment and Programming;
- Assess magnet mode;
- Program Nanostim™ LP per physician discretion;
- Obtain a 12-lead electrocardiogram (ECG) with pacing ON;
- Obtain a posterior/anterior (P/A) and lateral view chest x-ray to assess final LP position;
- Investigator will use medical judgment and provide institutional standard of care for post-pacemaker-implant monitoring.
- Collect medical billing information for implant (i.e. UB04 billing form)

Data Submission

Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Pre-Discharge Form (includes medication changes)
- Nanostim™ LP Assessment and Programming Form
- EQ-5D patient survey
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable

25.5.5.3 2-week and 6-week follow-up visits

All subjects will return to the investigation site for a 14-day and 42-day (±7 days) follow-up visit. During this visit, investigation team will:

- Assess for adverse events and deviations from investigation plan;

- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics;
- Measure and record LP performance, as described in 3.5.3.3 Nanostim™ LP Assessment and Programming;
- Program Nanostim™ LP and adjust programmable parameters of Nanostim™ LP, as needed.

Data Submission

Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Follow-up Visit Form (includes medication changes)
- Nanostim™ LP Assessment and Programming Form
- EQ-5D patient survey
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable
- Healthcare Utilization Form, if applicable

25.5.5.4 3-Month Visit

All subjects will return to the investigation site for a 90-day (±30 days) follow-up visit. During this visit, investigation team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics;
- Measure and record Nanostim™ LP performance, as described in 3.5.3.3 Nanostim™ LP Assessment and Programming;
- Program Nanostim™ LP and adjust programmable parameters of Nanostim™ LP, as needed;
- Holter Data Collection[9]

[9] Holter data collection can be done any time between the 3- month and 6-month follow-up visit.

- Connect each capable subject to 24-hour Holter monitor (until 30 subjects contribute to the analysis); set Nanostim™ LP to **VVIR** mode, if indicated (This test may be performed between 3 and 6 months post-implant).

- CAEP Protocol[10]
  - Administer CAEP protocol (until 30 subjects contribute to the analysis); with rate-response feature in **VVIR ON** mode (refer to CAEP protocol – this test may be performed between 3 and 6 months post-implant).
  - After completing CAEP protocol, program Nanostim™ LP and adjust programmable parameters of Nanostim™ LP, as needed.

Data Submission

Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Follow-up Visit Form (includes medication changes)
- Nanostim™ LP Assessment and Programming Form
- EQ-5D patient survey
- Medications, if any changes
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Graded Exercise Test Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable
- Healthcare Utilization Form, if applicable

25.5.5.5 6-Month Follow-up Visit

All subjects will return to the investigation site for a 180-day (±30 days) follow-up visit. During this visit, investigation team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics;

[10] Administration of the CAEP protocol can be done any time between the 3- month and 6-month follow-up visit, (until 30 subjects contribute to the analysis).

- Measure and record Nanostim™ LP performance, as described in 3.5.3.3 Nanostim™ LP Assessment and Programming.

Data Submission
Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Follow-up Visit Form (includes medication changes)
- Nanostim™ LP Assessment and Programming Form
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable
- Healthcare Utilization Form, if applicable

25.5.5.6 Follow-up Visit Every Subsequent 6-Months until Study Completion

All subjects will return to the investigation site every 180-days (±45 days) follow-up visit. During this visit, investigation team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics;
- Measure and record Nanostim™ LP performance, as described in 3.5.3.3 Nanostim™ LP Assessment and Programming;
- Program Nanostim™ LP and adjust programmable parameters of Nanostim™ LP, as needed.

Data Submission
Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Follow-up Visit Form (includes medication changes)
- Nanostim™ LP Assessment and Programming Form
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable

- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable
- Healthcare Utilization Form, if applicable

25.5.5.7 Unscheduled Follow-up Visits

If a subject returns to the investigational site for a visit that is related to the device or implant procedure, the research team will:

- Assess for adverse events and deviations from investigation plan;
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics;
- As applicable, measure and record Nanostim™ LP performance, as described in 3.5.3.3 Nanostim™ LP Assessment and Programming;
- Program Nanostim™ LP and adjust programmable parameters of Nanostim™ LP, as needed.

Data Submission

Complete and submit the following case report forms and device print outs to St. Jude Medical, Sylmar, CA using the EDC system.

- Follow-up Visit Form (includes medication changes)
- Nanostim™ LP Assessment and Programming Form
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Deviation Form, if applicable
- Product Out of Service Form, if applicable
- System Revision Form, if applicable
- Death Form, if applicable
- Healthcare Utilization Form, if applicable

25.6 Hospitalizations - See Section 4.0

25.7 Protocol Deviations - See Section 5.0

25.8 Adverse Events - See Section 6.0

25.9 Deaths - See Section 7.0

25.10 Committees and Core Laboratories

25.10.1 Data and Safety Monitoring Board (DSMB) - See Section 8.1

25.10.2 Clinical Events Committee (CEC) - See Section 8.2

25.10.3 Holter Core Laboratory

Sponsor will establish an independent core laboratory to review all 24-hour Holter monitors during Phase 1 of this investigation. The core laboratory's role is to evaluate and report Holter findings.

25.11 Withdrawals - See Section 9.0

25.12 Risk Analysis - See Section 10.0

25.13 Investigator Information - See Section 11.0

25.14 Monitoring Procedures - See Section 12.0

25.15 Labeling - See Section 13.0

25.16 Consent Materials - See Section 14.0

25.17 IRB/EC Information - See Section 15.0

25.18 Other Institutions - See Section 16.0

25.19 Records and Reports - See Section 17.0

For Phase 1 only: Sponsor will provide an IDE interim report to FDA within one month of completion of the 30th subject Holter monitor. Sponsor will provide to FDA on a quarterly basis an interim safety and adverse event report.

25.20 Publications

The Phase I study will be posted on ClinicalTrials.gov under the identifier NCT02030418.

26.0 Appendix VIII: CIP Summary (Synopsis) – Phase 1

CIP Summary (Synopsis) – Phase 1	
Title	A safety and effectiveness trial for a leadless pacemaker system – The LEADLESS II Study
Investigational Device	Nanostim™ Leadless Pacemaker (LP) – Model S1DLCP
Regulatory Classification of the Investigational Device	Class III
Number of Institutions	Up to sixty sites worldwide with up to 50 investigation sites in the United States
Number of Subjects	Up to 667 [redacted]
Trial Population	Subjects who are at least 18 years old, and who are indicated for a VVI(R) pacemaker
Schedule of Assessments	Enrollment, Implant, Pre-Discharge, 2-week, 6-week, 3-month, 6-month follow-up, and every 6 months thereafter until study completion. Subjects consent to continue in post-approval studies and will have follow-ups at one year and each year thereafter until seven years after implant.
Study Design	Prospective, non-randomized, single-arm, international multicenter, clinical safety and effectiveness investigation.
Study Objective	The primary objectives of Phase 1 of this study are to evaluate the clinical safety and effectiveness of the Nanostim™ LP system in subjects who are indicated for VVI(R) pacemaker.
Primary Safety Endpoint	The primary safety endpoint evaluates the 6-month complication-free rate.
Primary Effectiveness Endpoint	The primary effectiveness endpoint evaluates pacing thresholds and R-wave amplitudes within the therapeutic range through 6 months post-implant.
Secondary Endpoint	The secondary endpoint evaluates an appropriate and proportional rate response during graded exercise testing (CAEP protocol), performed between 3-month and 6- month visit.
[redacted]	[redacted]

Clinical Investigation Plan

CIP Summary (Synopsis) – Phase 1	
[redacted]	[redacted]
[redacted]	[redacted]
Inclusion Criteria	Eligible subjects will meet **all** of the following: 1. Subject must have one of the clinical indications before device implant in adherence with Medicare, ACC/AHA/HRS/ESC single chamber pacing guidelines including: ☐ Chronic and/or permanent atrial fibrillation with 2 or 3° AV or bifascicular bundle branch block (BBB block), including slow ventricular rates (with or without medication) associated with atrial fibrillation; or ☐ Normal sinus rhythm with 2 or 3° AV or BBB block and a low level of physical activity or short expected lifespan (but at least one year); or ☐ Sinus bradycardia with infrequent pauses or unexplained syncope with EP findings; and 2. Subject ≥18 years of age; and 3. Subject has life expectancy of at least one year; and 4. Subject is not enrolled in another clinical investigation; and 5. Subject is willing to comply with clinical investigation procedures and agrees to return for all required follow-up visits, tests, and exams; and 6. Subject has been informed of the nature of the study, agrees to its provisions and has provided written informed consent, approved by the IRB; and 7. Subject is not pregnant and does not plan to get pregnant during the course of the study.
Exclusion Criteria	Subjects will be excluded if they meet **any** of the following: 1. Subject has known pacemaker syndrome, has retrograde VA conduction or suffers a drop in arterial blood pressure with the onset of ventricular pacing; or 2. Subject is allergic or hypersensitive to <1 mg of dexamethasone sodium phosphate; or

[redacted]

CIP Summary (Synopsis) – Phase 1	
	3. Subject has a mechanical tricuspid valve prosthesis; or 4. Subject has a pre-existing endocardial pacing or defibrillation leads; or 5. Subject has current implantation of either conventional or subcutaneous implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT); or 6. Subject has an implanted vena cava filter; or 7. Subject has evidence of thrombosis in one of the veins used for access during the procedure; or 8. Subject had recent cardiovascular or peripheral vascular surgery within 30 days of enrolment; or 9. Subject has an implanted leadless cardiac pacemaker
Enrollment	Subjects who sign an IRB-approved informed consent and have an attempted or successful implant will be considered enrolled in the study.
[redacted]	[redacted]
[redacted]	[redacted]
Schedule of Assessments	<u>Pre-procedure Assessments</u> • Inclusion/exclusion criteria • Informed consent • Pregnancy assessment • 12-lead ECG • Medical history • Medications[11]

[11] Data are collected for beta blocker, ACE, ARB, anti-arrhythmic, anti-coagulant, and anti-platelet medications, at all visits.

[redacted]

CIP Summary (Synopsis) – Phase 1	
Schedule of Assessments (Cont'd)	Implant Assessments • Femoral vein assessment and access • Procedure details • Nanostim™ LP implant • Nanostim™ LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs Post-procedure Assessments • Access-site assessment • 12-lead ECG • X-ray of pacemaker • Nanostim™ LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs 2-week Visit • Nanostim™ LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs 6-week Visit • Nanostim™ LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs 3-month Visit • Nanostim™ LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs • 24-hour Holter monitor with diary (30 subjects) • Graded exercise test (CAEP protocol) until 30 subjects provide data contributing to the analysis) 6-month Visit • Nanostim™ LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs Every 6-month Visits • Nanostim™ LP assessment and programming • Assess for changes in medications or change in therapy • Assess for AEs

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