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Aveir™ DR i2i Study
Aveir Dual-Chamber Leadless i2i IDE Study
Study Document No: ABT-CIP-10428
Version B
Date: 23-NOV-2022

Sponsor

Abbott Medical
Cardiac Rhythm Management
15900 Valley View Court
Sylmar, CA 91342
U.S.

Clinical Investigation Plan for Europe

ABT-CIP-10428
CRD 1023
"Aveir™ DR i2i Study"
Aveir Dual-Chamber Leadless i2i IDE Study

Version Number	B
Date	November 23, 2022
National Coordinating Clinical Investigators	[redacted] (U.S. and Canada) [redacted] Europe and Asia Pacific)
Steering Committee	[redacted]
Planned Number of Sites and Region(s)	85 sites worldwide (U.S., Canada, Europe, and Asia-Pacific)
Clinical Investigation Type	Prospective, multi-center, international, single-arm, pivotal investigational study.
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Sponsor and Legal Manufacturer	Abbott Medical Cardiac Rhythm Management 15900 Valley View Court Sylmar, CA 91342 U.S. EU Sponsor Representative: St. Jude Medical Coordinaton Center BVBA Corporate Village Da Vincilaan 11 F1 1935 Zaventem Belgium
Electronic Data Capture Software	[redacted]

[redacted]

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Core Laboratory	[redacted]
CIP Author of Current Version	[redacted] Sr. Scientist, Clinical Research

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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:

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NATIONAL COORDINATING CLINICAL 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.

Coordinating Clinical Investigator – U.S. and Canada

Printed name:
Signature:
Date:

Coordinating Clinical Investigator – Europe and Asia-Pacific

Printed name:
Signature:
Date:

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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 ISO14155:2020) 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, PMDA, MHRA, etc.).

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1.0 INTRODUCTION

This clinical investigation is intended to evaluate the safety and effectiveness of the Aveir™ Dual-Chamber (DR) Leadless Pacemaker (LP) system in patients indicated for a DDD(R) pacemaker to support regulatory approval for the Aveir DR LP system for DDD(R) pacing indications and the Aveir atrial LP for AAI(R) pacing indications. This clinical investigation will be conducted under an investigational device exemption (IDE) and is intended to support market approval worldwide. This clinical investigation is sponsored by Abbott Medical.

This clinical investigation will be conducted in accordance with this clinical investigation plan (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.

1.1 Background and Rationale

1.1.1 Background

Cardiac pacing has been an established therapy for patients with bradyarrhythmia for over 50 years. However, this life-improving therapy is still associated with significant complications, primarily related to the transvenous lead and the subcutaneous pulse generator pocket. Short-term complication rates as high as 8% to 12% have been reported, and include pneumothorax, cardiac tamponade, pocket hematoma, and lead dislodgement.[1, 2, 3] In the long term, these leads are also prone to insulation breaks and conductor fracture, requiring re-intervention that puts the patient at risk for significant morbidity.[4] Furthermore, 0.7% to 2.4% of patients encounter serious complications related to the subcutaneously placed pulse generator that include skin erosion, pocket infection, and septicemia.[5]

The complications associated with the conventional transvenous pacemaker design have triggered the clinical need to eliminate the pacemaker lead, pockets and connectors through a fully self-contained leadless pacemaker system that can be implanted percutaneously with a steerable catheter, thus offering patients a less-invasive approach as compared to conventional pacemaker procedures that require more extensive surgery. The leadless concept was also designed to improve patient comfort by eliminating the visible lump and scar at a conventional pacemaker's pectoral implant site and by removing the need for activity restrictions to prevent dislodgement or damage of a conventional lead.

As of the end of 2020, only two single-chamber leadless pacemaker models are commercially available while others are in development or under clinical investigation. The Micra™ Transcatheter Pacing System VR and AV models (TPS; Medtronic, Minneapolis, Minnesota) are the only market-approved leadless pacemaker systems capable of providing single-chamber right ventricular pacing, sensing, and delivery of rate response in VVI(R) or VDD pacing modes, respectively. Patients implanted with a Micra VR experienced a 48% reduction in the risk of major complications at 12 months compared to patients with transvenous systems from a historical control group, resulting in 82% fewer system revisions and 47% fewer hospitalizations.[6]

Despite the cardiac rhythm management advances demonstrated from conventional transvenous pacemaker to single chamber leadless pacemaker systems, most patients require dual chamber pacing because of their clinical presentation. In the U.S. market, less

than 20% of patients who require permanent pacemakers receive traditional single-chamber devices while the remaining 80% receive traditional dual-chamber devices.[7] Therefore, most of the U.S. pacemaker population is represented by a need for dual-chamber pacing therapy. Currently, over 700,000 pacemakers are implanted annually worldwide for the treatment of bradyarrhythmias. A bradyarrhythmia may be due to disease in the heart's electrical system such as problems with the sinoatrial (SA) node or some interruption in conduction through the natural electrical pathways of the heart. High degree AV block and sick sinus syndrome are the major indications for the implantation of dual-chamber cardiac pacemakers.

Patients who are indicated for dual-chamber pacing would benefit from a dual-chamber leadless pacemaker system that provides atrial and ventricular bradycardia therapy while eliminating the long-term complications associated with the surgical pocket and transvenous atrial and ventricular leads that are associated with conventional pacing systems. In the FOLLOWPACE Study in a pacemaker population (n=1517) where 68.8% were implanted with dual-chamber devices, 140 patients (9.2%) experienced a complication after 2 months with conventional pacing systems. Of those, most were lead-related (n=84).[2]

Currently, there are no leadless pacing systems capable of DDD(R) pacing. The Aveir DR LP system is a promising new technology that can deliver DDD(R) pacing therapy while also offering advantages over transvenous dual-chamber pacemakers for the treatment of bradyarrhythmias. This technology has the same design advantages as single-chamber LP systems which have led to the better comparative clinical outcomes previously described. The Aveir DR LP system is expected to provide comparable bradycardia treatment as transvenous dual-chamber pacemakers for patients indicated for similar conditions.

The Aveir DR LP system is a programmable system comprising of two implanted leadless pacemakers that provide dual chamber rate-responsive bradycardia pacing therapy. A ventricular LP is intended for direct permanent implantation into the right ventricle, and an atrial LP is intended for direct implantation into the right atrium. Each leadless pacemaker is delivered to the target heart chamber percutaneously via the femoral vein.

Abbott Medical's Aveir leadless pacemaker technology also offers other clinical features including device retrievability and device upgradability from a single chamber leadless configuration to a dual chamber leadless configuration. The Aveir DR LP system is designed to be retrievable, where individual LPs of the implanted system can be removed and replaced at end of service by a dedicated retrieval catheter.

1.1.2 Rationale for Conducting this Clinical Investigation

The Aveir DR i2i study will be the first in-human evaluation of the Aveir DR LP system. The purpose of this clinical investigation is to evaluate the clinical safety and effectiveness of the Aveir DR LP system in a patient population indicated for a DDD(R) pacemaker. The results of this clinical investigation will support regulatory pre-market submissions for the Aveir DR LP system for DDD(R) pacing indications and the Aveir atrial LP for AAI(R) pacing indications in various geographies as outlined below.

To support the Aveir DR LP system for DDD(R) pacing indications, the primary safety endpoint will evaluate the dual-chamber system complication-free rate at 12 months post implant. The primary effectiveness endpoint #1 will evaluate atrial sensing/pacing, and the primary effectiveness endpoint #2 will evaluate AV synchrony performance at 3 months post implant. The ventricular LP (model LSP202V) in the Aveir DR LP system is the same

as the ventricular LP (model LSP112V) evaluated in the Leadless II IDE study (Phase II) (NCT04559945). This study included the evaluation of the ventricular sensing/pacing performance of the LSP112V within a single-chamber leadless system. The ventricular sensing/pacing performance is not affected by the ventricular LP's integration from a single-chamber leadless system into a dual-chamber leadless system. Therefore, this clinical investigation does not need to re-evaluate acceptable ventricular sensing/pacing of the ventricular LP (model LSP202V).

Clinical data from subjects implanted with the Aveir DR LP system will be leveraged to support the use of the Aveir atrial LP for AAI(R) pacing indications through the collective evaluation of its safety and performance through three endpoints: the primary effectiveness endpoint #1, a secondary safety endpoint, and a secondary effectiveness endpoint.

The secondary safety endpoint will evaluate the atrial-only complication-free rate at 12 months post-implant. The primary effectiveness endpoint #1 will evaluate the atrial sensing and pacing performance at 12 months post-implant, and the secondary effectiveness endpoint will evaluate the atrial rate response while programmed to AAI(R) mode during graded exercise testing. Rate response pacing is based on temperature measures from the *atrial* LP while programmed to AAIR mode only. [redacted]

2.0 CLINICAL INVESTIGATION OVERVIEW

2.1 Clinical Investigation Objective

2.1.1 Primary Objectives

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

2.1.2 Secondary Objectives

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

2.2 Device(s) Used in the Clinical Investigation

2.2.1 Name of the Device(s) Under Investigation

The Aveir™ DR LP system in this clinical investigation include the components listed in Table 1 below, all of which are currently approved for investigational use only. Further details regarding the devices under investigation are provided in the Instructions for Use (IFU).

Table 1. Identification of Devices Under Investigation

Device name	Model/Type/ Software version	Serial/Lot Controlled	Manufacturer	Region/ Country	Investigational or Market Released
Aveir™ Leadless Pacemaker	LSP201A (Right Atrial) LSP202V (Right Ventricular)	Serial number	Abbott Medical	United States Canada Europe Asia Pacific	Investigational
Aveir™ Delivery Catheter (DR)	LSCD201	Lot number	Abbott Medical	United States Canada Europe Asia Pacific	Investigational
Aveir™ Introducer, 30 cm	LSN25301	Lot number	Abbott Medical	United States Canada Europe Asia Pacific	Market Released Market Released Approved, Not Market Released Investigational
Aveir™ Introducer, 50 cm	LSN25501	Lot number	Abbott Medical	United States Canada Europe Asia Pacific	Market Released Market Released Approved, Not Market Released Investigational
Aveir™ Retrieval Catheter	LSCR111	Lot number	Abbott Medical	United States Canada Europe Asia Pacific	Market Released Market Released Approved, Not Market Released Investigational
Aveir™ Link Module	LSL02	Serial number	Abbott Medical	United States Canada Europe Asia Pacific	Market Released Market Released Investigational Investigational

Device name	Model/Type/ Software version	Serial/Lot Controlled	Manufacturer	Region/ Country	Investigational or Market Released
Aveir™ Programmer Software Application	Merlin Software (Model 3330 with Aveir IDE Software application (version 25.4.1 and higher)	N/A	Abbott Medical	United States Canada Europe Asia Pacific	Investigational

2.2.2 Indication for Use

The Aveir™ DR LP system is intended to be indicated for management of one or more of the following permanent conditions:

- Syncope
- Pre-syncope
- Fatigue
- Disorientation

Rate-Modulated Pacing is intended to be indicated for patients with chronotropic incompetence, and for those who would benefit from increased stimulation rates concurrent with physical activity.

Dual-Chamber Pacing is intended to be indicated for patients exhibiting:

- Sick sinus syndrome
- Chronic, symptomatic second- and third-degree AV block
- Recurrent Adams-Stokes syndrome
- Symptomatic bilateral bundle branch block when tachyarrhythmia and other causes have been ruled out

Atrial Pacing is intended to be indicated for patients with:

- Sinus node dysfunction and normal AV and intraventricular conduction systems

Ventricular Pacing is intended to be indicated for patients with:

- Significant bradycardia and normal sinus rhythm with only rare episodes of AV block or sinus arrest
- Chronic atrial fibrillation
- Severe physical disability

2.2.3 Description of the Device(s) Under Investigation

The Aveir™ DR LP system supports the implantation and use of an Aveir LP within the targeted chamber(s) of the heart for monitoring a patient's heart rate and providing rate-responsive bradycardia pacing therapy to regulate the heart rate.

The LP and all its accessories (except for the Link Module) are single-procedure devices and are furnished sterile. Detailed information regarding the Aveir™ DR LP system can be found in the Instructions for Use for each device.

2.2.3.1 Aveir LP

Intended Use: The Aveir™ LP (model LSP201A - right atrial and LSP202V - right ventricular) is designed to provide bradycardia pacing as a pulse generator with built-in battery and electrodes for implantation in the right ventricle and/or right atrium. The LP is intended to provide sensing of cardiac signals and delivery of cardiac pacing therapy within the implanted chamber for the target treatment group. The LP is also intended to operate optionally with another co-implanted LP to provide dual-chamber pacing therapy.

As a leadless device, the Aveir LP does not need a connector, pacing lead, or pulse generator pocket. The LP is delivered to the target heart chamber percutaneously via the femoral vein through an Aveir Introducer and Aveir Delivery Catheter. The proximal end of the LP has a feature for docking to delivery and retrieval catheters, providing for repositioning and retrieval capability. A distal non-retractable, helix affixes the LP to the endocardium of the target heart chamber. Three additional features on the outside of the LP nosecone are designed to provide secondary fixation securement.

Sensing and pacing occur between a distal electrode near the fixation helix and the external can of the LP. The tip electrode includes a single dose of dexamethasone sodium phosphate (DSP), intended to reduce inflammation. The distal tip electrode is a titanium-nitride coated platinum-iridium disc located at the center of the fixation helix. The ring electrode is the uncoated proximal part of the titanium pacemaker case.

The LP senses local blood pool temperature to provide rate modulated pacing with changes in metabolic demand.

<u>Communication Between Co-Implanted Leadless Pacemakers</u>

To allow dual-chamber synchronous sensing and pacing to occur, each LP communicates bidirectionally with the programmer system and also beat-to-beat with a paired, co-implanted LP. Through i2i™ (implant-to-implant) communication via two electrodes on each LP, electrical signals are output with data encoded in a series of short pulses delivered concurrently with each local paced or sensed event.

Generally, in a dual-chamber operating mode, the RV-implanted LP manages overall pacing and timing functions, while the pacing and timing functions of the RA-implanted LP are managed indirectly by the RV-implanted LP. The RV-implanted LP's activity sensor determines the target sensor-indicated rate to be used by both LPs and the rate is set (or updated) through i2i communication.

In the event of a sustained disruption in communication between the co-implanted LPs, the system will automatically revert to ventricular-only pacing mode until communication is restored.

<u>Communication Between Leadless Pacemaker and Programmer</u>

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Each LP communicates bi-directionally with the external Aveir Link Module in conjunction with a Merlin Patient Care System (PCS) Model 3650 programmer to interrogate and program the LP and to monitor electrocardiogram (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 electrogram (EGM) for current of injury assessment. An EGM shows the heart's electrical activity as sensed by the pacing system. The current of injury is a measure intended to assess implant integrity during the implant procedure, like conventional transvenous leads.

Each Aveir LP is supplied contained inside a Loading Tool to hold the LP until the implantation procedure. The Loading Tool with the LP facilitates connection of the LP to the Delivery Catheter. The Loading Tool does not have direct patient contact. Figure 1 and Table 2 below show the Loading Tool and features of both Aveir LPs.

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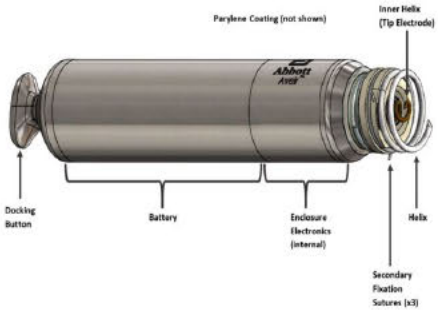
Figure 1 - Loading Tool and LPs

LP packaged in Loading Tool

Aveir LP (Right Atrial)



Aveir LP (Right Ventricular)

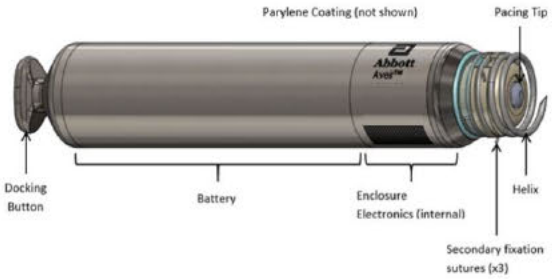


Table 2 – LP Features

Model	LSP201A (Right Atrial)	LSP202V (Right Ventricular)
Length	32.2 mm (1.27 in)	38.0 mm (1.50 in)
Diameter	6.5 mm (0.26 in)	6.5 mm (0.26 in)
Volume	1.0 cm^3	1.1 cm^3

Mass	2.1 grams	2.4 grams
Fixation Mechanism	Distal non-retractable helix	Distal non-retractable helix
Fixation Depth	Approximately 1.63 mm	Approximately 1.63 mm
Electrode Tip	Helical	Domed
Electrode spacing	≥ 24 mm	≥ 24 mm
Ring electrode geometric surface area	~124 mm^2	~244 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.

2.2.3.2 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 LP. Delivery and manipulation include implanting an LP within the target chamber of the heart.

The Aveir™ Delivery Catheter 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 introducer sheath hemostasis valve and advance the system into the femoral vein.

The delivery catheter system provides a means to perform these actions during the implantation procedure:

- Attach and dock a separate LP pre-loaded in the loading tool
- Position the protective sleeve over the LP's fixation 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 target heart chamber
- 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
- 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 leaving the LP tethered to the delivery catheter to measure thresholds with minimal force transmission from the delivery catheter
- Re-dock to the delivery catheter, unscrew and reposition the LP if necessary for acceptable thresholds
- Disconnect the LP from the tethers of the delivery catheter, leaving the LP implanted in the endocardium

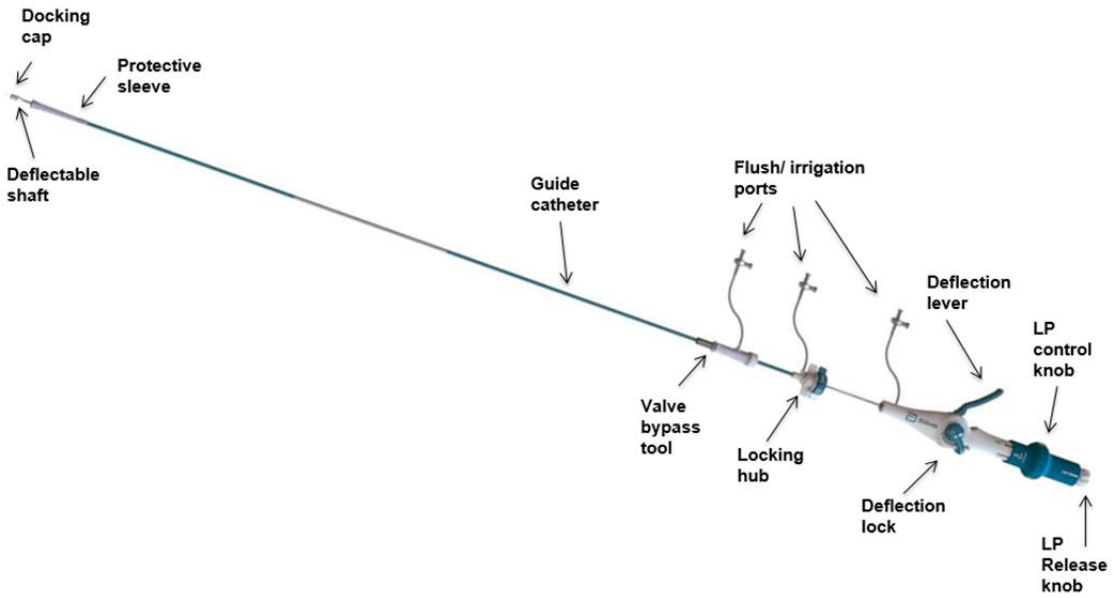
Apart from the docking mechanism, the delivery catheter and its control system (handle) have the same operating principle as a conventional steerable catheter and control system.

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

For further information refer to the Instructions for use for the Aveir™ Delivery Catheter.

Figure 2 below shows mechanical characteristics of the delivery catheter:

Figure 2– Aveir™ Delivery Catheter



2.2.3.3 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 to interrogate and program an Aveir LP and to monitor LP function during an implant, retrieval, or follow-up procedure.

The Aveir™ Link Module 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 interrogate and program 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 USB port of the Merlin™ PCS Model 3650.

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.

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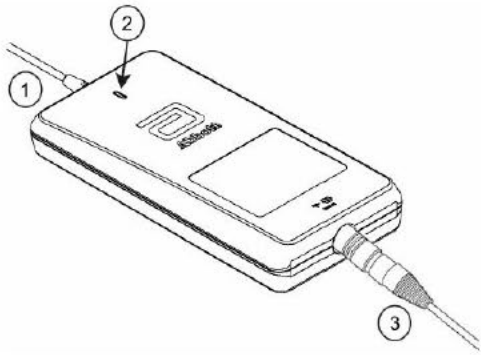
The Aveir™ Programmer Software interfaces with the Aveir™ Link Module and Merlin PCS Programmer to provide a communication link to one or more LPs implanted in a patient. The Programmer Software, Model 3330 with Aveir IDE software is used to configure the LP with appropriate features and pacing characteristics. The Aveir DR programmer software version used by all sites will be the same. Some variances in software versions will be released to different geographies to accommodate geographically-specific market approved pacemakers and ICD models. Please refer to the Investigator Brochure for the most current software version. 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.
Figure 3 and Table 3 below show the mechanical characteristics of the Link Module:

Figure 3 – 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 3 – 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

2.2.3.4 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.

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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 Catheter and Aveir™ Retrieval Catheter.

The Introducer is comprised of 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 and maintain hemostasis during insertion and/or exchange, a sideport with a three-way stopcock, and a suture loop. The introducer sheath 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 Instructions for use for the Aveir™ Introducer.

Figure *4* below shows the mechanical characteristics of the 25F introducer:

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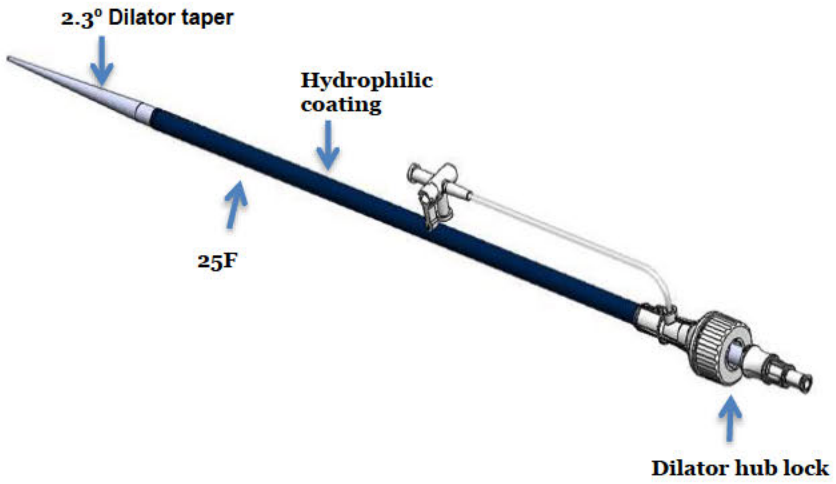
Figure 4 – Aveir™ Introducer and Dilator



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)

2.2.3.5 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 Abbott Medical leadless pacemaker (LP). Retrieval and manipulation includes removing the LP from the heart or peripheral vasculature.

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

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

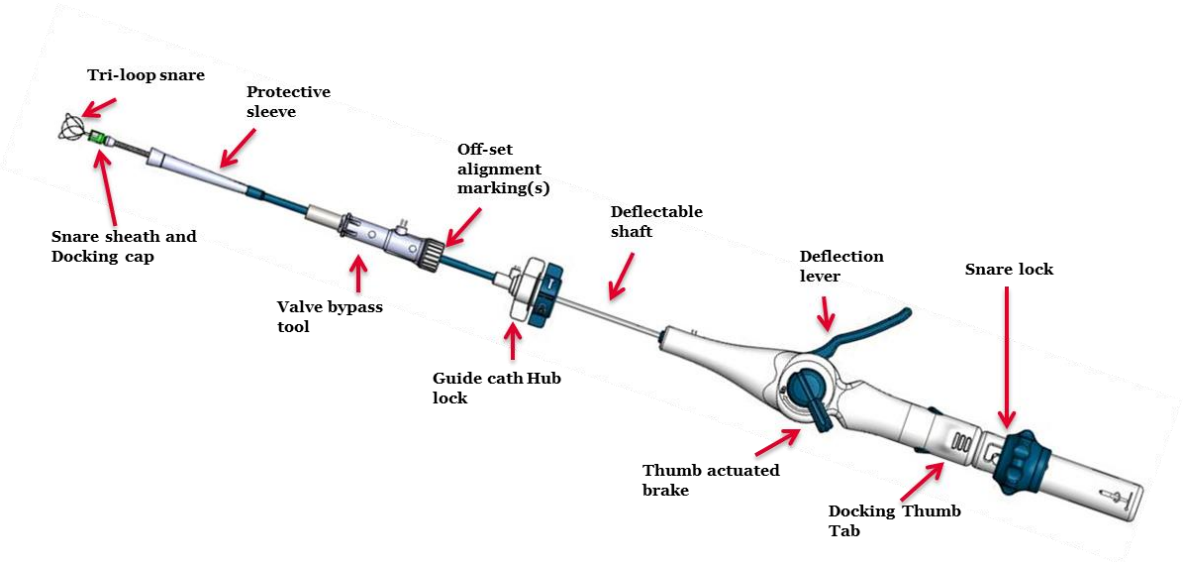
- Advance the retrieval catheter system from an access site in the groin (utilizing minimally invasive techniques) through the femoral vein into the heart
- Steer and position the snare toward the docking button of the LP
- Snare the docking button of the LP
- Dock the retrieval catheter to the LP
-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

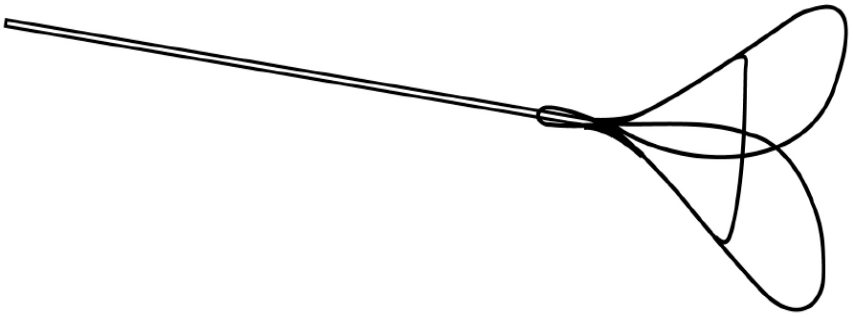
For further information refer to the Instructions for use for the Aveir™ Retrieval Catheter.

Figure 5 below shows the mechanical characteristics of the Retrieval Catheter.

Figure 5 – Aveir™ Retrieval Catheter



Catheter effective length = 105 cm (41.3 inches)



Snare loop inner diameter = 16.5 mm (0.65 inch)

2.2.4 Device Handling

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.

3.0 CLINICAL INVESTIGATION DESIGN

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

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

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

[redacted]

[redacted] Pre-market submissions to other country regulatory agencies will made be per local requirements.

The Sponsor has designed this clinical investigation 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.

Clinical Investigation Plan for Europe

3.1 Clinical Investigation Procedures and Follow-up Schedule

The flowchart and the follow-up requirements of this clinical investigation are described below.

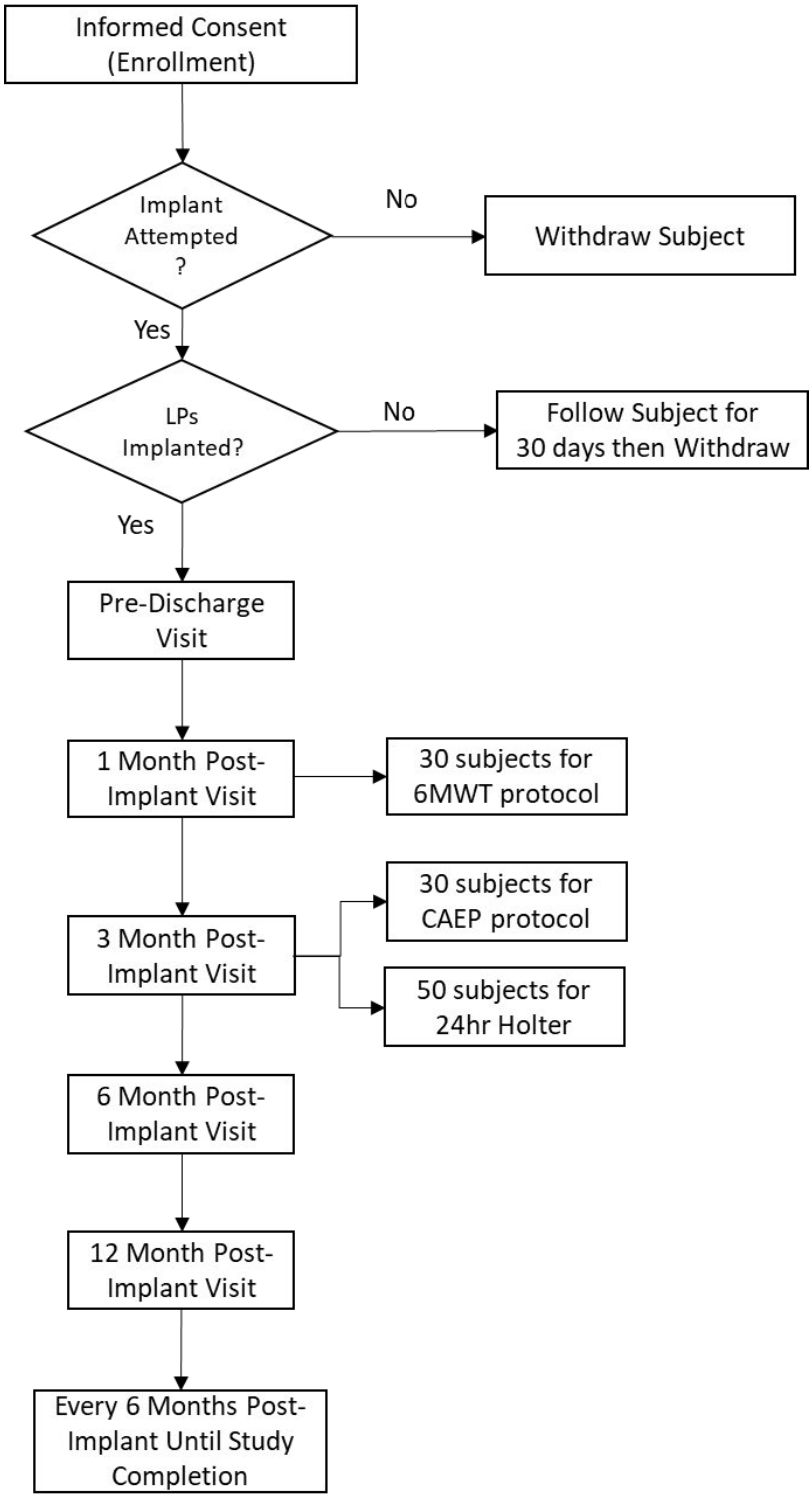
Subjects will be screened for study eligibility by the investigator and/or research staff per the inclusion and exclusion criteria listed in Section 5.3. Subjects that do not meet the inclusion and exclusion criteria will be exited from the study as a screen failure.

Clinical study assessments will occur at baseline, implant procedure, pre-discharge, 1 month, 3 months, 6 months, 12 months, and every 6 months thereafter until study completion.

Follow-up visits will be conducted in-person at the investigational site and will include a combination of standard of care and study-specific testing.

Clinical Investigation Plan for Europe

Figure 6: Clinical Investigation Flowchart



3.2 Measures Taken to Avoid and Minimize Bias

Multiple measures will be taken to avoid and minimize bias in this clinical investigation. This is a prospective clinical investigation in which the outcome is unknown at the time of enrollment and all subjects must meet the defined eligibility criteria to minimize selection bias. The Sponsor will provide guidance to sites regarding data collection for post-procedure follow-up visits. Additionally, the Sponsor will provide case report forms for data collection to sites, which will minimize inter-observer variability.

An independent Clinical Events Committee (CEC) will perform an evaluation of primary safety endpoint data . Additionally, an independent core laboratory will evaluate collected Holter data from sites to determine AV synchrony performance in subjects.

The Sponsor will use a CEC made up of physicians who are not investigators to adjudicate all adverse events (AEs) determined by the Sponsor's Safety group to potentially meet the criteria of 1) a serious AE and/or 2) an AE related to the investigational devices or procedures. To minimize bias, only the CEC's adjudication of the collected data will be used for the analysis of the primary safety endpoint.

Protocols are also in place to minimize subjects who are lost-to-follow-up (Section 5.5). Sensitivity analyses will be performed to evaluate the impact that missing data may have on the clinical investigation.

The Sponsor will establish an independent Data and Safety Monitoring Board (DSMB) (Section 10.9.3) that will serve in an advisory role to ensure safety by reviewing cumulative data from the clinical investigation at prescribed intervals for the purpose of safeguarding the interests of enrolled subjects and those patients yet to be enrolled, as well as the continuing validity and scientific merit of the clinical investigation.

3.3 Suspension or Early Termination of the Clinical Investigation

The CIP does not define a formal statistical rule for early termination of the clinical investigation for insufficient effectiveness of the device under investigation. However, the Sponsor reserves the right to discontinue the clinical investigation at any stage or reduce the follow-up period with suitable written notice to the investigator. Possible reason(s) may include, but are not limited to:

- Unanticipated adverse device effect (e.g., UADE) occurs and it presents an unreasonable risk to the participating subjects
- Serious health threat
- An oversight committee, (i.e. DSMB) makes a recommendation to stop or terminate the clinical investigation (such as higher frequency of anticipated adverse device effects)
- Further product development is cancelled

3.3.1 Subject Follow-up in cases of early termination or suspension

Should the Sponsor discontinue the clinical investigation, sites will follow subjects per routine hospital practice with device-related AEs reported to the Sponsor as per vigilance/commercial reporting requirements. The investigator shall return all clinical investigation materials (including

devices) to the Sponsor and provide a written statement to the IRB/EC (if applicable). All applicable clinical investigation documents shall be subject to the same retention policy as detailed in Section 11.5 of the CIP. A final report will be provided to investigators, competent authorities, and all IRBs/ECs within 3 months of the end of a study in the event of early termination or temporary halt.

If the Sponsor suspends or prematurely terminates the clinical investigation at an individual site in the interest of safety, the Sponsor will inform all other Principal Investigators.

If suspension or premature termination occurs, the Sponsor will remain responsible for providing resources to fulfill the obligations from the CIP and existing agreements for following the subjects enrolled in the clinical investigation, and the Principal Investigator or authorized designee will promptly inform the enrolled subjects at his/her site, if appropriate.

A Principal Investigator, IRB/EC, or regulatory authority may also suspend or prematurely terminate participation in the clinical investigation at the investigational site(s) for which they are responsible. The investigators will follow the requirements specified in the Clinical Trial Agreement.

If a suspended investigation is to be resumed, a prior approval should be obtained from the EC/IRB and a notification should be sent to the regulatory bodies.

4.0 ENDPOINTS

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

4.1 Primary Endpoints and Rationale

4.1.1 Primary Safety Endpoint

The primary safety endpoint evaluates the 12-month Aveir DR LP system complication-free-rate in *de novo* subjects based on CEC adjudication of adverse events.

A complication is defined as a device-or-procedure-related serious adverse event (SADE), including those that prevent initial implantation (includes both Atrial LP and Ventricular LP related complications and implant procedure-related complications).

4.1.1.1 Rationale for Selection of the Primary Safety Endpoint

The primary safety endpoint evaluates a device- or procedure-related SADE rate which is an appropriate measure for safety and consistent with the primary safety endpoints used in the Leadless II IDE trial (Phase 1: NCT02030418 and Phase 2: NCT04559945) and multiple pre-market leadless pacemaker trials. The 12-month follow-up period for the primary safety endpoint analysis is consistent with the minimum follow-up duration for CE-approved trials

recommended in the MHRA Leadless Expert Advisory Guidance document.[17] In addition, The 12-month timepoint for assessing the primary safety endpoint is an appropriate time period as outlined in FDA's Executive Summary on leadless pacemaker devices (February 2016): "based on publicly available clinical data for leadless pacemaker devices, it is known that the overwhelming majority of complications occur within 30 days, most within 14 days".[8] In the Leadless II IDE study, all SADEs for the primary safety endpoint analysis occurred within the 30-day early post-procedure period.[9]

4.1.2 Primary Effectiveness Endpoint #1

The primary effectiveness endpoint #1 evaluates the 12-month composite success rate of acceptable atrial pacing thresholds and P-wave amplitudes in *de novo* subjects. Acceptable ranges for sensing and pacing are shown below:

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

4.1.2.1 Rationale for Selection of the Primary Effectiveness Endpoint #1

The primary effectiveness endpoint #1 evaluates the ability of the atrial leadless pacemaker to pace and sense according to the intended use. The evaluation of a composite success rate of acceptable pacing thresholds and sensing amplitudes is consistent with the primary effectiveness endpoints used in the Leadless II IDE trial (Phase 1: NCT02030418 and Phase 2: NCT04559945) and multiple pre-market leadless pacemaker trials. This endpoint evaluates the atrial LP performance only since the ventricular LP performance is evaluated in the Leadless II IDE trial – Phase 2. The 12-month timepoint for assessing the primary effectiveness endpoint#1 is an appropriate time period since these electrical measurements have been demonstrated to be stable starting as early as 2 weeks post-implant based on data from the Leadless II IDE trial (Phase 1).[9]

4.1.3 Primary Effectiveness Endpoint #2

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

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

4.1.3.1 Rationale for Selection of the Primary Effectiveness Endpoint #2

The primary effectiveness endpoint #2 evaluates the ability of the atrial and ventricular LPs to maintain AV synchrony which is essential for a dual-chamber pacemaker system. A cardiac cycle will be considered synchronous if a paced or sensed ventricular beat is within 300 ms

following a paced or sensed atrial beat. The selection of this endpoint is based on the known clinical presentation of symptoms for patients with AV conduction abnormalities with PR intervals greater than 300 ms. Patients with marked prolongation of the PR interval >300 ms exhibit symptoms similar to those with pacemaker syndrome that is due to loss of AV synchrony and atrial contraction against closed atrioventricular valves[14]. The evaluation of AV synchrony at rest while seated and the definition of success with at least 70% of evaluable cardiac cycles is based on similar, predicate device studies for market approval. [15]

4.1.4 Secondary Safety Endpoint

The secondary safety endpoint evaluates the 12-month Aveir atrial LP complication free rate in *de novo* subjects based on CEC adjudication of adverse events.

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

4.2 Other Secondary Endpoint

4.2.1 Secondary Effectiveness Endpoint

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

4.3 Additional Data

The clinical investigation will collect and report the following additional data descriptively using only summary statistics. The Sponsor will not perform hypothesis tests with pre-specified criteria on this additional data collected.

- Demographics: gender, age, ethnicity/race (if provided), indication for pacemaker implant
    - Comparisons of demographics between the study population to the existing dual-chamber pacemaker population by region
- Medical history
- Use of beta blocker, ACE, ARB, anti-coagulation, anti-arrhythmic, and anti-platelet medications
- 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 repositionings at time of implantation
- Implant duration, fluoroscopy duration, and time from implant to hospital discharge

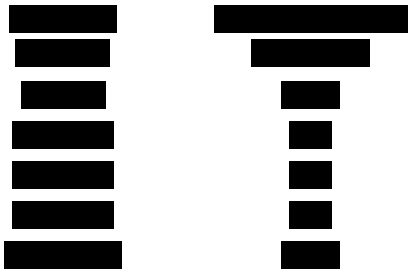
- Optional: Pre-procedure (i.e. MRI, CT, X-ray) and procedural imaging (i.e. ICE) measures to evaluate the right atrium and/or the atrial LP based on any imaging data provided to the Sponsor
- Final location of LP placement
- Remaining device longevity at the six-month visit, as displayed by the programmer based on delivered therapy, programmed settings, percent pacing, and measured pacing impedance
- Average base rate, impedance, pulse amplitude, pulse duration, and percentage pacing at all visits
- Hospitalizations
- Mortality
- Upgradeability of the Aveir ventricular LP (VR) into the Aveir DR LP system summarized by:
  - Success rate of VR to DR upgrades and reasons for unsuccessful upgrades.
  - Summary of adverse events related to upgrades
  - Summary of device measurements for subjects with an upgrade
- AV synchrony (at various positions and activity levels)
- EQ-5D Health-Related Quality of Life Analysis

4.3.1 24-hour Holter Monitor Data Analysis

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

The investigational plan does not require inclusion of pacer-dependent subjects to assess the device's pacing capabilities because it is expected that approximately 65% of subjects will have ≥60% pacing, based on data from transvenous pacemakers (for 1,395 subjects with a mean follow-up of 5.8 years, 74% dual-chamber pacemakers), provided below: [16]

Histogram of percentage pacing:



The Sponsor will provide a 24-hour Holter summary report to the respective in-country regulatory agency, which includes the following for each subject:

- Minimum, maximum, and average heart rate
- Percent atrial pacing
- A telemetry strip of the minimum heart rate and a telemetry strip during pacing (the pacing strip may be the same as the minimum heart rate strip, but is not required).
- Number of pauses seen (defined as RR interval greater than or equal to 2 sec or < 30 bpm)
- All telemetry strips of a pause greater than the programmed lower rate limit after accounting for any hysteresis programming
- All telemetry strips showing evidence of atrial oversensing, undersensing, or loss of capture
- Programmed parameters (which are necessary to assess if the pauses or minimum heart rate seen on Holter are appropriate or not)
- AV Synchrony
- Appropriate Automatic Mode Switching (AMS) due to atrial arrhythmias
- Reported adverse events and/or subject symptoms with diary entry that is timed and dated to correlate Holter findings with events and/or symptoms.

5.0 SUBJECT SELECTION AND WITHDRAWAL

5.1 Subject Population

This clinical investigation will enroll subjects of all genders over the age of 18 years who are indicated for a DDD(R) pacemaker. Patients must meet all general eligibility criteria and provide written informed consent prior to sites conducting any investigation-specific procedures not considered standard of care.

5.2 Subject Recruitment/Screening and Informed Consent

5.2.1 Subject Recruitment and Screening

The following assessments are performed as part of the subject recruitment process prior to obtaining informed consent:

- Demographics (age on consent date, gender)

- Medical history screening (including major cardiovascular, vascular, and other coexisting medical conditions associated with eligibility criteria)

A member of the site's clinical investigation team previously trained to the CIP must evaluate patients for the general clinical investigation eligibility criteria and will enter all screened patients into a site-specific recruitment/screening log. A patient who does not satisfy all general eligibility criteria prior to informed consent is considered a recruitment failure and should not be enrolled in the clinical investigation.

Sites will ask patients meeting general inclusion criteria and no general exclusion criteria to sign an Informed Consent form following the established Informed Consent process (described in Section 5.2.2) if they wish to participate in the clinical investigation. Sites will enter these patients into the recruitment/screening log.

Patients who have signed an informed consent and are subsequently found not to meet eligibility criteria prior to an attempted implant are considered screen failures and should be withdrawn.

5.2.2 Informed Consent

The Investigator or his/her authorized designee will conduct the Informed Consent process, as required by applicable regulations and the center's IRB/EC. This process will include a verbal discussion with the patient on all aspects of the clinical investigation that are relevant to the patient's decision to participate, such as details of clinical investigation procedures, anticipated benefits, and potential risks of clinical investigation participation. Sites must inform patients about their right to withdraw from the clinical investigation at any time and for any reason without sanction, penalty, or loss of benefits to which the patient is otherwise entitled. Withdrawal from the clinical investigation will not jeopardize their future medical care or relationship with the investigator.

During the discussion, the Principal Investigator or his/her authorized designee will avoid any improper influence on the patient and will respect the patient's legal rights. Financial incentives will not be given to patients. However, patients may be compensated for time and travel directly related to the participation in the clinical investigation. The site shall provide the patient with the Informed Consent form (ICF) written in a language that is understandable to the patient and that has been approved by the center's IRB/EC. The patient shall have adequate time to review, ask questions, and consider participation. The Principal Investigator or his/her authorized designee will make efforts to ensure that the patient understands the information provided. If the patient agrees to participate, they must sign and date the Informed Consent form, along with the person obtaining the consent prior to any clinical investigation-specific procedures. The site will file the signed original in the patient's hospital or research charts and provide a copy to the patient. The dated signatures can be electronic. The site will follow local hospital and local EC/IRB provisions for documenting electronic ICF signature.

Sites should report any failure to obtain informed consent from a patient to the Sponsor within 5 working days and to the reviewing center's IRB/EC according to the IRB's/ EC's reporting requirements.

Subjects must provide written informed consent prior to any clinical investigation-related procedure. If, during the clinical investigation, new information becomes available that can significantly affect a subject's future health and medical care, the Principal Investigator or his/her authorized designee (if applicable) will provide this information to the subject. If relevant, sites will ask the subject to confirm their continuing informed consent in writing.

5.2.2.1 Special Circumstances for Informed Consent

This clinical investigation excludes individuals unable to make the decision to participate in a clinical investigation on their own or who are unable to fully understand all aspects of the investigation that are relevant to the decision to participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response.

This clinical investigation excludes individuals under the age of 18 or age of legal consent from the clinical investigation population.

The clinical investigation excludes individuals unable to read or write.

The clinical investigation excludes pregnant or breastfeeding women.

All other aspects of the Informed Consent process will follow Section 5.2.2.

For live case presentations or live case remote observations, the patient needs to sign a specific Live Case ICF, approved by the IRB/EC and by the Sponsor, as well as by the respective regulatory or competent authorities, as applicable. The investigator must request Sponsor approval prior to performing a Live Case.

5.3 Eligibility Criteria

5.3.1 General Eligibility Criteria

Assessment for general eligibility criteria is based on medical records of the site and interview with a candidate patient. Patients must meet ALL general inclusion criteria to participate in the clinical investigation. If ANY general exclusion criteria are met, the patient is excluded from the clinical investigation and cannot be enrolled.

If any clinical and/or laboratory tests are required for patient screening and are not included in a site's standard tests, they must be completed after written informed consent is obtained.

5.3.2 Inclusion Criteria

5.3.2.1 General Inclusion Criteria

1. Subject must have at least one of the clinical indications before device implant in adherence with ACC/AHA/HRS/ESC dual chamber pacing guidelines
2. Subject is ≥ 18 years of age or age of legal consent, whichever age is greater
3. Subject has a life expectancy of at least one year
4. Subject is willing to comply with clinical investigation procedures and agrees to return to clinic for all required follow-up visits, tests, and exams
5. Subject has been informed of the nature of the clinical investigation, agrees to its provisions and has provided a signed written informed consent, approved by the IRB/EC

5.3.3 Exclusion Criteria

5.3.3.1 General Exclusion Criteria

1. Subject is currently participating in another clinical investigation that may confound the results of this study as determined by the Sponsor
2. Subject is pregnant or nursing and those who plan pregnancy during the clinical investigation follow-up period
3. Subject has presence of anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could confound the assessment of the investigational device and/or implant procedure, limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements of the clinical investigation results
4. Subject has a known allergy or hypersensitivity to < 1 mg of dexamethasone sodium phosphate or any blood or tissue contacting material listed in the IFU
5. Subject has an implanted vena cava filter or mechanical tricuspid valve prosthesis
6. Subject has pre-existing, permanent endocardial pacing or defibrillation leads (does not include lead fragments)
7. Subject has current implantation of either conventional or subcutaneous implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) device
8. Subject has an implanted leadless cardiac pacemaker (except for an Aveir ventricular LP)
9. Subject is implanted with an electrically-active implantable medical device with stimulation capabilities (such as neurological or cardiac stimulators)*
10. Subject is unable to read or write

*NOTE: Does not apply to a medical device with no known impact to the Aveir Leadless Pacemaker System, including the Aveir Link Module. Patient evaluation and the decision to implant the LP should take into account the presence of other active implantable devices and should include consultation with the Sponsor and/or manufacturer of the co-existing device.

5.4 Subject Enrollment

A patient is considered enrolled in the clinical investigation from the moment the patient provides written informed consent.

All enrolled subjects who meet eligibility criteria should undergo an attempted implant. A subject may withdraw or be withdrawn prior to the implant attempt. If an enrolled subject does not undergo an attempted implant, the subject should be withdrawn as soon as possible.

If subjects receive a device without meeting all the conditions listed above, they should still complete all follow-up requirements. These subjects are considered CIP deviations.

5.4.1 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

Historically, Phase 1 of the Leadless II IDE trial, mainly in the US, included 38% females, an average age of 75.8 years, and 9% non-white ethnic minorities[1]. This clinical investigation will also enroll subjects in the US and has identical criteria on the enrollment of female and minority ethnicity. As such, Abbott expects similar proportions of female and minority ethnicity for this study. The traditional barriers for female enrollment (such as fear or fetal consequence, family plan of new pregnancies that may limit the ability of time commitment to follow-up) are not applicable to this clinical investigation due to the expected average age of the patient population. Therefore, the eligibility criteria of this clinical study do not introduce gender or racial bias

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

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

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

5.5 Subject Withdrawal and Discontinuation

Each subject meeting all general and screening eligibility criteria shall remain in the clinical investigation until completion of the required follow-up period; however, a subject's participation in any clinical investigation is voluntary and the subject has the right to withdraw at any time without penalty or loss of benefit. Conceivable reasons for discontinuation may include, but are not limited to, the following:

- Subject death
- Subject voluntary withdrawal
- Subject lost-to-follow-up
- Subject's follow-up is terminated according to Section 3.3
- Unsuccessful Implant
- LP explanted and not re-implanted
- LP abandoned and Aveir LP not re-implanted

Sites must notify the Sponsor of the reason(s) for subject discontinuation. Investigators must also report this to their respective IRB/EC as defined by their institution's procedure(s).

No additional follow-up is required or data recorded from subjects once withdrawn from the clinical investigation, except for the status (deceased/alive).

However, if a subject withdraws from the investigation due to problems related to the safety or performance of the device under investigation, the investigator shall ask for the subject's permission to follow his/her status/condition outside of the clinical investigation according to standard of care.

Lost-to-Follow-up

[redacted]

If the subject misses two consecutive scheduled follow-up time points and the attempts at contacting the subject detailed below are unsuccessful, then the subject is considered lost-to-follow-up. Site personnel shall make all reasonable efforts to locate and communicate with the subject (and document these efforts in the source documents), including the following, at each contact time point:

- A minimum of two telephone calls on different days over the specified follow-up windows to contact the subject should be recorded in the source documentation, including date, time and initials of site personnel trying to make contact.
- If these attempts are unsuccessful, the site should send a certified letter to the subject.
- If a subject misses one or more non-consecutive follow-up contact time points, it will be considered a missed visit. The subject may then return for subsequent visits. If the subject misses two consecutive time points and the above-mentioned attempts at communicating with the subject are unsuccessful, the subject will be considered lost-to-follow-up.

Note: Telephone contact with a General Practitioner, non-clinical investigation cardiologist or relative without the presence of the subject or indirect documentation obtained via discharge letters will not be considered as subject contact.

5.6 Number of Subjects

The clinical investigation will enroll up to 550 subjects at up to 85 sites worldwide to analyze the primary endpoints that is based on the following:

- 300 *de novo* subjects to evaluate the primary endpoints, including attrition
- Up to 200 *de novo* subjects [redacted]
- Up to 50 subjects to assess the upgradeability to a Aveir DR LP system in subjects previously implanted with the Aveir VR LP single chamber system

[redacted]

Subjects previously implanted with an Aveir VR LP who are enrolled to assess the upgradeability to an Aveir DR LP system (up to 50) will be concurrently enrolled with the *de novo* subjects but will not contribute toward the evaluation of the primary and secondary endpoints.

No site may enroll more than 15% of the total subjects required to evaluate the primary endpoints.

[redacted]

5.7 Total Expected Duration of the Clinical Investigation

The expected duration of each subject's participation in the clinical study is 1 year including the scheduled visits and data collection as listed in Section 6.6. All enrolled subjects will be followed through subject withdrawal or site closure, whichever occurs first. Site closure will not begin until all active subjects across all active study sites have completed their 12-month follow up visits or the 12-month visit window has passed and approval for commercial use is received from local regulatory agencies. For more information about the clinical investigation conclusion and site closure, see Section 13.0.

[redacted]

6.0 TREATMENT AND EVALUATION OF ENDPOINTS

6.1 Baseline Assessment

Investigators will document each subject's demographics including age at consent, sex, height, weight, and race/ethnicity (if applicable). Investigators will also document each subject's baseline medical history, including cardiopulmonary history, patient LP status (e.g. *de novo* or pre-existing Aveir LP), and cardiac medications. Investigators will document the cardiac drug categories for the cardiac medications (e.g. beta blockers, ACE inhibitors, ARBs, anti-coagulants, anti-platelets, anti-arrhythmics) as well as any changes to these medications during the follow-up period.

Investigators will obtain a 12-lead ECG only if one has not already been recorded within the last 30 days prior to the implant date. Investigators will administer an EQ-5D 5L quality of life survey to each subject prior to implant and record the responses. All subjects will undergo routine laboratory assessment per the site's standard of care.

For female subjects of childbearing age, investigators will document a pregnancy assessment according to the site's standard test method, which may include obtaining a blood sample for conducting a pregnancy test. Any pregnancy test must be done after the subject signs an ICF. A negative pregnancy test result must be obtained within 7 days prior to the index procedure.

6.1.1 Data Submission

Once the site has collected the required information and completed the required testing, the site will complete and submit the following case report forms to Abbott Medical using the EDC system:

- Enrollment Form
- Medical History Forms
- Quality of Life Assessment (EQ-5D 5L)
- Adverse Event Form, if applicable

- Deviation Form, if applicable
- COVID-19 Assessment Log, if applicable
- Study Withdrawal Form, if applicable

6.2 Implant Procedure

Please refer to the IFU for instructions on handling and preparation of the Aveir DR LP system. All Investigators must read and understand the IFU and Investigator Brochure (IB), as applicable. Sponsor representatives may also assist the team in equipment setup prior to and during a procedure.

6.2.1 Medications

Investigators 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 LP and is left to the investigator's discretion. During the procedure, appropriate anticoagulant therapy should be considered to reduce potential thrombus formation. Investigators will record any cardiac medications given prior to and during the implant procedure including beta blockers, ACE inhibitors, ARB, anti-coagulants, anti-platelets, and anti-arrhythmics.

6.2.2 Imaging

At a minimum, proper equipment must be available for high resolution fluoroscopy to assist with delivery and implantation of the LPs. The fluoroscopy must have the ability to record and save images, to zoom, and to obtain images in multiple projections, in accordance with the manufacturer's IFU.

Optional Imaging to Characterize Right Atrium

Investigators are also encouraged to use any other appropriate imaging modalities available at their sites during the procedure that can help characterize the right atrium/appendage and evaluate how the atrial LP is positioned relative to the local anatomy. Imaging modalities may include intraprocedural intracardiac echocardiography (ICE). Use of any supplemental imaging modalities is optional and is left to the investigator's discretion.

In addition, any pre-existing imaging of a subject's right atrium/appendage, such as pre-procedural MRI or CT, should be submitted to the Sponsor.

All imaging data obtained for the purpose of right atrial characterization should be de-identified and submitted to the Sponsor.

6.2.3 Femoral Vein Assessment and Access

The Sponsor supports using either ultrasound or fluoscopic guidance techniques for assessing femoral vein access-site location, including evaluation of the size and presence of any disease. However, investigators will use medical judgment and follow institutional standards of care when

accessing the femoral vein for catheter-based procedures. Only approved investigators will perform femoral vein access.

Investigators will insert and remove any investigational introducer sheaths in accordance with the manufacturer's IFU.

6.2.4 LP Preparation and Implant

Investigators will prepare and implant the Aveir LPs in accordance with the manufacturer's IFU. Consult the IFU for implantation guidelines and general handling information. Only approved investigators will perform the implant procedure, including placement of the Aveir device.

If both atrial and ventricular LPs are implanted, pairing in dual-chamber mode and establishing i2i communication must be attempted at the end of the procedure to verify that the system can be programmed in a dual-chamber pacing mode. If verified, subjects should be discharged and remain in a dual-chamber pacing mode throughout the study period. Investigators are permitted to change the pacing mode at any time if clinically appropriate.

Following the placement of both LP devices, investigators should obtain a cinefluoroscopy for at least 2 cardiac cycles in orthogonal views to evaluate final LP placement.

6.2.5 LP Assessment and Programming

Investigators and/or Sponsor representatives will interrogate the Aveir DR LP system using the market-approved St. Jude Medical™ Merlin™ Patient Care System (Model 3330) with the Aveir Link Module (Model LSL02).

Sponsor representatives may assist investigators in assessing pacemaker effectiveness (for example pacing, sensing, and rate response effectiveness), downloading diagnostic information, and programming pacemaker parameters.

Investigators will measure and record the following parameters:

- Atrial and Ventricular LP Capture threshold at 0.4 ms pulse duration*
- Atrial and Ventricular LP Impedance
- Atrial and Ventricular LP Sense Amplitude*
- Atrial and Ventricular i2i throughput
- Atrial and Ventricular i2i setting level
- Battery Voltage**
- Device Longevity and Remaining Capacity to recommended replacement time (RRT)**

** Atrial and Ventricular sense amplitude measurements are not required if the subject's intrinsic rate has been established to be below 30 beats per minute. Atrial capture threshold and sense amplitudes are not required if the subject is in atrial fibrillation or atrial flutter. Ventricular capture thresholds are not required if a high ventricular rate is present.*

***Not required at implant or pre-discharge visits.*

To avoid potential complications associated with undersensing, Investigators 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).

6.2.6 LP Repositioning and/or Release

Once the investigator implants an Aveir LP and successfully demonstrates acute effectiveness, the investigator may release the Aveir LP. When the investigator has released the Aveir LP, s/he will use fluoroscopy to assess positioning of the implanted LP.

Investigators may reposition the Aveir LP, if determined necessary. For release and repositioning procedures, refer to the IFU.

Once the Aveir LP has been released, investigators will use an Aveir Retrieval Catheter for removal, if needed (Refer to the Aveir Retrieval Catheter IFU). Once the LP has been removed, investigators may attempt to implant another Aveir LP, or instead, choose to implant a different market-approved pacemaker.

6.2.7 Subjects with two (2) LPs implanted

Investigators will follow subjects who leave an attempted *de novo* implant procedure with two Aveir LPs implanted through a minimum of 12-months post-implant according to the clinical investigation flowchart described in Figure 6.

6.2.8 Subjects with one (1) LP implanted

<u>De Novo Subjects</u>

Investigators will follow subjects who leave an attempted *de novo* implant procedure with one Aveir LP implanted through a minimum of 12-months post-implant according to the clinical investigation flowchart described in Figure 6.

The investigator must document the nature of and reasons for the unsuccessful LP implant on the Implant Form. Subjects who leave an index procedure with one LP implanted will not be eligible for re-implantation attempts of a second LP in a different chamber at a later date during the study period.

<u>Upgrade Subjects</u>

Investigators will follow subjects who leave an attempted *upgrade* procedure with an unsuccessfully implanted atrial LP for a period of at least 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 and reasons for the unsuccessful implant on the Implant Form. Subjects who have an unsuccessful upgrade will not be eligible for re-implantation attempts of an atrial LP at a later date during the study period.

6.2.9 Subjects without any LPs implanted

Investigators will follow subjects who leave an attempted *de novo* implant procedure without any implanted Aveir LPs for a period of at least 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 and reasons for the unsuccessful implant on the Implant Form. Subjects who have an unsuccessful implant will not be eligible for re-implantation attempts of any Aver LPs at a later date during the study period.

6.2.10 Healthcare Utilization

Procedural and post-procedural healthcare utilization information will primarily be used for health economics and reimbursement research purposes. All inpatient hospitalizations, outpatient services, emergency room and urgent care visits for cardiac or non-cardiac reasons, including any associated with LP system revision procedure(s) should be reported to the Sponsor via a Healthcare Utilization Form. Any supporting documentation (i.e., Admission/Discharge Summary) that is available should also be submitted to the Sponsor via the EDC system.

Healthcare utilization data to be collected includes the type, a subject's final primary diagnosis, any procedures performed, and billing information (if applicable). Submission of a Healthcare Utilization Form for the index LP implant procedure itself, without associated adverse events, is optional.

6.2.11 Data Submission

Once the site has collected the required information and completed the required testing, the site will complete and submit the following case report forms to Abbott Medical using the EDC system:

- Implant Forms
- Aveir LP Assessment and Programming Form (Implant) with device session print out PDFs
- Device Accountability Log
- Healthcare Utilization Form, if applicable
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- COVID-19 Assessment Log, if applicable
- Study Withdrawal Form, if applicable

All imaging data obtained for the purpose of right atrial characterization (e.g. ICE) should be de-identified and submitted to the Sponsor.

Any cinefluoroscopy imaging should be de-identified and submitted to the Sponsor upon Sponsor request.

6.3 System Revision with a Replacement Aveir LP

In the event an Aveir LP must be replaced during the follow-up period, investigators may opt to replace the first Aveir LP with a new Aveir LP in one of the following ways:

- Retrieve the first Aveir LP and implant a new Aveir LP
- Deactivate the first Aveir LP and implant a second Aveir LP in close proximity to the first

When considering Aveir LP retrieval and replacement, investigators will refer to the respective IFUs. Sponsor representatives may also assist the team in equipment setup prior to and during a procedure. If the subject receives a new Aveir LP, the subject must continue with his/her ongoing follow-up schedule.

6.3.1 Data Submission

The site will complete and submit the following case report forms and device print outs to Abbott Medical using the EDC system:

- System Revision Form
- Device Accountability Log
- Healthcare Utilization Form
- Aveir LP Assessment and Programming Form (Follow-Up) with device session print out PDFs
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- COVID-19 Assessment Log, if applicable

6.4 System Revision without a Replacement Aveir LP

In the event an Aveir LP must be replaced during the follow-up period, investigators may opt to revise the Aveir LP without a replacement Aveir LP in one of the following ways:

- Retrieve the Aveir LP and implant a commercially available pacemaker, CRT device, ICD, or not opt for a replacement device.
- Deactivate the Aveir LP and implant a commercially available pacemaker, CRT device, ICD, or not opt for a replacement device.

When considering Aveir LP retrieval, investigators will refer to the respective IFUs. Sponsor representatives may also assist the team in equipment setup prior to and during a procedure.

If the subject has all Aveir LPs removed or deactivated at any time during the clinical investigation, and the subject will not receive a replacement Aveir LP, the site will follow the subject for at least 30 days. At the end of the 30 days, the investigator will withdraw the subject. If the subject has at least one active Aveir LP after a system revision procedure, the subject must continue with his/her ongoing follow-up schedule.

6.4.1 Data Submission

The site will complete and submit the following case report forms to Abbott Medical using the EDC system:

- System Revision Form
- Device Accountability Log
- Healthcare Utilization Form
- Aveir LP Assessment and Programming Form (Follow-Up) with device session print out PDFs
- Study Withdrawal Form, if applicable
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- COVID-19 Assessment Log, if applicable

6.5 Pre-Discharge (In-hospital)

6.5.1 Access-site Management During Hospital Stay

Investigators will manage vascular-access sites per standard of care for procedures using large bore venous access. Investigators will assess and document any post-procedural access-site bleeding events 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 or other pressure dressing as per standard of care).

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 requires intervention including wound exploration (e.g., acutely expanding hematoma, acute leg pain/numbness/swelling) and/or prolongation of hospital stay.

6.5.2 Pre-Discharge Assessment

Investigators will assess all subjects at the implant center prior to hospital discharge, or within 2-days post implant, whichever is shorter. The clinical 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 Section 6.2.5 LP Assessment and Programming
- Program Aveir LP per physician discretion
- Obtain a 12-lead 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

6.5.3 Data Submission

The site will complete and submit the following case report forms and device print outs to Abbott Medical using the EDC system:

- Pre-Discharge Form (includes medication changes)
- Aveir LP Assessment and Programming Form (Follow-Up) with device session print out PDFs
- Healthcare Utilization Form, if applicable
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- Device Accountability Log, if applicable
- System Revision Form, if applicable
- COVID-19 Assessment Log, if applicable
- Study Withdrawal Form, if applicable

Any post-procedure chest X-ray imaging should be de-identified and submitted to the Sponsor upon Sponsor request.

6.6 Follow-up Assessments

The site will perform the required clinical follow-up at the following intervals for all subjects implanted with an Aveir DR LP system:

- 1 month (± 15 days) follow-up site visit
- 3 month (± 30 days) follow-up site visit
- 6 month (± 30 days) follow up site visit
- 12 month (±45 days) follow up site visit
- Every 6 months thereafter until study completion (±45 days)

Please refer to Section 13.0 for more details on the conditions of study completion.

Dates for follow-up visits will be calculated from the date of the implant procedure. Follow-up assessments can be performed at any point within the pre-specified follow-up visit window.

Every effort should be made by the site personnel to have the subject return to the investigational site for all follow-up visits. If, despite all efforts, the subject is unable to return to the site during a follow-up window, subjects may undergo a remote follow-up assessment to collect applicable non-device performance data. Remote assessments should include telephone contact with the subject and/or a visit to a medical facility with all data that can be reasonably and legally collected remotely on the study subject. Follow-up visits occurring at non-study sites will be limited to standard of care data collection only. Authorization for the release of medical records from a non-study facility is the responsibility of the investigational site. Any missed testing will be considered a protocol deviation.

An enrolled subject may only be followed at another investigational site with prior agreement from that site's Investigator and from the Sponsor.

6.6.1 1-Month Follow-Up Visit

The 1-month follow-up visit will occur 30 days (±15 days) post-implant procedure and will include the following assessments:

- Assess for adverse events and deviations from investigation plan
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics
- Assess Quality of Life (EQ-5D 5L)
- Measure and record LP performance, as described in Section 6.2.5 LP Assessment and Programming
- Program Aveir LP and adjust programmable parameters of LP, as needed

- **Optional:** 6-Minute Walk Test (6MWT) only for those capable *de novo* subjects who may be appropriately programmed temporarily in AAIR mode and who have a tolerance of high sensor-driven rates[2]
  - Administer the 6MWT with the rate-response feature in **AAIR ON or Passive** mode using the Rate Response Optimization function of the programmer for the Aveir atrial LP (Refer to the 6MWT protocol in Appendix V).
  - Assess Magnet Mode in **AAIR ON or Passive**
  - After completing the 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 will be used to adjust programmable sensor parameters of the Aveir atrial LP in preparation for the CAEP protocol to be administered in a subsequent visit.

6.6.1.1 Data submission

The site will complete and submit the following case report forms and device print outs to Abbott Medical using the EDC system:

- Follow-up Visit Form (includes medication changes)
- Aveir LP Assessment and Programming Form (Follow-Up) with device session print out PDFs
- Quality of Life Assessment (EQ-5D 5L)
- 6 Minute Walk Test Form, if applicable
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- Device Accountability Log, if applicable
- System Revision Form, if applicable
- Healthcare Utilization Form, if applicable
- COVID-19 Assessment Log, if applicable
- Study Withdrawal Form, if applicable

All source documentation associated with the 6MWT, including device session printouts, source worksheets, and LP data files should be de-identified and submitted to the Sponsor.

[2] Administration of the 6MWT can be done any time between the 1-month and 3-month follow-up visit until 30 subjects contribute to the analysis. Subjects

6.6.2 3-Month Follow-Up Visit

The 3-month follow-up visit will occur 90 days (±30 days) post-implant procedure and will include the following assessments:

- Assess for adverse events and deviations from investigation plan
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics
- Assess Quality of Life (EQ-5D 5L)
- Measure and record LP performance, as described in Section 6.2.5 LP Assessment and Programming
- Measure and perform in-clinic AV Synchrony Assessment only for *de novo* subjects programmed in a dual-chamber pacing mode as described in Section 6.6.2.1
- Program Aveir LP and adjust programmable parameters of LP, as needed
- **Optional:** CAEP Protocol only for those capable *de novo* subjects who may be appropriately programmed temporarily in AAIR pacing mode and who have a tolerance of high sensor-driven rates[3]
    - 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 the CAEP protocol with rate-response feature in **AAIR ON** mode (refer to the CAEP protocol in Appendix V).
    - After completing the CAEP protocol, program Aveir LP and adjust programmable parameters of the LP, as needed.
- **Optional:** 24-hour Holter data collection and patient diary[4] only for *de novo* subjects programmed to DDD(R) mode and who demonstrate at least 25% atrial pacing during the most recent device interrogation

6.6.2.1 AV Synchrony Assessment – In-Clinic

Subject Population

All *de novo* subjects who can be programmed to a dual chamber pacing mode will be administered the in-clinic AV Synchrony Assessment.

Setup

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

Clinical Investigation Plan for Europe

After the 3-month LP Assessment and Programming is performed and device session printouts obtained, the site will clear the device diagnostics prior to starting the in-clinic AV Synchrony Assessment.

A Holter monitor will be setup and worn by the subject according to the instructions provided by the Sponsor and/or Core Lab. The setup may include adjusting the clock times on the Holter Monitor or Merlin Programmer so that the beginning and end of each position/activity can be identified on both devices.

The subject will also be connected to the Merlin Programmer at certain periods during the assessment. The investigator may also need to reprogram the base rate to improve the likelihood of atrial pacing for select patients. LP interrogation and Holter recording should not take place simultaneously to minimize device artifacts or noise on the Holter.

The site will be trained to properly set up the Holter and Merlin Programmer for the in-clinic AV Synchrony Assessment through separate instructional materials.

AV Synchrony Assessment For Primary Effectiveness Endpoint #2:

While wearing the Holter monitor, the subject should remain in a seated position at rest for 5 minutes while the Holter will record the subject's cardiac rhythm. The site will record the Holter start and stop recording times on the AV Synchrony Assessment CRF and then interrogate the LP. At the end of the assessment period, the site will obtain a device session printout. The site will be trained to administer the in-clinic AV Synchrony Assessment and send the Holter data to the Core Lab for AV Synchrony analysis.

The Sponsor will evaluate the data from this assessment for the primary effectiveness endpoint #2.

Additional AV Synchrony Assessment in Various Positions/Activity Levels:

While wearing the Holter monitor, the subject's cardiac rhythm wil be recorded while the subject assumes the following positions and activity levels in the following order for 2 minutes each:

- Supine
- Left Lateral
- Right Lateral
- Standing
- Normal Walk
- Fast Walk

Prior to each 2-minute assessment, the site will interrogate the LP system using the Merlin programmer and clear the device diagnostics. The site will record the Holter start and stop recording times for each 2-minute assessment on the AV Synchrony Assessment CRF. At the end of each 2-minute assessment, the site will obtain a device session printout. The site will be trained to administer the in-clinic AV Synchrony Assessment and send the Holter data to the Core Lab for AV Synchrony analysis.

The AV Synchrony analysis under these positions and activity levels will not contribute toward the primary effectiveness endpoint #2 but will be reported separately.

6.6.2.2 AV Synchrony Assessment – 24 Hours

Fifty (50) *de novo* subjects will be selected by investigators to wear a Holter monitor and complete a symptom diary for at least 24 hours. The assessment may be performed any time after the beginning of the 3-month visit window. The preferred window to perform the 24-hour Holter test is between the 3-month and 6-month visit. These recorded data will be examined for appropriate sensing, pacing, and AV synchrony during the activities of daily living for each subject. In addition, these data will be evaluated for any correlation between any subject symptoms and losses of AV synchrony, if present.

A 24-hour Holter will only be worn for subjects who can be programmed to DDD(R) mode and who demonstrate at least 25% atrial pacing on the most recent device interrogation. The site will connect each capable subject to a 24-hour Holter monitor until 50 subjects contribute to the analysis.

The site will be trained to administer the 24-Hour AV Synchrony Assessment and send the Holter data to the Core Lab for AV Synchrony analysis.

6.6.2.3 Data Submission

The site will complete and submit the following case report forms and device print outs to Abbott Medical using the EDC system:

- Follow-up Visit Form (includes medication changes)
- Aveir LP Assessment and Programming Form (Follow-Up) with device session print out PDFs
- AV Synchrony Assessment Form (In-clinic) with device session print out PDFs
- Quality of Life Assessment (EQ-5D 5L)
- 24 Hour AV Synchrony Assessment Form, if applicable
- 6 Minute Walk Test Form, if applicable
- CAEP Exercise Test Form, if applicable
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- Device Accountability Log, if applicable
- System Revision Form, if applicable

- Healthcare Utilization Form, if applicable
- COVID-19 Assessment Log, if applicable
- Study Withdrawal Form, if applicable

Any in-clinic Holter data or 24-Hour Holter data (if collected) should be de-identified and submitted to the Core Lab according to the instructions to be provided separately.

All source documentation associated with the AV Synchrony Assessment (In-Clinic and 24 Hour), 6MWT and CAEP, including device session printouts, source worksheets, and LP data files (if applicable) should be de-identified and submitted to the Sponsor.

6.6.3 6-Month Follow-Up Visit

The 6-month follow-up visit will occur 180 days (±30 days) post-implant procedure and will include the following assessments:

- Assess for adverse events and deviations from investigation plan
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics
- Assess Quality of Life (EQ-5D 5L)
- Measure and record LP performance, as described in Section 6.2.5 LP Assessment and Programming
- Program Aveir LP and adjust programmable parameters of LP, as needed

6.6.3.1 Data submission

The site will complete and submit the following case report forms and device print outs to Abbott Medical using the EDC system:

- Follow-up Visit Form (includes medication changes)
- Aveir LP Assessment and Programming Form (Follow-Up) with device session print out PDFs
- Quality of Life Assessment (EQ-5D 5L)
- CAEP Exercise Test Form, if applicable
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- Device Accountability Log, if applicable

- System Revision Form, if applicable
- Healthcare Utilization Form, if applicable
- COVID-19 Assessment Log, if applicable
- Study Withdrawal Form, if applicable

All source documentation associated with the CAEP, including device session printouts, source worksheets, and LP data files should be de-identified and submitted to the Sponsor.

6.6.4 12-Month Follow-Up Visit and Each Follow-up Visit Every Subsequent 6 Months until Study Completion

The 12-month follow-up visit will occur 365 days (±45 days) and subsequently every 180 days (±45 days) post-implant procedure and will include the following assessments:

- Assess for adverse events and deviations from investigation plan
- Assess for changes in beta blockers, ACE, ARB, anti-coagulants, anti-platelets, anti-arrhythmics
- Assess Quality of Life (EQ-5D 5L) - 12 month visit only
- Measure and record LP performance, as described in Section 6.2.5 LP Assessment and Programming
- Program Aveir LP and adjust programmable parameters of LP, as needed

6.6.4.1 Data submission

The site will complete and submit the following case report forms and device print outs to Abbott Medical using the EDC system:

- Follow-up Visit Form (includes medication changes)
- Aveir LP Assessment and Programming Form (Follow-Up) with device session print out PDFs
- Quality of Life Assessment (EQ-5D 5L) – 12 month visit only
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- Device Accountability Log, if applicable
- System Revision Form, if applicable
- Healthcare Utilization Form, if applicable
- COVID-19 Assessment Log, if applicable

- Study Withdrawal Form, if applicable

6.6.5 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 site will assess the following at the unscheduled visit:

- 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 Section 6.2.5 LP Assessment and Programming
- Program Aveir LP and adjust programmable parameters of LP, as needed

6.6.5.1 Data submission

The site will complete and submit the following case report forms and device print outs to Abbott Medical using the EDC system:

- Follow-up Visit Form (includes medication changes)
- Aveir LP Assessment and Programming Form (Follow-Up) with device session print out PDFs
- Adverse Event Form, if applicable
- Device Deficiency Form, if applicable
- Deviation Form, if applicable
- Device Accountability Log, if applicable
- System Revision Form, if applicable
- Healthcare Utilization Form, if applicable
- COVID-19 Assessment Log, if applicable
- Study Withdrawal Form, if applicable

6.6.6 Patient Reported Outcome (PRO) Measures

The Coordinator or designee will administer the patient-reported outcome questionnaires, via paper for later transcription to EDC, or electronically. If the patient reported outcome questionnaire is given to the patient electronically, the source data will be available in the EDC system for the site's records. It is important that the subject understands the meaning of all words and instructions in the questionnaires. The Coordinator or designee should instruct the subject to ask any questions about the questionnaires if further explanation is needed. Once the questionnaires are completed, the Coordinator or designee will review for completeness to verify that all questions have been answered according to the directions provided.

The CIP requires collecting the EQ-5D 5L as a PRO measure:

The EQ-5D Questionnaire version 5L is a widely used validated questionnaire that provides an indicator of overall health status. The self-administered/electronic questionnaire consists of 2 parts: a 5 item description of one dimension (Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression) and a thermometer-like visual analogue scale ranging from 0 to 100 (EQ-VAS) assessing overall state of health. Self-ratings on the five levels in the five dimensions (items) can be summarized to produce 3125 health states, also known as a health profile. Health profiles can be assigned index values derived from econometric techniques to elicit societal preference weights. These index values can then be used in economic evaluation of health programs. The questionnaire takes a few minutes to complete.

6.7 Schedule of Events

CIP Activity	Screening/ Enrollment	Baseline	Implant Procedure	Pre-Discharge (0-2 days)	1 Month (±15 days)	3 Month (±30 days)	6 Month (±30 days)	12 Month and Every 6 months until study completion (±45 days)
Eligibility Criteria	X							
Informed Consent Process	X							
Screening Log	X							
Pregnancy Test		X†						
Demographics and Medical History		X						
RA Characterization Imaging		Y	Y					
Changes in Medication			X	X	X	X	X	X
12-lead ECG		X		X				
Cine of Final LP Placement			X					
Chest X-ray of LP				X				
Aveir Assessment and Programming			X	X	X	X	X	X
In-clinic Holter AV Synchrony Protocol						X*		
Sensor optimization exercise test 6MWT					X**	X**		
Graded exercise test CAEP Protocol						X**	X**	
24 hour Holter monitor with patient diary						X**	X**	

CIP Activity	Screening/ Enrollment	Baseline	Implant Procedure	Pre-Discharge (0-2 days)	1 Month (±15 days)	3 Month (±30 days)	6 Month (±30 days)	12 Month and Every 6 months until study completion (±45 days)
EQ-5D 5L patient survey		X			X	X	X	X***
Device Accountability Log			X	(X)	(X)	(X)	(X)	(X)
Adverse Event		(X)	(X)	(X)	(X)	(X)	(X)	(X)
Deviation		(X)	(X)	(X)	(X)	(X)	(X)	(X)
Device Deficiency			(X)	(X)	(X)	(X)	(X)	(X)
System Revision				(X)	(X)	(X)	(X)	(X)
Withdrawal		(X)	(X)	(X)	(X)	(X)	(X)	(X)
COVID-19 Assessment log		(X)	(X)	(X)	(X)	(X)	(X)	(X)
Healthcare Utilization			(X)	(X)	(X)	(X)	(X)	(X)

X = Required for all subjects

X† = For female subjects of childbearing age

X* = For *de novo* subjects only

X** = For select appropriate *de novo* subjects only. CIP activity only needs to be done once among designated visits.

X*** = EQ-5D 5L patient survey required at 12-month visit only

(X) = If applicable for all subjects

Y = Optional, if available. Imaging at baseline visit applies to pre-existing subject imaging only (e.g. MRI, CT).

6.8 Requirement for Core Laboratories

The Sponsor will utilize an independent core laboratory for evaluating ECGs collected in the clinical investigation. Each investigational site will submit ECGs to the core laboratory for evaluation. The core laboratory will provide the required interpretation and documentation of each data submission according to their standard operating procedures and investigation-specific charter.

The Sponsor will use the data obtained from the core laboratory readings for clinical investigation purposes only and not for clinical treatment of the subject. The Sponsor will use the data provided by the core laboratory in data analyses, where measurements were collected by the core laboratory.

7.0 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.

7.1 Definition

7.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device under investigation and whether anticipated or unanticipated.

Note 1: This definition includes events related to the medical device under investigation or the comparator.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to medical devices under investigation or comparator.

The adverse event definition follows both ISO14155 Section 3.2 and MDCG 2020-10/1 guidance documents.

7.1.2 Serious Adverse Event

If the AE meets any of the criteria below, it is regarded as a serious adverse event (SAE).

a) Led to a death,

b) Led to a serious deterioration in 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 hospitalization or prolongation of existing 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.
   5. chronic disease

c) Led to fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment.

Note: A planned hospitalization for a pre-existing condition, or a procedure required by the CIP without a serious deterioration in health, is not considered to be an SAE.

7.1.3 Device Deficiency/Device Malfunction

Device deficiency is defined as an inadequacy of a medical device related to its identity, quality, durability, reliability, usability, safety or performance, such as malfunction, misuse or use error and inadequacy in the information supplied by the manufacturer including labeling. This includes the failure of the device to meet its performance specifications or otherwise perform as intended.

Note 1: performance specifications include all claims made in the labeling of the device.
Note 2: the definition includes device deficiencies related to investigational medical device or the comparator.

A device malfunction is the failure of a device to meet its performance specifications or otherwise perform as intended, when used in accordance with the instructions for use or CIP.

7.2 Device Relationship

Determination of whether there is a reasonable possibility that an investigational product or device under investigation caused or contributed to an AE is to be **determined by the Investigator** and recorded on the appropriate CRF form. Determination should be based on the assessment of temporal relationships, evidence of alternative etiology, medical/biologic plausibility and patient condition (pre-existing condition).

7.2.1 COVID-19 Relationship and Assessment Log

Determination of whether there is a reasonable possibility that COVID-19 caused or contributed to an AE is to be **determined by the Investigator** and recorded on the Adverse Event form. If an adverse event is determined to be related to COVID-19, the investigator must complete the COVID-19 Assessment Log to confirm the positive test result. Any COVID-19 assessment done by the investigative site as part of diagnostic tests for any adverse event should also be documented on the COVID-19 Assessment Log.

7.2.2 Unanticipated (Serious Adverse) Device Effect [UADE/USADE]

Unanticipated serious adverse device effect (UADE/USADE) refers to 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.

7.2.3 Serious Health Threat

Serious Health Threat is a signal from any adverse event or device deficiency that indicates an imminent risk of death or a serious deterioration in the health in subjects, users or other persons, and that requires prompt remedial action for other subjects, users or other persons Note: This would include events that are of significant and unexpected nature such that they become alarming as a potential serious health hazard or possibility of multiple deaths occurring at short intervals.

7.3 Adverse Event and Device Deficiency/Device Malfunction Reporting

7.3.1 Adverse Event Reporting

Safety surveillance and reporting starts as soon as the patient is enrolled in the clinical study. Safety surveillance and reporting will continue until sites perform the last follow-up visit, the subject is deceased, the subject concludes participation in the clinical investigation, or the subject withdraws from the clinical investigation. Sites will collect all adverse event data, including deaths and device deficiency data, throughout the period defined above and will report these events to the Sponsor on a CRF. Sites should update additional information regarding an adverse event on the appropriate CRF.

Unchanged, chronic, non-worsening or pre-existing conditions are not AEs and should not be reported.

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.

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

The Sponsor will provide an offline form to allow the investigator to report SAEs in the event the entry cannot be made in the EDC. This does not replace the EDC reporting system. Sites must still enter all information in the EDC system as soon as feasible.

Non-cardiac related abnormal laboratory values will not be considered AEs unless:

1. the investigator determined that the value is clinically significant,
2. the abnormal lab value required intervention, or
3. the abnormal lab value required subject withdrawal from the clinical investigation.

SAE Reporting

The investigator must report all SAEs to the Sponsor as soon as possible but no later than outlined below.

Clinical Site	Reporting timelines
All Sites	Sites must report SAEs 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 record the date the site staff became aware that the event met the criteria of an SAE 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.

7.3.2 Unanticipated Serious Adverse Device Effect Reporting to Sponsor and IRB (if applicable)

The Sponsor requires the Investigator to report any USADE to the Sponsor within 3 calendar days of the investigator's knowledge of the event, unless local requirements are more stringent, and to the IRB/EC per IRB/EC requirements.

If an unanticipated adverse event (UADE) occurs during a live case, it should be noted as such in the report to the sponsor and IRB including a discussion on how the nature of a live case could have impacted the adverse event.

7.3.3 Device Deficiency/Malfunction Reporting

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.

Sites will have access to an offline form to allow the investigator to report device deficiencies/malfunctions if sites cannot enter the information in the EDC system. This does not replace the EDC reporting system. Sites must still enter all information in the EDC system as soon as feasible.

In case a device deficiency/malfunction occurred before the patient ID has been assigned, sites should report the device deficiency to the Sponsor via the offline reporting form.

7.3.4 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.

8.0 STATISTICAL CONSIDERATIONS

The following section describes the statistical methods for the clinical investigation. A separate Statistical Analysis Plan will provide additional details on statistical analyses, including justification of clinical investigation design, sensitivity analyses, poolability analyses, subgroup analyses, and analysis of descriptive endpoints, if applicable.

8.1 Analysis Populations

The following analysis populations are defined for this study.

- **Full analysis population**: includes all subjects who have an attempted implant. An implant is considered attempted when the Aveir Introducer Sheath or Aveir dilator is inserted through the skin of the access site.
- [redacted]

The primary and secondary endpoint analysis will be based on the newly enrolled (de novo) subjects in the study.

8.2 Statistical Analyses

This section describes the analysis for the primary safety endpoint, primary effectiveness endpoints and descriptive endpoints. Further details are provided in a statistical analysis plan .

8.2.1 Primary Safety Endpoint Analyses

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

H_0: CFR ≤ 76.5% vs. H_1: CFR > 76.5%
where 76.5% is the performance goal.

The CFR will be estimated using a Kaplan-Meier survival analysis and the 97.5% lower confidence bound (LCB) of CFR will be calculated using the Greenwood formula. The null hypothesis is rejected at the 2.5% significance level if the LCB exceeds the Performance Goal (PG) of 76.5%. The p-value for the one-sided Z-test will be calculated and compared to the 2.5% significance level.

The primary analysis population for the primary safety endpoint analysis will be based on subjects in the full analysis population, and the analysis will be conducted on all subjects with data available for the evaluation.

8.2.2 Primary Effectiveness Endpoint #1 Analyses

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

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

The primary effectiveness endpoint #1 hypothesis is:

H_0: $Rate_{EP}$ ≤ 80% vs. H_1: $Rate_{EP}$ > 80%
where 80% is the PG

The $Rate_{EP}$ is the proportion of subjects who have met success criteria in the primary effectiveness endpoint #1.

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

The $Rate_{EP}$ will be estimated as a binomial proportion and the 97.5% LCB of the $Rate_{EP}$ will be calculated using the normal approximation. The null hypothesis is rejected at the 2.5%

significance level if the LCB exceeds the PG of 80%. The p-value for the one-sided Z-test will be calculated and compared to the 2.5% significance level.

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

8.2.3 Primary Effectiveness Endpoint #2 Analyses

The primary effectiveness endpoint #2 evaluates the 3-month AV synchrony success rate ($Rate_{AV}$) at rest/seated using a Holter monitor in-clinic. AV synchrony success is defined as subjects with a paced or sensed ventricular beat within 300 ms following a paced or sensed atrial beat for at least 70% of evaluable cardiac cycles. The primary effectiveness endpoint #2 hypothesis is:

$$H_0: Rate_{AV} \leq 83\% \text{ vs. } H_1: Rate_{AV} > 83\%$$
where 83% is the PG

The $Rate_{AV}$ is the proportion of subjects who have met success criteria in the primary effectiveness endpoint #2.

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

The Sponsor will analyze primary effectiveness endpoint #2 on the full analysis (primary analysis) population. In the primary analysis, subjects who don't meet AV synchrony success criteria at 3 months or subjects with an unsuccessful implant solely due to a failure to establish i2i communication at the end of implant procedure will be imputed as endpoint failures. Subjects with unsuccessful implants due to reasons other than AV synchrony (e.g., cardiac anatomy) will be excluded from the analysis.

8.2.4 Secondary Safety Endpoint Analyses

The Sponsor will test the secondary safety endpoint if the primary endpoints are met. This endpoint evaluates the 12-month Aveir Atrial LP related CFR based on CEC adjudication of adverse events. An atrial LP complication is defined as an atrial device- or procedure-related SADE, including those that prevent initial LP implantation. Complications that are exclusively related to the ventricular LP or its delivery/retrieval will not be considered atrial LP complications and will be excluded from this evaluation. Complications that cannot be exclusively determined to be related to the ventricular or atrial LP will be considered atrial LP complications (e.g.

femoral access complications, embolism, etc.). The secondary safety endpoint hypothesis is:

H_0: $CFR_A \leq 82\%$ vs. H_1: $CFR_A > 82\%$
where 82% is the PG

The CFR_A will be estimated using Kaplan-Meier analysis and 97.5% LCB of CFR_A will be calculated using the Greenwood formula. The null hypothesis is rejected at the 2.5% significance level if the LCB exceeds the PG of 82%. The p-value for the one-sided Z-test will be calculated and compared to the 2.5% significance level.

The Sponsor will analyze the secondary safety endpoint based on the full analysis population.

8.2.5 Secondary Effectiveness Endpoint Analyses

The secondary effectiveness endpoint includes evaluation of a CAEP exercise protocol for the atrial LP. The secondary effectiveness endpoint will be tested if all the primary endpoints are met and the secondary safety endpoint is also met. The following CAEP hypothesis will be evaluated:

H_0: Mean Slope < 0.65 or Mean Slope > 1.35

H_1: 0.65 ≤ Mean Slope ≤ 1.35

6 Minute Walk Test (6MWT)

All capable subjects will be asked to perform a minimal effort 6MWT simulating daily walking to identify the appropriate sensor parameters for each subject prior to conducting the CAEP exercise protocol. After completion of the 6MWT, the site will program the appropriate sensor parameters into the Aveir device for use in 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. Subjects will undergo the CAEP exercise test any time after the beginning of their 3-month visit window and before the end of 6-month visit window. Each subject will undergo this test at a single visit.

The analysis will include data from subjects who have completed the 6MWT protocol and have completed at least stage 3 of the CAEP exercise protocol, or 3.6 metabolic equivalent of task (METs). Any CAEP assessments performed which substantially deviate from the CAEP exercise protocol (See Appendix V) or where insufficient data is available will be excluded from the analysis. However, the results of subjects who did not meet the analysis criteria will still be reported. Up to thirty subjects among the implanted population will provide data contributing to the analysis.

A mixed effects model for repeated measures will be used to estimate the mean slope (through origin) and standard error of mean slope across N subjects. A no intercept model with unstructured covariance matrix for the random effect (subject) will be used for this analysis. A 95% confidence interval for the mean slope will be provided and if this interval falls within the equivalence bounds of (0.65,1.35), the null hypothesis is rejected.

[redacted] To ensure that a robust cross-section of subjects is evaluated, however, up to 30 subjects will undergo this assessment.

8.2.6 Descriptive Analyses

Summary statistics will be presented for the descriptive endpoints. Continuous variables will be summarized using mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using counts and percentages. Time-to-event variables will be analyzed using the Kaplan-Meier method, if applicable. The 95% confidence intervals for each type of data will be provided as appropriate. Difference between groups will be summarized using descriptive statistics including 95% confidence intervals, if applicable.

8.3 Sample Size Calculation

[redacted]

Sample size calculation for the primary safety endpoint at 12 months (CFR):

[redacted] 300 subjects [redacted] will provide [redacted] to meet a performance goal of 76.5% and reject the null hypothesis at a 2.5% one-sided significance level. [redacted]

Power calculation for the primary effectiveness endpoint #1 at 12 months ($Rate_{EP}$):

[redacted] 240 evaluable subjects [redacted] will provide [redacted] to meet a PG of 80% and reject the null hypothesis at a 2.5% one-sided significance level. [redacted]

Power calculation for the primary effectiveness endpoint #2 at 3 months ($Rate_{AV}$):

[redacted]

[redacted] 267 evaluable subjects [redacted] to meet a PG of 83% and reject the null hypothesis at a 2.5% one-sided significance level. [redacted]

Power calculation for the secondary safety endpoint (CFR_A):

Assuming an underlying complication-free rate of 90%, 300 subjects [redacted] to meet a PG of 82% and reject the null hypothesis at a 2.5% one-sided significance level. [redacted]

[redacted]

8.4 Planned Interim Analysis

[redacted]

[redacted]

8.5 Timing of Analysis

[redacted] The Sponsor will perform the primary endpoint analysis when all subjects have completed their 12-month follow-up visits or pass their 12-month post implant procedure follow-up visit window.

8.6 Multiplicity

[redacted]

[redacted]

[redacted].

[redacted]

8.7 Procedures for Accounting for Missing Data

Every effort will be made to collect all required data. All available safety and effectiveness data will be used in the analysis. Sensitivity analysis will be performed to evaluate the potential impact of the missing data on the primary safety and effectiveness endpoints. The details of missing data handling will be described in the Statistical Analysis Plan.

8.8 Deviations from Statistical Plan

The Sponsor will document any major changes to the statistical plan in an amendment to the statistical plan and any less significant changes to the planned analyses in the final report.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator/institution will permit direct access to source data/documents for performing clinical investigation-related monitoring, audits, IRB/EC review and regulatory inspections.

Subjects providing informed consent are agreeing to allow clinical investigation monitors or regulatory authorities, including foreign countries, to review in confidence any records identifying the subjects in this clinical investigation. This information may be shared with regulatory agencies; however, the Sponsor undertakes not to otherwise release the subject's personal and private information.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

10.1 Selection of Clinical Sites and Investigators

The Sponsor will select investigators qualified by training and experience to participate in the clinical investigation. Sites will be selected based upon review of a recent site assessment, if applicable, and the qualifications of the investigators who will participate in the clinical investigation. A list of the participating sites would be provided upon request (refer to Appendix III).

10.2 Clinical Investigation Finances and Agreements

Abbott will finance the clinical investigation and will compensate investigational sites for participation in the clinical investigation per the conditions of agreement between Abbott and the investigational site.

10.3 CIP Amendments

The Sponsor will provide approved CIP amendments to the Investigators prior to implementing the amendment. The Sponsor is responsible for notifying the IRB/EC or equivalent committee of the CIP amendment if it contains administrative changes only or obtaining IRB's/EC's approval

of the CIP amendment for changes that affect subject care or safety. The Sponsor will submit the CIP Amendment to regulatory bodies per applicable regulation and await regulatory approval before implementing the CIP amendment.

Sites and Sponsor must document in writing acknowledgement/approval of the CIP amendment by the IRB/EC prior to implementation of the CIP amendment. For a history of CIP Amendments please see Appendix X.

10.4 Training

10.4.1 Site Training

All Investigators and clinical investigation personnel are required to attend Sponsor training sessions, which may be conducted at an Investigator's meeting, a site initiation visit, or other appropriate training sessions. Over-the-phone or self-training may take place as required. Training of Investigators and clinical investigation personnel will include, but is not limited to, the CIP requirements, investigational device usage, electronic case report form completion, and clinical investigation personnel responsibilities. All Investigators and clinical investigation personnel that are trained must sign a training log (or an equivalent) upon completion of the training. Prior to signing the training log, Investigators and clinical investigation personnel must not perform any CIP-related activities that are not considered standard of care at the site.

10.4.2 Training Required for the Use of the Device

The Sponsor will train implanting physicians on the Aveir™ DR LP system prior to their first case in accordance with the appropriate training plan(s). The Sponsor will manage proof of training records as controlled documents in an appropriate archiving system. If updates are made to the training plan, physicians will be required to complete the revised training plan prior to their next case.

10.5 Monitoring

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.

Prior to initiating any procedure, the Sponsor monitor (or delegate) will ensure that the following criteria are met:

- The investigator understands and accepts the obligation to conduct the clinical investigation according to the CIP and applicable regulations and has signed the Clinical Trial Agreement.
- The Investigator and his/her staff should have sufficient time and facilities to conduct the clinical investigation and should have access to an adequate number of appropriate subjects to conduct the clinical investigation.
- Sites must have source documentation (including original medical records) to substantiate proper informed consent procedures, adherence to CIP procedures,

adequate reporting and follow-up of adverse events, accuracy of data collected on case report forms, and device information.

- The Investigator/site will permit access to such records and will maintain a monitoring visit sign-in log at the site. The Investigator will agree to dedicate an adequate amount of time to the monitoring process. The Investigator and/or research coordinator will be available for monitoring visits. It is expected that the Investigator will provide the monitor with a suitable working environment for review of clinical investigation-related documents.

10.6 Deviations from CIP

The Investigator should not deviate from the CIP for any reason except in cases of medical emergencies when the deviation is necessary to protect the rights, safety, and well-being of the subject, or to eliminate an apparent immediate hazard to the subject. In that event, the Investigator will notify Sponsor immediately by phone or in writing.

The Sponsor will not grant any waivers for CIP deviations. Sites must report all deviations to the Sponsor using the Deviation CRF. The Sponsor will monitor the occurrence of CIP for evaluation of investigator compliance to the CIP and regulatory requirements and handle according to written procedures. Investigators will determine the cause on deviations and inform their IRB/EC or equivalent committee of all CIP deviations in accordance with their specific IRB/EC or equivalent committee reporting policies and procedures.

In the event of repeated non-compliance, as determined by the Sponsor, a Sponsor's monitor or company representative will attempt to secure compliance by one or more of the following (and not limited to):

- Visiting the investigator and/or delegate
- Telephoning the investigator and/or delegate
- Corresponding with the investigator and/or delegate

The investigator will be requested to implement corrective actions to address the events of non-compliance. Repeated non-compliance with the signed agreement, the CIP, or any other conditions of the clinical investigation may result in further escalation in accordance with the Sponsor's written procedures, including securing compliance or, at its sole discretion, the Sponsor may terminate the investigator's participation in the clinical investigation.

10.7 Quality Assurance Audit

A Sponsor representative or designee may request access to all clinical investigation records, including source documentation, for inspection during a Quality Assurance audit.

If an investigator is contacted by a Regulatory Agency in relation to this clinical investigation, the Investigator will notify the Sponsor immediately. The Investigator and Research Coordinator must be available to respond to reasonable requests and audit queries made during the audit

process. The Investigator must provide the Sponsor with copies of all correspondence that may affect the review of the current clinical investigation (e.g., Form FDA 483, Inspectional Observations, Warning Letters, Inspection Reports, etc.). The Sponsor may provide any needed assistance in responding to regulatory audits.

10.8 Sponsor Auditing

Sponsor audits may be conducted for the clinical investigation in accordance with the below requirements:

1. The Sponsor shall prepare an audit plan as well as the operating procedures for the related duties and conduct audits in accordance with the audit plan and the operating procedures.
2. Individuals engaged in auditing (hereinafter referred to as "auditor") shall be different than those in charge of medical device development or monitoring.
3. The auditor shall prepare an audit report documenting the matters confirmed in the audit to certify and verify that the audit has been conducted and submit them to the Sponsor.

10.9 Committees

10.9.1 Steering Committee

The Steering Committee is assigned by the Sponsor and consists of investigators. The Sponsor will also be represented on the committee. A core laboratory representative and other sponso personnel may also participate in the Committee meetings if appropriate. Meeting minutes from this committee will be filed with the sponsor.

The Steering Committee is responsible for overseeing the scientific and operational aspects of the clinical investigation. This committee will meet regularly to monitor subject enrollment, general data collection and non-compliance with the CIP at individual centers, to review and act upon recommendations of the Data and Safety Monitoring Board (DSMB), to review operational issues that may arise and warrant a CIP amendment or other corrective action, and to determine policy regarding any publications arising from data generated from the performance of the clinical investigation.

10.9.2 Publication Committee

A Publication Committee shall be established to oversee clinical investigations publications, including publication planning and authorship determinations. Publication Committee membership may include members of the Steering Committee, Principal Investigators, a representative of the Sponsor, and a statistician. The Publication Committee will determine policy and strategies regarding individual presentations and/or publications arising from clinical investigation generated data. The committee will also review all external requests for accessing clinical investigation-related data and strategies aligning with the Sponsor’s presentation and publication team expectations. The committee will also follow the Sponsor’s applicable policies and Standard Operating Procedures.

10.9.3 Data and Safety Monitoring Board (DSMB)

The DSMB is an independent multidisciplinary group restricted to individuals free of apparent significant conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. The DSMB is typically composed of at least two physicians with experience relevant to the clinical investigation and a biostatistician.

The DSMB will serve in an advisory role to the Sponsor to ensure safety by reviewing cumulative data from the clinical investigation at prescribed intervals for safeguarding the interests of enrolled subjects and those patients yet to be enrolled, as well as the continuing validity and scientific merit of the clinical investigation. The composition, frequency of the meetings, and the statistical monitoring guidelines are described in detail in the DSMB charter.

The DSMB may consider a recommendation for modifications or termination of the clinical investigation based on any perceived safety concerns regardless of statistical significance. The recommendations of the DSMB are not binding, and all final decisions related to clinical investigations modifications rest with the Sponsor.

10.9.4 Clinical Events Committee (CEC)

The CEC is an independent adjudication body comprised of qualified physicians who are not participants in the clinical investigation. The CEC will review and adjudicate pre-specified events reported by investigators or identified by Safety personnel for the clinical investigation as defined in the CEC charter and according to definitions provided in this CIP.

11.0 DATA HANDLING AND RECORD KEEPING

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 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 end 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, if requested.

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 (if applicable), correspondence with the IRB/EC and clinical investigation monitor/Sponsor, adverse event reports, and information regarding subject discontinuation or completion of the clinical investigation.

11.1 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 enter only pseudonymous Personal Information (key-coded) necessary to conduct the clinical investigation, such as the patient's medical condition, treatment, dates of treatment, etc., into Sponsor's data management systems. 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. All parties will observe confidentiality of Personal Information always throughout the clinical investigation. All reports and data publications will preserve the privacy of each subject and confidentiality of his/her information.

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.

11.2 Data Management Plan

A Data Management Plan (DMP) will describe procedures used for data review, data cleaning, issuing and resolving data discrepancies, and database locking. If appropriate, the Sponsor may update the DMP throughout the duration of the clinical investigation. The Sponsor will track and document control all revisions.

11.3 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. To comply with these regulatory requirements/GCP, sites should include the following information 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)
- AEs 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.
- 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. This serves as source documentation.

11.4 Case Report Form Completion

Site research personnel trained on the CIP and CRF completion will perform the primary data collection clearly and accurately based on source-documented hospital and/or clinic chart reviews. The investigator will ensure accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor on the CRFs and in all required reports.

Sites will collect data on all subjects enrolled into the clinical investigation.
Only authorized site personnel will be permitted to enter the CRF data through the EDC system deployed by the Sponsor. The Sponsor will use an electronic audit trail to track any subsequent changes of the entered data.

11.5 Record Retention

The Sponsor and Investigator/Site will archive and retain all documents pertaining to the clinical investigation as per the applicable regulatory record retention requirements. The Investigator must obtain permission from Sponsor in writing before destroying or transferring control of any clinical investigation records.

11.6 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/lot number, and serial number (if applicable), date used, subject identification, and treating physician.

Storage locations for the devices at investigational sites must be locked with access restricted only to investigators and authorized personnel.

Sites must return all investigational devices associated with a device failure or device deficiency immediately to the Sponsor.

The clinical investigation will use an Inventory (Device) Accountability Log supplied by the Sponsor for device accountability. The Inventory Accountability Log must document the disposition of all investigational devices including those that have been returned to Sponsor.

12.0 ETHICAL CONSIDERATION

12.1 Institutional Review Board/Medical Ethics Committee Review and Approval

The Principal Investigator at each investigational site will obtain IRB/EC approval for the CIP and ICF/other written information provided to the patient prior to consenting and enrolling patients in this clinical investigation. The site must receive the approval letter prior to the start of this clinical investigation and provide a copy to the Sponsor.

Sites will submit any amendments to the CIP as well as associated ICF changes 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).

Until the clinical investigation is completed, the Investigator will advise his/her IRB/EC of the progress of this clinical investigation, per IRB/EC requirements. Written approval must be obtained from the IRB/EC yearly to continue the clinical investigation, or according to each institution's IRB/EC requirements.

Sites will not perform any investigative procedures, other than those defined in this CIP, on the enrolled subjects without the written agreement of the IRB/EC and the Sponsor.

13.0 CLINICAL INVESTIGATION CONCLUSION

The study is complete when all active subjects across all active study sites have completed their 12-month follow up visits or the 12-month visit window has passed and approval for commercial use is received from local regulatory agencies. Site closure for enrolling centers will begin once the study is complete.

A final report will be generated and submitted to all sites, all competent authorities, and all IRBs/ECs within one year of study completion.

The clinical investigation will be closed when:

- All sites are closed AND
- The final report has been provided to investigators or the Sponsor has provided formal documentation of clinical investigation closure.

14.0 PUBLICATION POLICY

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. 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. The Sponsor must review and approve any proposals for publications or presentations by the investigators in a timely manner in compliance with the Sponsor's publication policy set forth in the Clinical Trial Agreement.

Upon receiving IDE approval from the FDA, the Sponsor will be responsible for registering this clinical investigation on ClinicalTrials.gov website, 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.

15.0 RISK ANALYSIS

15.1 Anticipated Clinical Benefits

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

- Percutaneous procedure with no incision or generator pocket needed;
- Eliminates the need for lead (no risk of lead fracture, lowers risk of infection);
- Eliminates the need for a pocket (no scar and/or evidence of the presence of a pacemaker);
- Eliminates the need for connectors (eliminates connector complications);
- Eliminates the visible scar at the pectoral implant site used for transvenous implants;

- May reduce the need for activity restrictions of the left upper extremity after transvenous pacemaker implantation;

15.2 Foreseeable Adverse Events and Anticipated Adverse Device Effects

Risks associated with the specified device and procedure, together with their likely incidence, are described in the IB. There may be risks related to the device under investigation that are unknown at present. Likewise, the exact frequency of the risk may be unknown. A list of foreseeable adverse events and anticipated adverse device effects can be found in Appendix IV.

15.3 Residual Risks Associated with the Device Under Investigation, as Identified in the Risk Management Report / Risk Analysis Report

Risk analysis of the Aver DR LP system has been performed in accordance with the Risk Analysis Plan, Failure Mode Effect Analysis), and Hazard Analysis to systemically identify potential hazards associated with the design and use of this device. Based upon bench testing and prior Abbott sponsored clinical study data, all risks have been identified and mitigated as far as possible through application of appropriate controls and inspections and determined to be within acceptable levels.

Residual risks are likewise disclosed in the IFU in the form of clear instructions of what actions to take or to avoid, to avoid a hazardous situation of harm from occurring (contra-indications, warnings, and precautions). The anticipated AEs disclosed in the IFU (and Appendix IV) provide further information to enable the user, and potentially the patient, to make an informed decision that weighs the residual risk against the benefit of using the device.

15.4 Risks Associated with Participation in this Clinical Investigation

Protocol-required assessments are summarized in Section 6.7. Possible risks and discomforts associated with participation in the study will be similar to those associated with any routine dual-chamber pacemaker implantation procedure and related follow-up procedures.

Study-specific assessments that are not considered standard of care include femoral vein access instead of subclavian vein access, six-minute walk test and treadmill tests for rate response evaluation, in-clinic AV Synchrony assessments, 24-hour Holter monitoring, and EQ-5D quality of life assessment. A subject may experience fatigue, shortness of breath, chest pain and/or leg cramps during six minute walk and treadmill tests; this is mitigated by performing this test under the supervision of a trained professional and in a testing area where medical care is immediately available.

15.5 Steps Taken to Control or Mitigate Risks

In-depth recommendations, special precautions, and instructions regarding patient selection, vessel sizing, device handling, device placement and system removal are included in the IFU/IB.

The IFU/IB also states that the devices can only be used by physicians who have received appropriate training on how to use the device. This statement is interpreted to mean that the physician users are expected to be aware of the known and foreseeable safety risks associated with the use of the devices including the surgical and/or non-surgical treatment of these conditions.

Risks associated with the use of the device under investigation are minimized through device design, investigator selection and training, pre-specified patient eligibility requirements, study monitoring to ensure adherence to the protocol, and the use of a DSMB.

Sites will report all adverse events and device deficiencies to the Sponsor and the Sponsor will monitor internally for safety surveillance purposes.

15.6 Risk to Benefit Rationale

It is concluded from preclinical data (risk analysis and literature review) that clinical risks are comparable to those associated with currently available therapy (transvenous dual-chamber pacing). 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 favorable.

16.0 APPENDICES

APPENDIX I: ABBREVIATIONS AND ACRONYMS

Abbreviation	Definition	Abbreviation	Definition
LP	Leadless Pacemaker	ICF	Informed Consent Form
DR	Dual-Chamber	EC	Ethics Committee
CIP	Clinical Investigational Plan	IFU	Instructions for Use
VR	Single-Chamber (Ventricular)	ICD	Implantable cardioverter defibrillator
i2i	Implant-to-implant	CRT	Cardiac resynchronization therapy
RA	Right Atrium	ICE	Intracardiac Echocardiography
RV	Right Ventricle	RRT	Recommended Replacement Time
ECG	Electrocardiogram	PG	Performance Goal
EGM	Electrogram	EDC	Electronic Data Capture
CFR	Complication Free Rate	CAEP	Chronotropic Assessment Exercise Protocol
CEC	Clinical Events Committee	6MWT	Six-Minute Walk Test
DSMB	Data Safety Monitoring Board	CRF	Case Report Form
SADE	Serious Adverse Device Effect	SAE	Serious Adverse Event
AV	Atrioventricular	UADE	Unanticipated Adverse Device Effect
AMS	Automatic Mode Switching	LCB	Lower Confidence Bound
IB	Investigator Brochure	HRS	Heart Rhythm Society
ESC	European Society of Cardiology	AHA	American Heart Association

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APPENDIX II: DEFINITIONS

Adverse Event: An adverse event (AE) is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the medical device under investigation and whether anticipated or unanticipated.

Note 1: This definition includes events related to the medical device under investigation or the comparator.
Note 2: This definition includes events related to the procedures involved.
Note 3: For users or other persons, this definition is restricted to events related to medical devices under investigation.

The adverse event definition follows both ISO14155 Section 3.2 and MDCG 2020-10/1 guidance documents.

Attempted Implant: An implant procedure when the Aveir Introducer Sheath or Aveir dilator is inserted through the skin of the access site.

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.

De Novo: Subjects who do not have an implanted pacemaker on the date of consent through the date of the Aveir LP implant.

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

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 LP separates from the endocardium after the implant procedure has been completed.

Elevated Pacing Thresholds (RV): 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.

Elevated Pacing Thresholds (RA): Atrial pacing thresholds > 4.0 V at 0.4ms on or after the pre-discharge assessment, or if there is an increase in atrial pacing thresholds of 1.2V 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.

Established i2i Communication: A situation at the end of an implant procedure where non-zero i2i throughput in either LP transmission direction (i.e. A2V or V2A) has been demonstrated. If any of the following situations occur, i2i communication will NOT be considered established:

a) Implanter decides to retrieve 1 or 2 LPs and not replace them exclusively due to unacceptable i2i communication; OR
b) Implanter deliberately programs the LPs to a non-dual chamber pacing mode due to unacceptable i2i communication; OR
c) There is zero i2i throughput in both LP transmission directions (i.e. atrial LP to ventricular LP AND ventricular LP to atrial LP)

Intermittent or loss of i2i communication: When the subject either (a) has their Aveir DR system programmed to a non-dual chamber pacing mode at the end of any pre-discharge or follow-up visit solely due to unsatisfactory i2i communication even in the absence of untoward clinical signs, or (b) undergoes a system revision intervention due to unsatisfactory i2i communication.

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

Implant success rate: Defined as the number of *de novo* subjects leaving the implant procedure with both implanted and functioning LP devices, divided by the number of subjects in whom implantation is attempted.

Inadequate Fixation: When an LP separates from the endocardium after being released from the Delivery Catheter during the implant procedure.

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.

Migration: The movement of the LP to a different position outside the right ventricle and RVOT (for ventricular LP) or right atrium (for atrial LP).

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.

Premature Deployment: When an LP completely separates from the Delivery Catheter before the LP was intended to be released by the implanter during the implant procedure

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
    5. Chronic disease
    c. Led to fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment.

    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 or right atrial 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.

Successful Implant: A subject who leaves an attempted *de novo* implant procedure with functioning atrial and ventricular LPs implanted, including established i2i communication

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Successful Upgrade: A subject with a pre-existing Aveir ventricular LP who was successfully implanted with an Aveir atrial LP, and the Aveir VR LP can be programmed to a dual-chamber mode

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.

Unsuccessful Implant: A subject who leaves an attempted *de novo* implant procedure without a functioning atrial or ventricular LP implanted, or where i2i communication was not established.

Unsuccessful Upgrade: A subject with a pre-existing Aveir ventricular LP who leaves an attempted upgrade procedure without an Aveir atrial LP or where the Aveir VR LP cannot be programmed into dual-chamber mode.

Upgrade success rate: Defined as the number subjects with pre-existing Aveir ventricular LPs leaving the upgrade procedure with an Aveir atrial LP and can be programmed in a dual-chamber mode, divided by the number of subjects in whom an upgrade is attempted.

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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
Abbott Medical
15900 Valley View Court
Sylmar, CA 91342
TEL: +1 (818) 493-3297
FAX: +1 (800) 254-6411

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APPENDIX IV: FORESEEABLE ADVERSE EVENTS AND ANTICIPATED ADVERSE DEVICE EFFECTS

Access site bleeding event*	Interruption of desired LP function due to electrical interference, either electromyogenic or electromagnetic
Air embolism	Ischemic Stroke
Ateriovenous fistula	Loss of normal device function due to component malfunction
Cardiac arrhythmias	Nausea
Cardiac perforation	Oversensing
Cardiac tamponade	Pacemaker syndrome
Death	Palpitations
Device dislodgement	Pericardial effusion or rub
Dizziness	Pericarditis
Dyspnea	Peripheral nerve damage
Embolization of foreign material	Phrenic nerve/diaphragmatic/extra-cardiac stimulation
Embolism	Pneumothorax/Hemothorax
Endocarditis	Premature battery depletion
Excessive bleeding	Premature deployment with LP migration
Exit block	Premature deployment without LP migration
Failure to capture/loss of capture	Programmer/software anomaly
General surgery risks and complications from comorbidities such as hypotension, hypertension, groin pain, respiratory failure, pneumonia, cardiac failure, reaction to sedation, renal failure/kidney injury, anemia, and death	Pseudoaneurysm formation
Heart Failure	Pulmonary embolism
Helix Distortion	Reaction/Toxic Effect due to contrast media
Hematoma formation, including retroperitoneal hematoma/hemorrhage	RV pacing induced cardiomyopathy
High impedance	Syncope
Hypersensitivity reaction to device materials or substances	Threshold elevation
Inability to disengage snare from docking button	Thromboembolism

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Inability to interrogate or program due to programmer or LP malfunction	Thrombosis
Inability to release and/or redock the LP	Transient ischemic attack
Inadequate Fixation during implant with LP migration	Tricuspid valve damage and/or regurgitation
Inadequate Fixation during implant without LP migration	Undersensing
Inappropriate rate sensor response	Vascular dissection
Infection, local at access site, or systemic	Vascular perforation
Intermittent capture	Vascular puncture
Intermittent or loss of i2i communication	Venous occlusion
Intermittent or loss of sensing	

***Access site bleeding event is defined in section 6.5.1**

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

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APPENDIX V: SIX-MINUTE WALK AND GRADED EXERCISE TEST (CAEP PROTOCOL)

The Aveir atrial LP senses right-atrial blood temperature to provide an increase in pacing rate with increased metabolic demand. The Aveir atrial LP employs algorithms with rate response parameters customized for each patient.

The sensor gain can also be programmed to different settings to adjust the responsiveness of the rate response algorithm and can be optimized for each patient. The programmer has an optimization tool and provides a graphic view of the effects of revised sensor parameter settings on the device's rate response to the patient's exercise during a programming session.

The temperature-based rate response feature in the Aveir atiral LP will be assessed in Aveir DR i2i Study to support the secondary effectiveness endpoint by evaluating whether an appropriate and proportional rate response of the atrial LP in *de novo* subjects can be achieved during a graded exercise test.

It is estimated that a minimum sample size of 8 subjects would be sufficient to evaluate this feature. To ensure that a robust cross-section of subjects is evaluated, however, up to 30 subjects are targeted to undergo this assessment.

Rate Response Protocols

Six Minute Walk Test (6MWT)

All capable subjects at participating centers will be asked to perform a six-minute walk test (6MWT) simulating daily walking activity to identify the appropriate sensor parameters for each subject prior to conducting the graded exercise protocol. The rate response feature should be programmed in AAIR ON or passive mode. Subjects who have an intolerance of high-sensor driven rates are contraindicated for rate-responsive pacing and should not be selected in this assessment. After completion of the 6MWT, the appropriate sensor parameters are to be programmed into the Aveir device and used for the subsequent exercise protocol. The 6MWT may be performed any time after the beginning of the 1-month visit window through the end of the 3-month visit window.

Chronotropic Assessment Exercise Protocol (CAEP)

All capable subjects who completed the 6MWT will be asked to perform the following maximal effort chronotropic assessment exercise protocol (CAEP) to demonstrate an appropriate and proportional response of sensor-indicated rate in graded exercise tests. Subjects who have an intolerance of high-sensor driven rates are contraindicated for rate-responsive pacing and should not be selected for this assessment. The CAEP is designed specifically for chronotropic assessment and is structured to collect heart rate data at submaximal and peak exercise intensities. This protocol has been applied to support mathematical models to describe the normal cardiac chronotropic response to exercise.[i]

The CAEP protocol must be performed after completion of the 6MWT protocol and at any time after the beginning of the 3-month visit window through the end of the 6-month visit window. If the 6MWT

protocol is conducted the same day as the CAEP protocol, subjects are to wait at least 1 hour after the 6MWT protocol has been completed before starting the CAEP protocol.

The CAEP protocol must be administered on a treadmill that could be programmed to the speed and grade/incline settings for each stage of the protocol shown below.

Prior to administration, the Aveir LP rate response settings should be programmed with the same optimized sensor gain that was derived from the 6MWT. However, the physician has discretion to alter these parameters if medically appropriate. The CAEP protocol should be administered the with rate-response feature in **AAIR ON** mode. After a short period of rest, subjects will begin exercise on the treadmill at stage 0 and only progress to the next stage after 2 minutes of exercise. Subjects should be instructed to exercise as long as possible until maximal effort is achieved. Subjects should be instructed to stop if they feel dizzy, chest pain, shortness of breath, fatigue, etc. or any other symptoms. Additionally, at least 5 minutes of rest should be recorded after the patient has ended exercise.

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

[i] 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

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APPENDIX VI: LABELS

Sponsor will provide all implants and accessories with labels stating, **"CAUTION—Exclusively for Clinical Investigation."** 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.

Copies of all current labeling and Instructions for Use documents for investigational devices listed in Section 2.2.3 will be provided under separate cover to competent authorities and to clinical sites included with other study documentation/information or as part of the Investigator Brochure.

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APPENDIX VII: CASE REPORT FORMS

Final draft case report forms (CRFs) will be provided under a separate cover

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APPENDIX VIII: INFORMED CONSENT FORM

A template informed consent form will be provided under a separate cover.

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APPENDIX IX: MONITORING PLAN

A copy of the Monitoring Plan can be obtained upon request from the Sponsor Clinical Project Manager for the clinical investigation.

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APPENDIX X: REVISION HISTORY

[redacted]

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			[redacted]	[redacted]

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APPENDIX XI: CIP SUMMARY

Clinical Investigation Name and Number	Aveir DR i2i Study ABT-CIP-10428
Title	Aveir Dual-Chamber Leadless i2i IDE Study
Objective(s)	The purpose of this clinical investigation is to evaluate the clinical safety and effectiveness of the Aveir DR LP system in a patient population indicated for DDD(R) pacing to support regulatory pre-market submissions for both DDD(R) and AAI(R) pacing indications in various geographies.
Device Under Investigation	Aveir DR Leadless Pacemaker system
Number of Subjects Required for Inclusion in Clinical Investigation	Up to 550 subjects from up to 85 sites worldwide (United States, Canada, Europe, Asia-Pacific)
Clinical Investigation Design	This is a prospective, multi-center, international, single-arm, pivotal investigational study
Primary Endpoint(s)	**Primary Safety Endpoint:** The primary safety endpoint evaluates the 12-month Aveir DR LP system Complication Free Rate (CFR) in *de novo* subjects based on CEC adjudication of adverse events. **Primary Effectiveness Endpoint#1:** The primary effectiveness endpoint #1 evaluates the 12-month composite success rate of acceptable atrial pacing thresholds and P-wave amplitudes in *de novo* subjects. **Primary Effectiveness Endpoint#2:** The primary effectiveness endpoint #2 evaluates the 3-month AV-synchrony success rate at rest while seated in *de novo* subjects.
Major (Powered) Secondary Endpoints	**Secondary Safety Endpoint:** The secondary safety endpoint evaluates the Aveir Atrial LP complication free rate (CFR) at 12-months post-implant in *de novo* subjects based on CEC adjudication of adverse events.
Subject Follow-up	• Baseline, Implant, Pre-discharge, 1-month, 3-month, 6-month, 12-month, and every 6 months thereafter

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Inclusion Criteria	1. Subject must have at least one of the clinical indications before device implant in adherence with ACC/AHA/HRS/ESC dual chamber pacing guidelines 2. Subject is ≥ 18 years of age or age of legal consent, whichever age is greater 3. Subject has a life expectancy of at least 1 year 4. Subject is willing to comply with clinical investigation procedures and agrees to return to clinic for all required follow-up visits, tests, and exams 5. Subject has been informed of the nature of the clinical investigation, agrees to its provisions and has provided a signed written informed consent, approved by the IRB/EC
Exclusion Criteria	1. Subject is currently participating in another clinical investigation that may confound the results of this study as determined by the Sponsor 2. Subject is pregnant or nursing and those who plan pregnancy during the clinical investigation follow-up period 3. Subject has presence of anatomic or comorbid conditions, or other medical, social, or psychological conditions that, in the investigator's opinion, could confound the assessment of the investigational device and/or implant procedure limit the subject's ability to participate in the clinical investigation or to comply with follow-up requirements of the clinical investigation results 4. Subject is a known allergy or hypersensitivity to < 1 mg of dexamethasone sodium phosphate or any blood or tissue contacting material listed in the IFU 5. Subject has an implanted vena cava filter or mechanical tricuspid valve prosthesis 6. Subject has pre-existing, permanent endocardial pacing or defibrillation leads (does not include lead fragments) 7. Subject has current implantation of either conventional or subcutaneous implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) device 8. Subject has an implanted leadless cardiac pacemaker (except for an Aveir ventricular LP) 9. Subject is implanted with an electrically-active implantable medical device with stimulation capabilities (such as neurological or cardiac stimulators) * 10. Subject is unable to read or write **NOTE: Does not apply to a medical device with no known impact to the Aveir Leadless Pacemaker System, including the Aveir Link Module. Patient evaluation and the decision to implant the LP should take into account the presence of other active implantable devices and should include consultation with the Sponsor and/or manufacturer of the co-existing device.

17.0 REFERENCES

[redacted]

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[redacted]