SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: DR Leadless Pacing System; Implantable pacemaker pulse generator

Device Trade Name: Aveir™ DR Leadless System

- Aveir™ Leadless Pacemaker (Right Ventricular)
- Aveir™ Leadless Pacemaker (Right Atrial)
- Aveir™ Delivery Catheter
- Aveir™ Link Module

Device Procode: PNJ

Applicant's Name and Address: Abbott Medical
15900 Valley View Court
Sylmar, CA 91342

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P150035/S003

Date of FDA Notice of Approval: 6/29/2023

Breakthrough Device: Granted breakthrough device status on March 27, 2020 because the proposed combination product and proposed indication for use meet the criteria.

The original PMA P150035 was approved on March 31, 2022 and the Aveir™ Leadless Pacemaker System is indicated for patients with bradycardia and:

- Normal sinus rhythm with only rare episodes of A-V block or sinus arrest
- Chronic atrial fibrillation
- Severe physical disability

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

MR Conditional Aveir™ Leadless Pacemaker is conditionally safe for use in the MRI environment and according to the instructions in the MRI-Ready Leadless System Manual.

Aveir™ Delivery Catheter: 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.

Aveir™ Link Module: The Aveir Link Module is intended to be used in conjunction with a Merlin™ PCS Programmer to interrogate and program an Aveir LP and to monitor LP function during an implant, retrieval, or follow-up procedure.

The SSED to support the indication is available on the CDRH website and is incorporated by reference here. The current supplement was submitted to expand the indication for the Aveir DR Leadless System.

II. INDICATIONS FOR USE

The Aveir DR Leadless System is indicated for management of one or more of the following permanent conditions:

- Syncope
- Pre-syncope
- Fatigue
- Disorientation

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

Dual-Chamber Pacing is 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 indicated for patients with:

- Sinus node dysfunction and normal AV and intraventricular conduction systems

Ventricular Pacing is 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

MR Conditional: Aveir Leadless Pacemaker is conditionally safe for use in the MRI environment when used according to the instructions in the Abbott MRI-Ready Leadless System Manual.

Aveir Delivery Catheter: 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 includes implanting an LP within the target chamber of the heart.

Aveir Link Module: The Aveir Link Module is intended to be used in conjunction with a Merlin™ PCS Programmer to interrogate and program an Aveir LP and to monitor LP function during an implant, retrieval, or follow-up procedure.

III. CONTRAINDICATIONS

The use of Aveir Leadless Pacemaker (LP) is contraindicated in these cases:

- Use of any pacemaker is contraindicated in patients with a co-implanted ICD because high-voltage shocks damage the pacemaker, and the pacemaker could reduce shock effectiveness.
- Single-chamber ventricular demand pacing is relatively contraindicated in patients who have demonstrated pacemaker syndrome, have retrograde VA conduction, or suffer a drop in arterial blood pressure with the onset of ventricular pacing.
- Programming of rate-responsive pacing is contraindicated in patients with intolerance of high sensor-driven rates.
- Use is contraindicated in patients with an implanted vena cava filter or mechanical tricuspid valve because of interference between these devices and the delivery system during implantation.
- Persons with known history of allergies to any of the components of this device may suffer an allergic reaction to this device. Prior to use on the patient, the patient should be counseled on the materials (listed in IFU Product Materials) contained in the device and a thorough history of allergies must be discussed.

For the MRI contraindications for patients implanted with Aveir Leadless Pacemaker, refer to the MRI Procedure Manual.

There are no contraindications for use of the Aveir Link Module.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Aveir Leadless System Product Instructions for Use.

V. DEVICE DESCRIPTION

Aveir™ Leadless System:

The Aveir™ Leadless System contains the following components:

- **Aveir™ Leadless Pacemakers (Models LSP201A and LSP202V)**
- **Aveir™ Delivery Catheter (Model LSCD201)**
- **Aveir™ Link Module (Model LSL02)**

Aveir DR Leadless Pacemakers (Models LSP201A and LSP202V)

The Aveir DR Leadless Pacemaker (LP) System provides bradycardia pacing as a pulse generator with built-in battery and electrodes for implantation into the target heart chamber (right atrium – model number LSP201A, right ventricle – model number LSP202V). **Figure 1** includes both the Atrial Aveir LP (LSP201A) and the Ventricular Aveir LP (LSP202V). The Aveir Leadless Pacemaker is intended to provide sensing of intrinsic cardiac signals and delivery of cardiac pacing therapy to the target population.

Aveir DR LPs achieve their dual-chamber functionality by communicating bi-directionally and on a beat-to-beat basis via conducted electrical signaling — a paradigm termed implant-to-implant (i2i) communication. The tip electrode includes a single dose of dexamethasone sodium phosphate (DSP), intended to reduce local inflammation. The proximal end has the docking button for docking to the Aveir Delivery Catheter and Aveir Retrieval Catheter for positioning and retrieval.

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

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

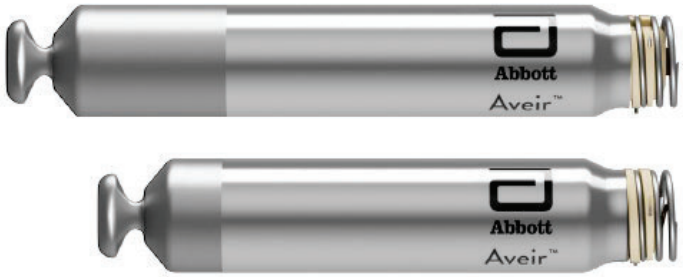


Figure 1: Aveir DR Leadless Pacemakers (Bottom: Atrial LP, Top: Ventricular LP)

Aveir Delivery Catheter (Model LSCD201)

The Aveir Delivery Catheter (**Figure 2**) includes a steerable 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 25Fr inner diameter Introducer sheath hemostasis valve and advance the system into the femoral vein.

Figure 2: Aveir DR Delivery Catheter

Aveir Link Module (Model LSL02)

The Aveir Link Module (**Figure 3**) communicates with an implanted Aveir Leadless Pacemaker via conducted communication through the patient cable and skin electrodes. Safe, high frequency electrical pulses are sent between the LP and programmer system to program and interrogate the Aveir Leadless Pacemaker. The Link Module also uses the patient cable and skin electrodes to acquire a patient's ECG waveform. The Link Module is powered via USB port of the Merlin Patient Care System Model 3650.

Figure 3: Aveir Link Module

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the rate adaptive pacing. Each alternative has its own advantages and disadvantages. Alternative therapies include the use of commercially available conventional pacemaker systems or other marketed leadless pacing systems. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The Aveir Leadless Pacemakers (LSP201A and LSP202V) and Aveir Delivery Catheter (LSCD201) have not been marketed in the United States or any foreign country.

The Aveir Link Module (LSL02) was approved by the FDA on March 31, 2022 as part of the P150035/A009 PMA Amendment and remains unchanged as part of this PMA Supplement.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the Aveir Leadless Pacemaker System.

The potential complications associated with the use of the Aveir Leadless Pacemaker System are the same as the use of single or dual chamber pacemakers with active fixation pacing leads including but not limited to:

- Cardiac perforation
- Cardiac tamponade
- Pericardial effusion
- Pericarditis
- Endocarditis
- Valve damage or regurgitation
- Heart failure
- Pneumothorax/hemothorax
- Cardiac arrhythmias
- Diaphragmatic/ phrenic nerve stimulation/ extra-cardiac stimulation
- Palpitations
- Hypotension
- Syncope
- Cerebrovascular accident
- Infection
- Hypersensitivity reaction to device materials, medications, or direct toxic effect of contrast media on kidney function
- Pacemaker syndrome
- Inability to interrogate or program the LP due to programmer or LP malfunction
- Intermittent or complete loss of capture, pacing or sensing (non-battery related)
- Oversensing
- Increased capture threshold
- Inappropriate sensor response
- Corrupted, intermittent, or loss of i2i communications
- Interruption of desired LP function due to electrical interference, either electromyogenic or electromagnetic
- Battery malfunction/ premature battery depletion
- Device-related complications:
    - Premature deployment
    - Device dislodgment/ embolization of foreign material
    - Inability to release/re-dock of the LP from catheter
    - Helix distortion
- Additional surgery or intervention
- Death

As with any percutaneous catheterization procedure, potential complications include, but are not limited to:

- Vascular access complications, such as perforation, dissection, puncture, groin pain
- Bleeding or hematoma
- Thrombus formation
- Thromboembolism
- Air embolism
- Local and systemic infection

- Peripheral nerve damage
- General surgery risks and complications from comorbidities, such as hypotension, dyspnea, respiratory failure, syncope, pneumonia, hypertension, cardiac failure, reaction to sedation, renal failure, anemia, and death

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

A. Laboratory Studies

i. Design Verification Tests

Design verification testing and material characterization was performed on the Aveir DR system devices (LP, delivery catheter and Link Module) to ensure the design meets all required inputs per the product specification. The test results demonstrate that the Aveir DR system devices meet all design requirements. The testing is summarized in **Table 1 - Table 3** below.

Each device in the Aveir DR system (LP, delivery catheter and Link Module) underwent verification testing utilizing standard test suites, including tests such as automated functional test, functional interrogation test, visual/X-ray inspection, applicable EMI, electrical, and mechanical testing. The samples used in the testing passed applicable verification tests, confirming compliance with respective product requirements, and providing assurance that each device in the Aveir DR system will perform safely and effectively in their intended use.

The system functional verification and validation testing was conducted successfully for the Aveir DR system devices (LP, delivery catheter and Link Module) with passing results and demonstrated that the system design input functionality requirements have been met. Clinical test flows followed in the validation testing were intended to mimic use of the system in clinically relevant scenarios where multiple system functionalities were tested. System functions were tested during scenarios that include: (1) during implant use, (2) out-of-clinic use, and (3) in-clinic follow-up use.

Table 1: Aveir DR LP Non-Clinical Bench Testing Results

Test	Test Description / Acceptance Criteria	Results
System Compatibility	Functional tests assessed the ability of the connections between various component of the Aveir DR Leadless System to properly communicate and interconnect, as appropriate.	Pass

Biocompatibility	The biological evaluation of the LP devices was performed to demonstrate the biocompatibility of the products, or extracts of the products, resulting from contact of the device/component materials with the body as appropriate to the intended use of the device. Biological evaluation and the selection of testing requirements were performed in accordance with ISO 10993-1:2018 and in accordance with the FDA Biocompatibility Guidance issued September 04, 2020 (*Use of international standard ISO 109931, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process"*). Results demonstrated that the LP devices are biologically safe for their intended use. See Section iii below for details.	Pass
Packaging	The LP devices are packaged separately. The packaging is designed to protect the device from damage and prevent contamination during storage, shipping, handling and introduction to the sterile field. Qualification testing was successfully completed to verify that the packaging protects the system during transportation and storage.	Pass
Shelf Life	The LP device shelf life is based on a combination of battery capacity, package sterility, and steroid stability. Testing was performed to support a shelf-life labeling of 12 months.	Pass
Device Level Verification Testing intended to verify the specified physical attributes of the Aveir Leadless Pacemaker (LP). The design verification testing was performed according to the product specifications as well as to ISO 14708-1, ISO 14708-2 and ISO 14117.		
Physical Dimensions	The test verified the following dimensions: Atrial Aveir DR LP: • Length: 32.2 mm (1.27 in) • Diameter: 6.5 mm (0.26 inches) • Volume: 1.0 cm^3 • Mass: 2.1 grams • Fixation depth: approximately 1.63 mm (0.064 in) • Tip electrode geometric surface area: approximately 5 mm^2 • Ring electrode geometric surface area: approximately 124 mm^2 Ventricular Aveir DR LP: • Length: 38.0 mm (1.50 in) • Diameter: 6.5 mm (0.26 inches) • Volume: 1.1 cm^2 • Mass: 2.4 grams • Fixation depth: approximately 1.63 mm (0.064 in) • Tip electrode geometric surface area: approximately 2 mm^2 • Ring electrode geometric surface area: approximately 244 mm^2	Pass

Mechanical Shock and Vibration	Assess the mechanical performance and safety of the LP to withstand mechanical shock loads and vibration imposed during handling, implantation, and intended use per standards EN 45502-2-1 and ISO 14708-2-1.	Pass
Pressure	Evaluate LP device safety and functionality after exposure to multiple cycles of low-pressure and high-pressure as specified by applicable clauses of ISO 14708-2.	Pass
Corrosion	Assess corrosion resistance of the blood and tissue contacting materials chosen for the LP.	Pass
Hermeticity Leak Test	Verify the hermeticity helium leak rate of the LP device is equal to or less than 1.8×10^{-9} atm-cc/sec air equivalent as specified per applicable clauses of MIL-STD-883.	Pass
Electromagnetic Compatibility (EMC)	Evaluate LP device safety and functionality with regard to exposure to external EM fields, as per the applicable requirements of ISO 14708-2 and ISO 14117.	Pass
EMI-EAS, RFID, Tag deactivators, Metal Detectors	Evaluate LP device safety and functionality with regard to exposure to EAS and RFID, with no irreversible damage or effect on device programmed parameters caused by the exposure to EAS systems, EAS tag deactivators, RFID systems, or metal detector systems.	Pass
Safety-Exposure to Electrosurgery	Evaluate the LP device safety and functionality with regard to exposure to electrosurgery conditions as specified by the applicable clauses of ISO 14117.	Pass
Safety- Exposure to External Defibrillation	Evaluate the LP device safety and functionality with regard to exposure to external defibrillation conditions as specified by the applicable clauses of ISO 14117.	Pass
Safety-Ultrasound	Evaluate the LP device safety and functionality with regard to exposure to ultrasound conditions as specified by the applicable clauses of ISO 14708-1.	Pass
Safety- Protection against device heat generation	Verify the outer surface of the LP device does not exceed 2˚C above the normal surrounding body temperature of 37˚ C when implanted in normal operating mode as specified per ISO 14708-1 and EN 45502-2-1.	Pass
Safety – Irradiation	Verify the LP device remains electrically functional after exposure to irradiation levels of at least 7000 rads (70 Gy) per the applicable clauses of MIL-STD-883E.	Pass
MRI Compatibility Testing	Assess the compatibility of the LP device with MRI scanning. Additional MRI Information is provided in section ii below.	Pass
Firmware	Firmware verification testing was conducted to ensure that the LP device firmware was tested to its specified requirements. Testing included unit testing, integration testing and system testing. Firmware verification testing was successfully completed and demonstrated that the LP device firmware meets its requirements.	Pass
Merlin PCS Programmer Software	Programmer software verification testing of all software requirements was conducted to ensure that the Programmer software was tested to its specified requirements. Testing included unit testing, integration testing and system testing.	Pass

	Software verification testing demonstrated that the Programmer Software meets its requirements.	
Cybersecurity	The Aveir DR System was developed and tested using methodologies intended to ensure product quality and patient safety.	Pass
Component Level Testing intended to verify the specified component specifications are met. Safety testing, capacity testing and long-term performance testing and stability testing were performed. All the tests were successfully performed, and all pre-determined acceptance criteria were met.		
Button Tensile	Verify that the LP docking button can withstand a minimum axial tensile force of at least 18 lb-f without separation from the LP body.	Pass
Button Fatigue	Verify the LP device docking button fatigue limit.	Pass
Fixation Helix Fatigue	Verify the LP device fixation helix survives 400 million cycles without helix fracture or detachment from helix mount.	Pass
Fixation Helix Deformation	Verify the LP device fixation helix length maintains an axial plastic deformation of less than or equal to 20% of its original length after an extension force is applied to the tip of the helix.	Pass
Feedthrough	• Verify that the LP feedthrough insulation resistance is 10 giga-ohm minimum. • Verify that the LP feedthrough does not exhibit a leak rate greater than $1.5x10^{-9}$ atm-cc/sec air. • Verify that the LP feedthrough does not exhibit any signs of breakage, fracture or cracks under load.	Pass
Hybrid	Confirm that the LP hybrid can pass all substrate level electrical tests after withstanding stress conditions (thermal cycling and burn-in).	Pass
Battery	• The LP battery meets the UN Recommendations on the Transport of Dangerous Goods, Manual of Tests and Criteria. • Accelerated discharge testing of LP battery capacity from Beginning of Service to End of Service at 37°C.	Pass

Table 2: Aveir Delivery Catheter Non-Clinical Bench Testing Results

Test	Test Description / Acceptance Criteria	Results
Biocompatibility	The biological evaluation of the delivery catheter was performed to demonstrate the biocompatibility of the products, or extracts of the products, resulting from contact of the device/component materials with the body as appropriate to the intended use of the device. Biological evaluation and the selection of testing requirements were performed in accordance with ISO 10993-1:2018 and in accordance with the FDA Biocompatibility Guidance issued September 04, 2020 (*Use of international standard ISO 109931, "Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management*	Pass

	process"). Results demonstrated that the delivery catheter is biologically safe for its intended use. See Section iii below for details.	
Torque	The catheter withstands at least one full rotation prior to kinking.	Pass
Tensile	The tensile strength of the delivery catheter assembly was assessed based on ISO 10555-1.	Pass
Flexibility/ Deflection	The device was verified to have sufficient flexibility to enable navigation through clinically relevant anatomical configurations.	Pass
Corrosion	The corrosion resistance of the blood- and tissue-contacting materials chosen for the delivery catheter was verified.	Pass
Particulate Testing	The particulate levels generated from the delivery catheter, when used with the introducer and DR LPs during simulated clinical use, meets USP <788>.	Pass
Shelf Life	The shelf-life testing was performed to support shelf-life labeling of 15 months.	Pass
Packaging	The delivery catheter is packaged separately from the LP and Link Module. The packaging is designed to protect the delivery catheter from damage and maintain sterility during storage, shipping, handling and introduction to the sterile field (see Section iv for additional sterilization information). Qualification testing verified that the packaging protects the delivery catheter during transportation and storage.	Pass

Table 3: Aveir Link Module Non-Clinical Bench Testing Results

Test	Test Description / Acceptance Criteria	Results
Physical Dimensions	• The Link Module shall have weight less than or equal to 0.7 kg (1.5 lbf). • The Link Module's length, width and height shall be less than or equal to 230mm, 155 mm and 40 mm, respectively. • The measured cable length shall be between 0.9 m to 1.1 m.	Pass
Mechanical	• The tensile strength of the USB cable shall be at least 65 N • The USB cable shall survive at least 1000 flex cycles without demonstrating any of the electrical failure conditions	Pass
Security	• The Link Module shall use tamper resistant screws. • The Link Module shall include snap retainer features. • The Link Module shall include tamper evident labels. • The Link Module AES key shall be un-readable and unmodifiable from an external device.	Pass
Electrical	• The Link Module shall interrogate, program, and read information from the device when connected to	Pass

	a power supply of approximately 5V. • The Link Module transmission pulses shall be biphasic with period 4 μs ±15%	
Safety	• The Link Module shall pass applicable safety compliance tests per IEC 60601-1 Ed. 3.1. • The Link Module shall not exceed the radiated and conducted emissions limit requirements per IEC 60601-1-2. • The Link Module shall pass radiated electromagnetic fields per IEC 61000-4-3 and 61000-4-6. • The Link Module shall pass test requirements related to basic safety and essential performance for medical electrical equipment per IEC 60601- 1-2	Pass
Cleaning	The test verifies the integrity of the label, marking, and mechanical enclosure after cleaning the Link Module, as per the cleaning and disinfection instructions.	Pass
Packaging	The Link Module is packaged separately from the LP devices and delivery catheter. The packaging is designed to protect the device from damage during storage, shipping and handling. Qualification testing was successfully completed to verify that the packaging protects the Link Module unit during transportation and storage.	Pass

ii. Magnetic Resonance Imaging (MRI) Compatibility

MRI safety of the MR Conditional Aveir Leadless Pacemaker has been tested per the requirements in ISO/TS 10974. The test results demonstrate that the Aveir Leadless Pacemaker is conditionally safe for use in the MRI environments when used according to the instructions in the MRI Manual using the 1.5T and 3T MR scanner.

A patient with the Aveir Leadless Pacemaker can be safely scanned in a MR system under following conditions (see **Table 4**).

Table 4: Magnetic Resonance Imaging (MRI) Compatibility Testing Conditions

Parameter	1.5 MRI Scan Parameter Setting	3T MRI Scan Parameter Setting
Static Magnetic Field Strength and Type of Nuclei	1.5T/64 MHz excitation frequency (hydrogen atom only)	3 T/128 MHz excitation frequency (hydrogen atom only)
Magnet Type and Static Magnetic Field Orientation	Cylindrical-bore magnet, horizontal field orientation	Cylindrical-bore magnet, horizontal field orientation
Maximum Spatial Field Gradient	30 T/m (3000 Gauss/cm)	30 T/m (3000 Gauss/cm)
Maximum Gradient Slew Rate per axis	200 T/m/s	200 T/m/s

Scan Region / Patient Landmarking Criteria	Full body scans allowed. Any landmark is acceptable	Full body scans allowed. Any landmark is acceptable

iii. Biocompatibility

All biocompatibility testing was conducted in accordance with ISO 10993-1, Biological Evaluation of Medical Devices and Good Laboratory Practices Regulation (21 CFR 58). According to ISO 10993, the Aveir DR LPs are classified as a long-term (>30 days) implantable device with circulating blood contact. The accessory Aveir Delivery Catheter packaged separately is classified as externally communicating with limited (<24 hours) circulating blood contact device. The required testing for the implant and delivery catheter was determined based on these classifications, in accordance with ISO 10993-1. A summary of the tests performed, and test results are presented in **Table 5** below.

Table 5: Biocompatibility Test and Results

Biological Endpoint and ISO Standard	Test Name/ Description	Leadless Pacemaker	Delivery Catheter	Results*
Cytotoxicity ISO 10993-5:2009	ISO Minimum Essential Medium Elution Assay	✓	✓	Pass Non-cytotoxic
Sensitization ISO 10993-10:2021	ISO Guinea Pig Maximization Sensitization	✓	✓	Pass Non-sensitizer
Irritation or Intracutaneous Reactivity ISO 10993-23:2021	Intracutaneous Reactivity Test Irritation	✓	✓	Pass Non-irritant
Systemic Toxicity ISO 10993-11:217	ISO Acute Systemic Toxicity	✓	✓	Pass No evidence of systemic toxicity
	USP Material Mediated Rabbit Pyrogen	✓	✓	Pass Non-pyrogenic
	Subacute/Sub-Chronic/Chronic Systemic Toxicity (17 and 26 weeks)	✓	N/A	Pass No evidence of systemic toxicity
Genotoxicity ISO 10993-3:2014	ISO Bacterial Reverse Mutation	✓	N/A	Pass Non-mutagenic

	ISO Mouse Lymphoma Assay	✓	N/A	Pass Non-genotoxic
Implantation ISO 10993-6:2016	90-day Chronic implantation in ovine	A	N/A	Pass Non-irritant
Hemocompatibility ISO 10993-4:2017	Hemolysis – Direct Contact and Extract	B	✓	Pass Acceptable hemocompatibility profile
	Complement Activation Assay – SC5b-9	B	✓	Pass Not a complement activator
	In vivo Thrombogenicity	B	✓	Pass Clinically acceptable response
Chemical Characterization ISO 10993-18:2020	GC-MS, LC-MS, and ICP-MS	✓	B	No leachables of toxicological concern
Toxicological Risk Assessment ISO 10993-17:2002	Toxicological Risk Assessment	✓	N/A	

Key:

A: Biological endpoint was covered in the GLP animal studies B: indicates justification provided for not testing

N/A: indicates testing was not required per ISO 10993-1

✓: indicates testing was conducted

* "Pass" denotes that the test results met the product specifications or acceptance criteria.

For the Aveir DR LPs, endpoints of sub-chronic systemic toxicity and 90-day chronic implantation were performed as part of the in vivo study (GLP animal studies) conducted to evaluate the safety and effectiveness of the device. The overall results of the GLP animal study indicate there was no signs of systemic toxicity or inflammation post implantation of the Aveir DR LPs and therefore, the device is considered clinically acceptable.

Additionally, the omission of the carcinogenicity testing was supported by chemical characterization data. Toxicological risk assessment concluded that extractables and leachable chemicals from the Aveir DR LPs were not present in quantities to present a systemic toxicity or carcinogenicity risk. Toxicological evaluation of the extractables detected concluded there was no toxicological concerns from the compounds detected.

Based on the acceptable results provided, the Aveir DR LPs and delivery catheter are biocompatible and considered safe for the device's intended use.

iv. Sterilization

The Aveir DR LPs are an implant device and provided sterile for single use only. The Aveir Delivery Catheter is also provided sterile and for single use only. These tests assessed the ability of the device packaging system to maintain sterility of the package. The Aveir LP devices and the delivery catheter are sterilized using 100% Ethylene oxide (EO). Sterilization validation established a minimum Sterility Assurance Level (SAL) of 10-6 as defined in EN 556-1, for routine sterilization of the pacemaker and catheter, per EN ISO 11135. The devices are intended for single use only and labeled sterile. The Aveir Link Module is an external non-sterile medical device.

v. Shelf-Life and Packaging

The shelf life of a combination product is defined not only based on the capability of a drug component in a specific container/closure system to remain within its physical, chemical, microbiological, toxicological, protective and informational specifications, but also based on the device design characteristics and sterile barrier system materials in relation to the device being packaged, sterilized, shipped, and stored. The Aveir DR LPs shelf life is labeled for 12 months and Aveir Delivery Catheter shelf life is labeled for 15 months. Both devices were validated to ensure that the device performance and package integrity is maintained for this shelf life.

Package performance and package stability are evaluated independently, built to the worst-case manufacturing sealing process settings (i.e., low and high settings), and exposed to the worst case environmental, distribution, and accelerated aging conditioning, to cover both evaluations.

B. Animal Studies

The following five (5) GLP animal evaluations were conducted:

- **91-Day Chronic Safety Evaluation of the Atrial Aveir DR LP (LSP201A)**
  - Purpose: To demonstrate the safety and performance of the Atrial Aveir DR LP model LSP201A as well as the acute safety and handling of the Aveir DR Delivery Catheter model LSCD201. A total of nine (9) sheep were used in this study.
  - Safety Objective Results: There were no dislodgements or embolization of the LP during the follow-up period in any study animals. There was no cardiac or vascular perforation that resulted in significant blood loss or death in any of the animals. There were no tricuspid valve leaflet

tears, endocardial/myocardial tears, or ruptured chordae in any of the animals which meets the acceptance criteria of none to mild tears. All test articles had acceptable handling and performance.

- Performance Objective Results: The LP was able to pace the heart at implant and each follow-up in all animals. The LP was able to sense intrinsic heart beats throughout the study in all animals. Throughout the study, impedance measurements could be collected in all animals. Throughout the study, the programmer was able to communicate with implanted LPs to retrieve diagnostics, program parameters, and perform electrical performance tests. There were no visual or mechanical anomalies from typical implant handling that affected the functionality of the leadless pacer.

- **91-Day Chronic Retrieval Study for the Atrial Aveir DR LP (LSP201A)**
  - Purpose: To demonstrate the safety of retrievability of the Atrial Aveir DR LP device at least 91 days post implant. Retrieval procedures were performed by clinicians familiar with pacemaker implantation/retrieval and catheter handling. A total of seven (7) sheep were used in this study.
  - Safety Objective Results: All animals received a rating of "0", denoting acceptable clear to light yellow/serous pericardial fluid. There were no ratings of "2", frank blood in the pericardial sac at necropsy. All animals had a rating of "0" – no change present in the IVC as assessed at necropsy. All animals had a rating of "0" – no change present in the femoral vein as assessed at necropsy. There were no tricuspid leaflet tears, endocardial/ myocardial tears, or ruptured chordae in any animal. All lung findings in all animals were acceptable as assessed at necropsy.
  - Performance Objective Results: Physicians evaluated the safety and performance of the Aveir Retrieval Catheter. All ratings were the highest rating of 4 (very good and acceptable). There was no clear pattern of errors to suggest an issue with the design or training that may lead to unacceptable patient harm.
- **Chronic Evaluation of Safety and Performance for the Aveir DR System (LSP201A, LSP202V)**
  - Purpose: To demonstrate the chronic safety and performance of the Aveir DR System and the acute safety and handling of the Aveir DR Delivery Catheter. The animals were implanted with one Atrial Aveir DR LP LSP201A in the right atrium (RA) and one Ventricular Aveir DR LP LSP202V in the right ventricle (RV). The LPs were implanted for 91 days. A total of nine (9) sheep were used in this study.
  - Safety Objective Results: There were no dislodgements or embolization of the LPs during the follow-up study period in any of the animals. There was no cardiac or vascular perforation that resulted in significant blood loss or death in any of the animals. There were no tricuspid valve leaflet tears, endocardial/myocardial tears, or ruptured chordae in any of the animals. All lung findings in all animals were acceptable at necropsy. There was no thrombus found in any of the animals. All test articles had acceptable handling and performance.

- Performance Objective Results: Throughout the study, the programmer was able to communicate with implanted LPs to retrieve diagnostics, program parameters, and perform electrical performance tests. The RA to RV and RV to RA i2i throughput (overall: good marker) was ≥70% between day 42 and day 91 follow-up for all animals. There were no visual or mechanical anomalies from typical implant handling that affected the functionality of the leadless pacer.

- **77-Day Chronic Evaluation of Side-by-Side LPs Study**
  - Purpose: To demonstrate the chronic safety of retrievability of the side-by-side functionality of an active Aveir DR LP implanted next to an inactive Aveir DR LP in the ovine. A total of five (5) sheep were used in this study.
  - Safety Objective Results: There were no tricuspid leaflet tears, endocardial/myocardial tears, or ruptured chordae in any of the animals meeting the acceptance criteria of none to mild tears. All lung findings in all animals were acceptable at necropsy. There was no thrombus found in any of the animals. There were no dislodgements or embolization of the LPs (20 of 20) during the follow-up study period in any (5 of 5) of the animals.
  - Performance Objective Results: All Aveir DR LPs (5 atrial and 5 ventricular) could be permanently deactivated using the Merlin programmer at time of secondary implant. All Aveir DR LPs (5 atrial and 5 ventricular) could communicate with the programmer, be programmed, and electrical performance data can be collected when co-implanted in the same chamber with an inactive LP. The Merlin programmer software supported the ability to program: a) one active LP within the RV; b) one active LP within the RA; and c) one new LP to replace an existing LP.
- **182-Day Chronic Retrieval Study for the Atrial Aveir DR LP (LSP201A)**
  - Purpose: To demonstrate the safety of retrievability of the Aveir Atrial Leadless Pacemaker (LP) device model LSP201A at least 182 days post-implant. A total of nine (9) sheep were used in this study.
  - Safety Objective Results: All animals (implanted with an Atrial Aveir LP) received a rating of "0", denoting acceptable clear to light yellow/serous pericardial fluid. There were no ratings of "2", frank blood in the pericardial sac at necropsy. No ratings of "2" moderate to severe injury from the retrieval of an atrial LP were observed. There were no tears present the IVC for all animals at necropsy. One animal had a rating of "1"- present, but minimal feature due to acute focal hemorrhage in the wall of the IVC. Four (4) animals had a rating of none/"0" – no change present and five (5) animals had a rating of "1"- present, but minimal feature in the femoral vein at necropsy. There were no tricuspid leaflet tears, endocardial/myocardial tears, or ruptured chordae as a result of the atrial LP retrieval procedure in any animal at necropsy. All lung findings in all animals chronically implanted with an atrial LP were acceptable at necropsy.

- Performance Objective Results: Physicians evaluated the safety and performance of the Aveir Retrieval Catheter while retrieving an atrial LP. All ratings were the highest rating of 4 (very good and acceptable). There were no observed use errors. 100% of the retrievals in animal were successful.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the Abbott Medical Aveir Dual-Chamber (DR) Leadless Pacemaker (LP) system in patients indicated for DDD(R) pacing in the US, Canada, Europe, and Asia Pacific under IDE #G210339. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

The Aveir DR i2i Study was a first-in-human clinical evaluation of the Aveir DR Leadless Pacemaker System (ClinicalTrials.gov identifier: NCT05252702). The Aveir DR LP system is considered an expanded technology from the Abbott Medical single-chamber Aveir VR Leadless System.

The Aveir DR LP system is a programmable system comprising of two implantable LPs that provide dual-chamber rate-responsive bradycardia pacing therapy. The first LP is the Aveir DR Ventricular LP (model LSP202V) that is physically identical to the single-chamber Aveir VR LP (model LSP112V) for the implantation into the right ventricle (RV). The Aveir VR LP (LSP112V) was previously evaluated in the Leadless II IDE Study- Phase 2 (ClinicalTrials.gov identifier: NCT04559945) and has received FDA approval (P150035) on March 31, 2022. The second LP is the Aveir DR Atrial LP (model LSP201A) for the implantation into the right atrium. Each leadless pacemaker is delivered to the target heart chamber percutaneously via the femoral vein.

A. Study Design

The Aveir DR i2i study was a prospective, multi-center, international, single-arm, pivotal investigational study designed to evaluate the safety and effectiveness of the Aveir DR system in a subject population indicated for a DDD(R) pacemaker. The primary objectives of this study were to evaluate the safety and effectiveness of the Aveir DR system through 3 months post-implant in a subject population indicated for a DDD(R) pacemaker system.

Patients were treated between February 2, 2022 and August 5, 2022. The database for this Panel Track Supplement reflected data collected through October 26, 2022.

The clinical investigation was designed to enroll up to 550 subjects from up to 85 participating centers from the United States, Canada, Europe, and Asia Pacific. The 550 subjects included at least 300 *de novo* subjects (i.e., no prior pacemaker implantation) in a "full analysis population" to evaluate the primary endpoints and up

to 200 additional *de novo* subjects that were enrolled continuously after the first 300 *de novo* subject enrollments. The additional 200 *de novo* subjects were included in the study design in the event more subjects were needed to evaluate the primary endpoints based on the results of a planned interim analysis.

In addition to the 300 enrolled *de novo* subjects, up to 50 subjects who were previously implanted with the Aveir VR LP single chamber system were also permitted to concurrently enroll with the *de novo* subjects from the full analysis population to evaluate the upgradeability to an Aveir DR LP system. This part of the study evaluated *upgradeability*, a key feature of the Aveir DR System, in which an Atrial LP is implanted and functionally paired with a pre-existing Aveir VR LP, resulting in dual-chamber therapy in a DDD(R) (or other) pacing mode. Since the Aveir VR upgrade population is a separate population from the full analysis cohort, the clinical outcomes from this population did not contribute toward the primary or secondary endpoints and are thus reported separately.

The study used an independent Data Safety Monitoring Board (DSMB) that was responsible for informing Abbott Medical of any safety or compliance issues and a Clinical Events Committee (CEC) that was responsible for adjudicating adverse events reported during the IDE study. The study also used an independent ECG Core Laboratory that evaluated Holter data collected from sites to determine AV synchrony success.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the Aveir DR i2i study was limited to patients who met the following inclusion criteria:

   i. Subject must have at least one of the clinical indications before device implant in adherence with ACC/AHA/HRS/ESC dual chamber pacing guidelines
   ii. Subject is ≥ 18 years of age or age of legal consent, whichever age is greater
   iii. Subject has a life expectancy of at least one year
   iv. Subject is willing to comply with clinical investigation procedures and agrees to return to clinic for all required follow-up visits, tests, and exams
   v. 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

   Patients were not permitted to enroll in the Aveir DR i2i study if they met any of the following exclusion criteria:

   i. Subject is currently participating in another clinical investigation that may confound the results of this study as determined by the Sponsor
   ii. Subject is pregnant or nursing and those who plan pregnancy during the clinical investigation follow-up period

iii. 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
iv. 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
v. Subject has an implanted vena cava filter or mechanical tricuspid valve prosthesis
vi. Subject has pre-existing, permanent endocardial pacing or defibrillation leads (does not include lead fragments)
vii. Subject has current implantation of either conventional or subcutaneous implantable cardioverter defibrillator (ICD) or cardiac resynchronization therapy (CRT) device
viii. Subject has an implanted leadless cardiac pacemaker (except for an Aveir ventricular LP)
ix. Subject is implanted with an electrically-active implantable medical device with stimulation capabilities (such as neurological or cardiac stimulators)*
x. 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.

2. Follow-up Schedule

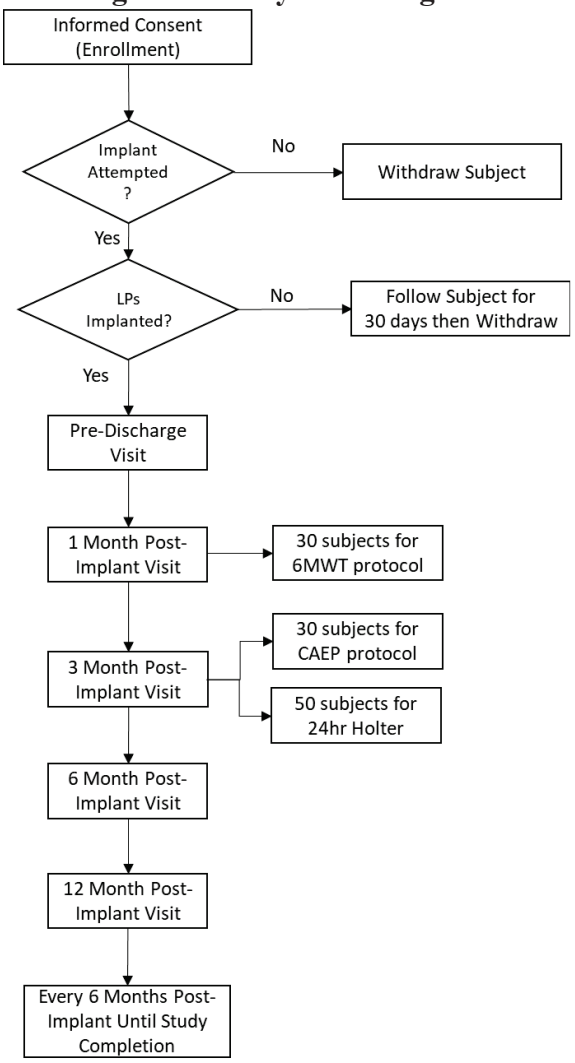
The following study evaluations were to occur after implant:

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

Follow-up schedules were to be calculated from the date of implant procedure. The subject follow-up period was necessary to demonstrate safety and effectiveness. Additionally, during this follow-up period, the Sponsor would identify any residual risks and complications. Subjects were to undergo the following assessments as described in the study flow diagram in **Figure 3** below.

The key timepoints are shown below in the tables summarizing safety and effectiveness.

Figure 3: Study Flow Diagram



3. Clinical Endpoints

Primary Objectives
The primary objectives of this study were to evaluate the safety and effectiveness of the Aveir DR LP system through 3 months post-implant in a subject population indicated for a DDD(R) pacemaker system.

Secondary Objectives
The secondary objectives of this study were to evaluate the safety and effectiveness of the Aveir Atrial LP through 3 months post-implant in a subject population indicated for a DDD(R) pacemaker system to support an indication for AAI(R) pacing.

Primary Safety Endpoint
The primary safety endpoint evaluated the 3-month Aveir DR LP system complication-free rate (CFR) based on CEC adjudication of adverse events. A complication is defined as a device-or-procedure-related serious adverse device effects (SADE), including those that prevented initial implantation (includes both Atrial LP and Ventricular LP complications and implant procedure-related complications).

The primary safety endpoint hypothesis at 3 months was formally expressed as:

$$H_0: \ CFR \leq 78\% \quad \text{vs.} \quad H_1: \ CFR > 78\%$$

where 78% was the performance goal.

The CFR was estimated as a binomial proportion and a one-sided 97.5% (or the two-sided 95%) lower confidence bound (LCB) of the CFR was calculated using the normal approximation. The null hypothesis was to be rejected at the 2.5% significance level if the LCB exceeded the Performance Goal (PG) of 78%. The p-value from a one-sided Z-test for the binomial proportion was to be calculated and compared to the 0.025 significance level.

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

Secondary Safety Endpoint
The secondary safety endpoint evaluated the 3-month Aveir Atrial LP related CFR based on CEC adjudication of adverse events. The secondary safety endpoint was evaluated if the primary endpoints were met. An Atrial LP complication was defined as an atrial device- or procedure-related SADE, including those that prevented initial LP implantation. Complications exclusively related to the ventricular LP, or its delivery/retrieval were not considered atrial LP complications and were excluded from this evaluation. Complications where the relationship could not exclusively be determined to be related to the ventricular or atrial LP were considered Atrial LP

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

$$H_0: CFR_A \leq 84\% \text{ vs. } H_1: CFR_A > 84\%$$
where 84% is the PG

The CFR_A was estimated as a binomial proportion and a one-sided 97.5% LCB (or the two-sided 95%) LCP of the CFR_A was calculated using the normal approximation. The null hypothesis was rejected at the 2.5% significance level if the LCB exceeds the PG of 84%. The p-value for the one-sided Z-test was calculated and compared to the 2.5% significance level.

The secondary safety endpoint analysis was based on *de novo* subjects in the full analysis population.

Primary Effectiveness Endpoint #1

The primary effectiveness endpoint #1 evaluated the 3-month composite success rate (Rate) evaluating acceptable atrial pacing thresholds and P-wave amplitudes in *de novo* subjects. These *de novo* subjects are the evaluable population within the full analysis population.

The primary effectiveness endpoint #1 hypothesis at 3 months was formally expressed as:

$$H_0: \ Rate_{EP} \leq 82.5\% \quad \text{vs.} \quad H_1: \ Rate_{EP} > 82.5\%$$
where 82.5% was the performance goal (PG).

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

Table 6: Acceptable Ranges for Sensing and Pacing

Parameter	Acceptable test values
Pacing voltage	Pacing threshold < 3.0 V at 0.4 ms
P Sensitivity	P-wave amplitude > 1.0 mV

Success Criteria: A subject was considered to have met the primary effectiveness endpoint #1 if the pacing threshold voltage was ≤ 3.0 V at 0.4 ms at the 3-month visit **and** the sensed P-wave amplitude was ≥ 1.0 mV at the 3-month visit.

The $Rate_{EP}$ at 3 months was estimated as a binomial proportion and the one-sided 97.5% LCB of the Rate was calculated using the normal approximation. The null hypothesis was to be rejected at the 2.5% significance level if the LCB exceeded the PG of 82.5%. The p-value for the one-sided Z-test was to be calculated and compared to the 2.5% significance level.

Primary Effectiveness Endpoint #2
The primary effectiveness endpoint #2 evaluated the 3-month AV synchrony success rate ($Rate_{AV}$) at rest/seated using a Holter monitor in-clinic. AV synchrony success was 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 met success criteria in the primary effectiveness endpoint #2.

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

Secondary Effectiveness Endpoint
The secondary effectiveness endpoint included the evaluation of a Chronotropic Assessment Exercise Protocol (CAEP). If the primary endpoints and the secondary safety endpoint were met, then the following hypothesis was to be evaluated in *de novo* subjects:

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

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

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

full analysis population with a successful implant would provide data contributing to the analysis.

A mixed effects model for repeated measures were to 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) was used for this analysis. A 95% confidence interval for the mean slope were to be provided and if this interval falls within the equivalence bounds of (0.65,1.35), the null hypothesis was rejected.

Based on recently reported studies of marketed rate-responsive pacemakers the expected slope for similar devices, including the Aveir device, was estimated to be approximately 77%, with an associated standard deviation of 14%. It was estimated based on these data that a sample size of 8 subjects would be sufficient to demonstrate that the lower and upper 95% confidence bounds meet the success criterion, based on a normally distributed random variable. To ensure that a robust cross-section of subjects was evaluated, however, up to 30 subjects would undergo this assessment.

The 6MWT was to be performed any time after the beginning of the 1-month visit window and 3-month visit window. The CAEP protocol was to be performed after completion of the 6MWT protocol and any time after the beginning of the 3-month visit window and the 6-month visit window. The CAEP protocol was to be administered on a treadmill that could be programmed to the speed and grade/incline settings for each stage of the protocol.

B. Accountability of PMA Cohort

The Aveir DR i2i Study enrolled a total of 300 subjects within the full analysis population from 55 investigational sites. The full analysis population included the first 300 consecutive *de novo* subjects who provided written informed consent and had an attempted implant. A *de novo* subject was a subject who did not have an implanted pacemaker on the date of consent through the date of the attempted Aveir LP implant.

The study enrolled the first subject on February 2, 2022 and enrolled the final subject in the full analysis population on August 5, 2022. A total of 184 subjects (61.3%) were enrolled in the United States, 89 subjects (29.7%) were enrolled in Europe, and 27 subjects (9%) were enrolled in Canada. In total, 116 subjects (38.7%) were enrolled outside the United States (OUS).

The final 6-month follow-up visit for all subjects within the full analysis cohort occurred on February 1, 2023. The maximum enrollment per site was less than 15% of the total subjects required to evaluate the primary endpoints (i.e., 45 subjects). By the cut-off date of February 3, 2023, the full analysis population had a mean follow-up duration of 6.4 ± 1.6 subject-months (median duration 6.0 subject-months) with a cumulative total of 1,907 subject-months.

Figure 4 shows the disposition of all 300 subjects within the full analysis population. All subjects within this population had an attempted implant procedure where there was an attempt to implant both the Atrial and Ventricular LPs. All subjects either completed their 6-month visit or passed the window for their 6-month visit by the data cut-off date.

Figure 4: Disposition of Subjects

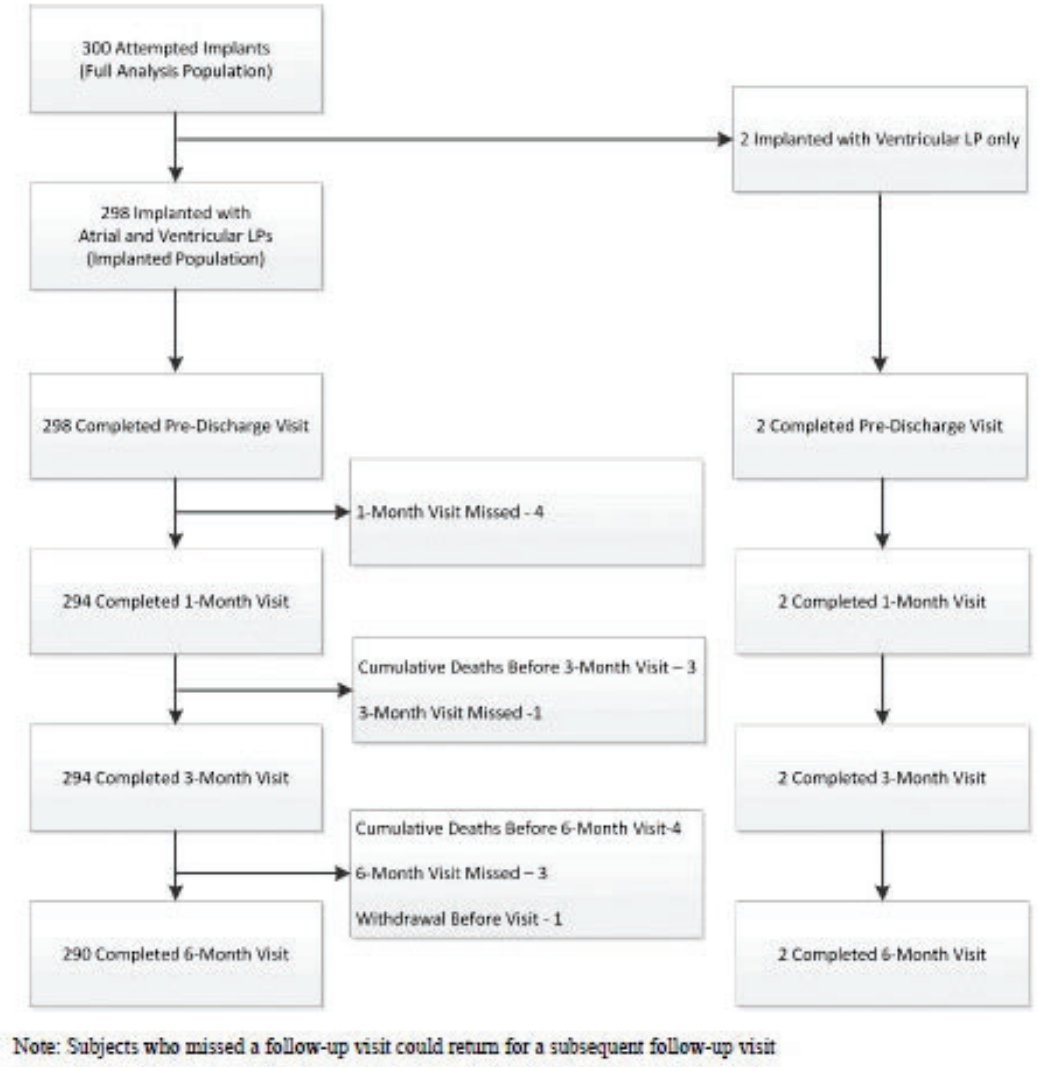


Table 7 below summarizes the reasons for all subject discontinuations and withdrawals.

Table 7: Subject Withdrawals and Discontinuations through 6 Months (Full Analysis Population)

Withdrawal Reason	Percent (Number) of Subjects (N=300)
System Explant and Not Re-Implanted	0.3% (1/300)
Subject Death	1.3% (4/300)
Total	**1.7% (5/300)**

Five (5) subjects (1.7%) withdrew or discontinued from the study by the end of each subject's 6-month visit window (210 days post-implant). Four (4) subjects discontinued due to subject death. Among these 4 deaths, 3 subjects died prior to their 3-month visit, while 1 subject died between the 3-month and 6-month visits.

One subject discontinued due to system explant between the 3-month and 6-month visits. This subject had both Atrial and Ventricular LPs explanted due to a medical condition change and commercial CRT-P device upgrade and was not re-implanted with Aveir LPs.

C. Study Population Demographics and Baseline Parameters

Table 8 shows the baseline demographics for all 300 subjects within the full analysis population. Overall, the demographics represent a typical dual-chamber pacemaker population, with a mean subject age of 69.2 ± 13.5 years (median age 72 years); 62.3% were male.

Race and ethnicity data were not collected at European centers due to local data privacy regulations. For this reason, the race and ethnicity data below represent the demographics from US and Canadian centers only.

Among the 211 subjects where demographic data was provided (excluding declined data), 94.8% identified as white or Caucasian, 2.8% identified as Black or African American, and 2.4% identified as Asian. Additionally, 4.7% identified with the ethnicity of Hispanic or Latino. One subject who identified as white also identified as American Indian or Alaskan Native. This is similar to the typical US population who have recently received dual-chamber transvenous pacemakers. Among US Medicare Fee-For-Service patients implanted with dual-chamber pacemakers between January 2019 and December 2019, 88.8% identified as white or Caucasian, 5.7% identified as Black, and 1.4% identified as Asian.

Table 8: Baseline Demographics (Full Analysis Population)

Characteristics	All Subject (N=300)
Gender	
Male	62.3% (187/300)
Female	37.7% (113/300)
Age (years)	
Mean ± SD (n)	69.2 ± 13.5 (300)
Median (Q1,Q3)	72.0 (63.0, 79.0)
(Min, Max)	(20.0, 90.0)
Height (cm)	
Mean ± SD (n)	171.6 ± 10.1 (300)
Median (Q1,Q3)	172.7 (164.5, 180.0)
(Min, Max)	(140.0, 195.6)
Weight (kg)	
Mean ± SD (n)	82.9 ± 19.1 (300)
Median (Q1,Q3)	81.7 (70.0, 92.5)

(Min, Max)	(43.5, 163.3)
BMI (kg/m^2)	
Mean ± SD (n)	28.1 ± 5.6 (300)
Median (Q1,Q3)	27.5 (24.4, 31.2)
(Min, Max)	(15.1, 49.7)
Ethnicity	
Hispanic or Latino	3.3% (10/300)
Not Hispanic or Latino	67.0% (201/300)
Declined/Unable to Disclose	29.7% (89/300)
Race	
American Indian or Alaska Native	0.3% (1/300)
Asian	1.7% (5/300)
Chinese	60.0% (3/5)
Korean	20.0% (1/5)
Other Asian	40.0% (2/5)
Black or African American	2.0% (6/300)
White	66.7% (200/300)
Declined/Unable to Disclose	29.7% (89/300)

Table 9 summarizes the medical history for all subjects in the full analysis population. Only subjects who had at least one of the indications in the ACC/AHA/HRS/ESC dual chamber pacing guidelines were eligible to enroll.

The most common primary indication in the Aveir DR full analysis population was sinus node dysfunction (63.3%). This indication included patients with the following conditions: sinus bradycardia, sinus arrest, brady-tachy syndrome, sick sinus syndrome, supra-ventricular tachycardias alternating with periods of bradycardia or asystole, and symptomatic chronotropic incompetence. New sinus node dysfunction (SND) associated with symptoms or hemodynamic instability unresolved after surgery were also included within this population.

The second most common indication was AV block (33.3%). Among this population, the most predominant heart block severities were 3rd degree AV Block (41.0%) and 2nd degree – Type 2 (34.0%), irrespective of symptoms. The AV block population also included symptomatic 1st degree AV block (11.0%) and symptomatic 2nd degree – Type 1 AV block (14.0%).

Finally, 2.0% and 1.3% of the population included those with vasovagal syncope and conduction disorders with 1:1 AV ventricular conduction, respectively. Subjects with these conduction disorders included those with alternating bundle branch block, Kearns-Sayre syndrome, and Anderson Fabry disease with QRS prolongation.

Table 9: Medical History (Full Analysis Population)

Characteristics	**All Subjects (N=300)**
Primary Pacemaker Indication	
Sinus Node Dysfunction	63.3% (190/300)

Atrio Ventricular (AV) Block	33.3% (100/300)
1st Degree	11.0% (11/100)
2nd Degree – Type 1	14.0% (14/100)
2nd Degree – Type 2	34.0% (34/100)
3rd Degree	41.0% (41/100)
Conduction Disorder with 1:1 Atrio Ventricular Conduction	1.3% (4/300)
Vasovagal (Reflex) Syncope	2.0% (6/300)
Congestive Heart Failure	
Congestive Heart Failure	12.3% (37/300)
Class I	18.9% (7/37)
Class II	56.8% (21/37)
Class III	8.1% (3/37)
NYHA Assessment Not Done	16.2% (6/37)
No Congestive Heart Failure	87.7% (263/300)
LV Ejection Fraction	
Mean ± SD (n)	59.6 ± 6.9 (226)
Median (Q1, Q3)	60.0 (55.0, 65.0)
(Min, Max)	(40.0, 77.0)
History of Tobacco Use	35.7% (107/300)
Hypertension	67.0% (201/300)
Controlled with Medication(s)	95.0% (191/201)
Uncontrolled	4.5% (9/201)
Diabetes	25.0% (75/300)
Type I	6.7% (5/75)
Type II	93.3% (70/75)
Diabetes Current Status	
Controlled with Diet	12.0% (9/75)
Controlled with Medication(s)	88.0% (66/75)
Hyperlipidemia	61.3% (184/300)
Controlled with Diet	13.6% (25/184)
Controlled with Medication(s)	82.1% (151/184)
Uncontrolled	4.3% (8/184)
Peripheral Vascular Disease	13.0% (39/300)
Cardio-Pulmonary History	
Coronary Artery Disease	34.0% (102/300)
Myocardial Infarction	11.7% (35/300)
Unstable Angina	5.7% (17/300)
Prior Ablation	20.0% (60/300)
AV Junction	1.7% (1/60)
AFib / Aflutter	78.3% (47/60)
SVT	11.7% (7/60)
Other	13.3% (8/60)
Tricuspid Valve Disease	24.3% (73/300)
Insufficiency / Prolapse / Regurgitation	98.6% (72/73)
Repair / Replacement	4.1% (3/73)
Arrhythmia History	
Ventricular	4.3% (13/300)
Non-Ventricular / Supraventricular	45.0% (135/300)
Medications	
Antiarrhythmics (Class I)	4.7% (14/300)
Antiarrhythmics (Class III)	9.7% (29/300)
Anticoagulants	31.0% (93/300)
Anti-platelets	39.0% (117/300)

ACE Inhibitors	22.0% (66/300)
Angiotensin II Receptor Blockers	23.0% (69/300)
Beta Blockers	23.7% (71/300)
Prior Extractions	
Transvenous Lead Extraction	8.0% (24/300)
Leadless Pacemaker Extraction	0.7% (2/300)
Prior Percutaneous Procedures	
TAVR	2.3% (7/300)
Mitral Valve Replacement/Repair	2.7% (8/300)
Tricuspid Valve Intervention	1.0% (3/300)
Percutaneous Coronary Intervention	16.3% (49/300)
Left Atrial Appendage Closure (LAAC)	3.7% (11/300)
Peripheral Vascular Intervention of Femoral Veins	2.3% (7/300)
Prior Open Heart Surgical Procedures	
CABG	10.3% (31/300)
Heart Transplant	0.3% (1/300)
Ventricular Assist Device	0.3% (1/300)
Aortic Valve replacement	4.7% (14/300)
ASD/PFO Closure	0.3% (1/300)
Other	1.7% (5/300)
Right Atrial Tissue Modification	6.7% (20/300)
Right Atrial Appendix Removed	10.0% (2/20)
Uncorrected Atrial Septal Defect	0.3% (1/300)

A majority of the full analysis population was comprised of patients with hypertension, hyperlipidemia, and a history of cardio-pulmonary disease with rates of 67.0%, 61.3%, and 51.3% respectively. Additionally, at least 25% of subjects had any of the following comorbidities: diabetes, a history of non-ventricular/supraventricular arrhythmias, and a history of tobacco use. Thirty-nine percent (39.0%) and 31.0% of subjects were on antiplatelet or anticoagulation drug therapy at the time of consent, respectively.

Overall, 20.0% of the full analysis population had a prior history of ablation, of which 78.3% had prior atrial fibrillation or atrial flutter ablation.

Most of the subject population also had prior cardiovascular interventions or surgeries, including 26 subjects (8.7%) with a history of transvenous lead or leadless pacemaker extraction. There were 53 subjects (17.7%) with prior open heart surgical procedures. The study did not require a waiting period between prior percutaneous or surgical procedures and the Aveir DR implant procedure. Subjects were only excluded if, in the investigator's opinion, the presence of anatomic or comorbid conditions 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.

Finally, there were 20 subjects (6.7%) with a history of a surgery or intervention where the right atrial tissue may have permanently been modified during the procedure, two of which had their right atrial appendix removed. These modification

procedures also included right atrial ablation, Cox-Maze, aortic valve replacement, and bypass surgery cannulation.

D. Safety and Effectiveness Results

1. Primary Safety Results

The primary analysis population for the primary safety endpoint was based on subjects in the full analysis population. The full analysis population included the first 300 consecutive *de novo* subjects who provided written informed consent and had an attempted implant. The primary safety endpoint evaluated a 3-month complication-free rate (CFR) based on CEC adjudication of adverse events. In addition, a 6-month primary safety analysis evaluated a 6-month CFR based on CEC adjudication of adverse events. Complications included Atrial LP, Ventricular LP, and implant procedure-related complications. The key safety outcomes for this study are presented below in **Table 10**. Adverse effects are reported in **Table 11**.

The primary safety endpoint analysis was only conducted on subjects within the full analysis population with data available for evaluation. For the 3-month endpoint analysis, subjects who withdrew from the study or died prior to the 3-month follow-up visit (lower window) without an event (SADE) were excluded from this analysis. Only SADE events that occurred on or before the 3 months (up to 90 days from the attempted implant date) were included. For the 6-month analysis, subjects who withdrew from the study or died prior to the 6-month follow-up visit (lower window) without an event (SADE) were excluded from this analysis. Only SADE events that occurred on or before the 6 months (up to 180 days from the attempted implant date) were included. To eliminate the possible impact of COVID-19, safety events (SADEs) that were adjudicated as related or possibly related to COVID-19 by the CEC were excluded from the analyses.

For the 3-month endpoint analysis, among the 300 evaluable subjects, 29 subjects experienced 35 complications (i.e., SADEs as adjudicated by the CEC). Therefore, 90.3% of subjects were free from complications within 3-months post-implant. The one-sided 97.5% lower confidence bound (or the lower bound of the two-sided 95% confidence interval) for the CFR was 87.0% and exceeded the performance goal of 78% ($p<0.0001$). Hence, the null hypothesis is rejected at the 2.5% significance level, and it is concluded that the primary safety endpoint was met.

For the 6-month analysis, among the 294 evaluable subjects, 32 subjects experienced 38 complications (i.e., SADEs as adjudicated by the CEC). Therefore, 89.1% of subjects were free from complications within 6-months post-implant. The one-sided 97.5% lower confidence bound (or the lower bound of the two-sided 95% confidence interval) for the CFR was 85.6%.

Table 10: Primary Safety Analysis (Full Analysis Population)
(Excludes COVID-19 Complications)

Analysis	Number of Subjects Analyzed (N)	Number of Complications	Number of Subjects with Complications (n)	Freedom from Complications (1-(n/N)) *100%	95% Confidence Interval[1]	P-value[2] (PG = 78%)	Endpoint Met?
Primary Safety Endpoint at 3 months	300	35	29	90.3%	(87.0%, 93.7%)	<0.0001	Yes
Primary Safety Analysis at 6 months	294	38	32	89.1%	(85.6%, 92.7%)	N/A	N/A

Source: S:\SHRDATA\AMD\AVG\CRD_1023 LEADLESS DR\Regulatory Reports\PMA\6M\Sasprog\CRD1023_PSEP.sas (March 30, 2023 (17:37). Data Cutoff Date: 03FEB2023 Data Snapshot Date: 17FEB2023)

[1] Normal approximation interval

[2] Z-test

Adverse effects that occurred in the PMA clinical study:

A complication was defined as a device-or-procedure-related serious adverse event. This definition of complication was equivalent to the term "SADE" (Serious Adverse Device Effect).

A serious adverse device effect (SADE) is any untoward medical occurrence that would happen in a subject or other person and related to the investigational device, comparator, or procedure, and meets the definition of serious, but is not unanticipated. Serious is defined as meeting at least one of the following criteria:

a) Led to death
b) Led to serious deterioration in the health of the subject that either resulted in:
    - Life-threatening illness or injury; or
    - Permanent impairment of a body structure or a body function; or
    - Inpatient or prolongation of existing hospitalization; or
    - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function; or
    - Chronic disease
c) Led to fetal distress, fetal death or a congenital abnormality or birth defect

Table 11 summarizes all 40 SADEs that took place within the 6-month visit window among the full analysis population.

Thirty-five (35) of the SADEs within Table 11 contributed toward the 3-month primary safety endpoint analysis; two events were not included. One pulmonary

embolism complication was related to COVID-19 and therefore did not contribute toward the primary safety endpoint analysis. One pre-syncope complication took place after 90 days post-implant but was still within the 3-month visit window, and therefore it also did not contribute toward the primary safety endpoint analysis.

Thirty-eight (38) of the SADEs within Table 11 contributed toward the 6-month primary safety analysis; two events were not included. One pulmonary embolism complication was related to COVID-19 and therefore did not contribute toward the primary safety endpoint analysis. One oversensing complication took place after 180 days post-implant but was still within the 6-month visit window, and therefore it also did not contribute toward the primary safety analysis.

Table 11: Serious Adverse Device Effects through 6 Months (CEC Adjudicated, Full Analysis Population)

Event Description	Number of Events	Percent of Subjects with Events %(n/N)	Related to Aveir Implant Procedure	Related to Aveir Ventricular LP	Related to Aveir Atrial LP	Related to Aveir Delivery Catheter RV	Related to Aveir Delivery Cather RA	Related to COVID-19
Cardiac Arrhythmia - Atrial Fibrillation	9	3.0% (9/300)	8	0	7	0	1	0
Device Dislodgement	5	1.7% (5/300)	0	0	5	0	0	0
Inadequate Fixation During Implant Without LP Migration	3	0.7% (2/300)	3	0	1	0	2	0
Urinary Retention	3	1.0% (3/300)	3	0	0	0	0	0
Threshold Elevation	2	0.7% (2/300)	0	1	1	0	0	0
Pericardial Effusion or Rub	2	0.7% (2/300)	2	0	2	0	0	0
Inadequate Fixation During Implant With LP Migration	2	0.7% (2/300)	2	1	1	0	0	0
False Magnet Mode	1	0.3% (1/300)	0	0	1	0	0	0
Syncope	1	0.3% (1/300)	0	0	1	0	0	0
Intermittent Capture	1	0.3% (1/300)	0	1	0	0	0	0
Intermittent or Loss of i2i Communication	1	0.3% (1/300)	0	1	0	0	0	0
Oversensing	1	0.3% (1/300)	0	1	0	0	0	0
Pre-Syncope	1	0.3% (1/300)	0	1	0	0	0	0

Access Site Bleeding Event	1	0.3% (1/300)	1	0	0	0	0	0
Heart Failure	1	0.3% (1/300)	1	0	0	0	0	0
Hematoma Formation, Including Retroperitoneal Hematoma/Hemorrhage	1	0.3% (1/300)	1	0	0	0	0	0
Pain	1	0.3% (1/300)	1	0	0	0	0	0
Pleural Effusion	1	0.3% (1/300)	1	0	0	0	0	0
Pulmonary Embolism	1	0.3% (1/300)	1	0	0	0	0	1
Other	2							
Mechanical Device Dislodgement	1	0.3% (1/300)	1	0	0	0	0	0
Complete Av Block	1	0.3% (1/300)	1	0	0	1	0	0
Total	40	11.0% (33/300)	26	6	19	1	3	1
Note: Subjects may experience more than one event. Note: Related includes Probable, Possible, or Causally related. Note: Covid-Related includes Related or Possibly Related. Note: Cardiac Arrhythmias –Supraventricular arrhythmia exclude atrial fibrillation events that are presented as a separate category in this table.								

There were 40 SADEs reported in 33 subjects constituting 11.0% of the full analysis population. Twenty-six (26) events were considered to be related to the Aveir DR implant procedure, 19 events were related to the Aveir Atrial LP, and 6 events were related to the Aveir Ventricular LP. Additionally, 3 events were related to the Aveir Delivery Catheter used to implant the Atrial LP, while 1 event was related to the Aveir Delivery Catheter used to implant the Ventricular LP. There was one pulmonary embolism event related to COVID-19.

The most frequent complications were 9 atrial fibrillation events in 9 subjects (3.0%), 5 device dislodgement events in 5 subjects (1.7%), and 5 inadequate fixation events in 4 subjects (1.3%), 2 of which resulted in LP migration.

Among all SADEs, 75% (30/40) were peri-procedural events that occurred within 30 days of the implant date (28 events occurred within 2 days of the implant date). The remaining 25% (10/40) all occurred between 32 and 200 days post-implant. Three (3) events of threshold elevation, false magnet mode, and oversensing took place between 3 and 6 months post-implant (after 120 days).

All events, apart from the pulmonary embolism and pre-syncope event, were resolved by the data cut-off date of this report. The pulmonary embolism remains in stable condition after medical therapy. The pre-syncopal symptoms remained ongoing at the time of subject study withdrawal due to system explant.

2. Secondary Safety Results

The primary analysis population for the secondary safety endpoint was based on subjects in the full analysis population, which included the first 300 consecutive *de novo* subjects who provided written informed consent and had an attempted

implant. The secondary safety endpoint evaluated a 3-month Atrial LP related complication-free rate (CFR_A) based on CEC adjudication of adverse events. In addition, a 6-month secondary safety analysis evaluated a 6-month CFR_A based on CEC adjudication of adverse events. An Atrial LP complication was defined as an atrial device-or-procedure-related serious adverse event. This definition of complication was equivalent to the term "SADE" (Serious Adverse Device Effect). The key safety outcomes for this study are presented below in **Table 12**.

The secondary safety endpoint analysis was only conducted on subjects with data available for evaluation. For the 3-month endpoint analysis, subjects who withdrew from the study or died prior to the 3-month follow-up visit (lower window) without an atrial complication were excluded from this analysis. For the 6-month analysis, subjects who withdrew from the study or died prior to the 6-month follow-up visit (lower window) without an atrial complication were excluded from this analysis.

For the 3-month endpoint analysis, among the 300 evaluable subjects, 26 subjects experienced 32 atrial device or procedure related complications. Therefore, 91.3% of subjects were free from atrial complications within 3 months post-implant. The one-sided 97.5% lower confidence bound (or the lower bound of the two-sided 95% confidence interval) for the CFR_A was **88.1%** and exceeded the performance goal of **84%** (p=0.0003). Hence, the null hypothesis is rejected at the 2.5% significance level, and it is concluded that the secondary safety endpoint was met.

For the 6-month analysis, among the 293 evaluable subjects, 26 subjects experienced 32 atrial device or procedure related complications. Therefore, 91.1% of subjects were free from atrial complications within 6-months post-implant. The one-sided 97.5% lower confidence bound (or the lower bound of the two-sided 95% confidence interval) for the CFR_A was 87.9%.

Table 12: Secondary Safety Analysis (Full Analysis Population) (Excluding COVID-19 Complications)

Analysis	Number of Subjects Analyzed (N)	Number of Complication(s)	Number of Subjects with Complications (n)	Freedom from Complication(s) (1-(n/N)) *100%	95% Confidence Interval[1]	P-value[2] (PG = 84%)	Endpoint Met?
Secondary Safety Endpoint at 3 months	300	32	26	91.3	(88.1%, 94.5%)	0.0003	Yes
Secondary Safety Analysis at 6 months	293	32	26	91.1%	(87.9%, 94.4%)	N/A	N/A

Source: S:\SHRDATA\AMD\AVG\CRD_1023 LEADLESS DR\Regulatory Reports\PMA\6M\Sasprog\CRD1023_SSEP.sas (March 30, 2023 (17:38). Data Cutoff Date: 03FEB2023 Data Snapshot Date: 17FEB2023)
[1] Normal approximation interval
[2] Z-test

3. Primary Effectiveness Endpoint #1 Results

The primary effectiveness endpoint #1 analysis was based on subjects in the full analysis population. Subjects with unsuccessful implants due to reasons other than atrial pacing/sensing (e.g., cardiac anatomy) were excluded from the analysis. The primary effectiveness endpoint #1 evaluated the 3-month composite success rate (Rate) evaluating acceptable atrial pacing thresholds and P-wave amplitudes in de novo subjects. In addition, a 6-month primary effectiveness #1 analysis evaluated the 6-month composite success rate (Rate) evaluating acceptable atrial pacing thresholds and P-wave amplitudes in de novo subjects. Key effectiveness outcomes are presented in **Table 13**.

For the 3-month endpoint analysis, subjects who did not meet pacing/sensing success criteria at 3 months or subjects with an unsuccessful implant solely due to inadequate Atrial LP pacing or sensing were counted as failures. In addition, for subjects with missing 3-month pacing threshold or P-wave amplitude data, multiple imputation was used to impute success or failure. Of the 300 subjects in the full analysis population, 297 subjects were included within the primary effectiveness endpoint #1 analysis. Among the 297 subjects in the evaluable population, the 3-month composite success Rate was 90.8%. The one-sided 97.5% lower confidence bound for the success Rate was **87.5%** and exceeded the performance goal of **82.5%** ($p<0.0001$). Hence, the null hypothesis is rejected at the 2.5% significance level, and it is concluded that the primary effectiveness endpoint #1 was met.

For the 6-month analysis, subjects who did not meet pacing/sensing success criteria at 6-month or subjects with an unsuccessful implant solely due to inadequate Atrial LP pacing or sensing were counted as failures. A complete case analysis was conducted so that data was only used for subjects who completed the 6-month visit and had data available for evaluation. Among the 300 subjects in the full analysis population, 282 subjects had 6-month data available and were thus included within the analysis. Among the 282 subjects in the evaluable population, the 6-month composite success Rate was 90.8%. The one-sided 97.5% lower confidence bound for the success Rate was **87.4%.**

Table 13: Primary Effectiveness #1 Analysis (Full Analysis Population)

Analysis	Number of Subjects Analyzed (N)	Number of Subjects Meeting Success Criteria (n)	Success Rate (n/N)%	95% Confidence Interval[1]	P-value[2] (PG = 82.5%)	Endpoint Met?
Primary Effectiveness#1	297	270	90.8%	(87.5%, 94.1%)	<0.0001	Yes

Endpoint at 3 months						
Primary Effectiveness #1 Analysis at 6 months	282	256	90.8%	(87.4%, 94.2%)	N/A	N/A

Source: S:\SHRDATA\AMD\AVG\CRD_1023 LEADLESS DR\Regulatory Reports\PMA\6M\Sasprog\CRD1023_PE1EP.sas (March 30, 2023 (17:36). Data Cutoff Date: 03FEB2023 Data Snapshot Date: 17FEB2023)

[1]Normal approximation interval

[2] Z-test

For the 3-month endpoint analysis, among the population with data available, there were 27 subjects who did not meet success criteria for the primary effectiveness endpoint #1. One (1) subject who failed the success criteria had both their capture threshold and the P-wave amplitudes measured outside of their acceptable ranges. The remaining 26 subjects only failed one of the two electrical performance criteria. Five (5) subjects failed the capture threshold criteria *only*, and 21 subjects failed the P-wave amplitude criteria *only*.

For the 6-month analysis, among the population with data available, there were 26 subjects who did not meet success criteria for the primary effectiveness #1 analysis. Two (2) subjects who failed the success criteria had both their capture threshold and the P-wave amplitudes measured outside of their acceptable ranges. The remaining 24 subjects only failed one of the two electrical performance criteria. Three (3) subjects failed the capture threshold criteria *only*, and 21 subjects failed the P-wave amplitude criteria *only*.

The rate of subjects who failed capture threshold criteria in this study and in the Leadless II – Phase 2 study at 6-months was similar. For the Atrial LP, the rate of threshold failure among subjects with 6-month data available was 1.8% (5/281) and, similarly for the Aveir VR LP, the rate of threshold failure was 2.0% (4/196) based on 6-month data available from the Leadless II – Phase 2 study.

4. Primary Effectiveness Endpoint #2 Results

The primary effectiveness endpoint #2 analysis was based on subjects in the full analysis population. Subjects with unsuccessful implants solely due to a failure to establish i2i communication at the end of the implant procedure were included and imputed as failures. Subjects with unsuccessful implants due to reasons other than AV Synchrony (e.g., cardiac anatomy) were excluded from the analysis. Among the 300 subjects in the full analysis population, 2 subjects were excluded from the evaluable population. Two of these subjects were those who had an unsuccessful atrial device implant. Within this cohort, there were 277 subjects with AV Synchrony data available to define endpoint success. Key effectiveness outcomes are presented in **Table 14**.

The primary effectiveness endpoint #2 evaluated the 3-month AV synchrony success rate ($Rate_{AV}$) at rest while seated in *de novo* subjects. AV synchrony success was defined as subjects with a paced or sensed ventricular beat within 300 ms following a paced or sensed atrial beat (i.e., a synchronous cycle) for at least

70% of evaluable cardiac cycles. An independent core laboratory evaluated collected Holter data from sites and determined AV synchrony success in subjects.

Among the 277 subjects in the evaluable population, the success $Rate_{AV}$ was 98.2%. The one-sided 97.5% lower confidence bound for the success $Rate_{AV}$ was **96.6%** and exceeded the performance goal of **83%** ($p<0.0001$). Hence, the null hypothesis is rejected at the 2.5% significance level, and it is concluded that the primary effectiveness endpoint #2 was met.

Table 14: Primary Effectiveness Endpoint #2 Analysis (Full Analysis Population)

Analysis	Number of Subjects Analyzed (N)	Number of Subjects Meeting Success Criteria (n)	Success Rate (n/N)%	95% Confidence Interval[1]	P-value[2] (PG=83%)	Endpoint Met? (Yes/No)
Primary Analysis – AV Synchrony	277	272	98.2%	(96.6%, 99.8%)	<0.0001	Yes

Source: S:\SHRDATA\AMD\AVG\CRD_1023 LEADLESS DR\Regulatory Reports\PMA\6M\Sasprog\CRD1023_PE2EP.sas (February 21, 2023 (10:11). Data Cutoff Date: 03FEB2023 Data Snapshot Date: 17FEB2023)

[1]Normal approximation interval

[2]Z-test

5. Secondary Effectiveness Endpoint Results

Rate-response pacing for patients programmed in an AAIR pacing mode is driven by the sensor in the Aveir Atrial LP. The secondary effectiveness endpoint evaluated the temperature-based rate response feature in the Aveir Atrial LP only. All capable subjects at participating centers were 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 test. All capable subjects who completed a 6MWT were subsequently asked to perform a maximal effort chronotropic assessment exercise protocol (CAEP) to demonstrate an appropriate and proportional response of sensor-indicated rate in graded exercise tests. Key effectiveness outcomes are presented in **Table 15**.

A total of 22 subjects underwent the CAEP assessment. Among the 22 subjects, 20 completed at least stage 3 of the CAEP exercise protocol, thus achieving a workload of at least 3.6 metabolic equivalent of task (METs). Two of the 20 subjects who completed stage 3 did not optimize the sensor gain as intended during the 6MWT, and therefore the CAEP was not performed using an optimized sensor gain. For this reason, these two subjects were not considered to be analyzable. Therefore, a total of 18 subjects were considered analyzable

('Analyzable Subjects') for the secondary effectiveness endpoint and exceeded the minimum sample size of 8 required for this assessment.

Table 15: 6-Month Secondary Effectiveness Analysis (Slope Through the Origin) (Analyzable Subjects)

	Slope Mean ± SE (n)	95% Confidence Interval (CI)	Equivalence Bounds	P-value[1]
Primary Analysis: Slope through Origin	0.94 ± 0.07 (18)	(0.80,1.08)	0.65< CI <1.35	< 0.001

Source: S:\SHRDATA\AMD\AVG\CRD_1023 LEADLESS DR\Regulatory Reports\PMA\6M\Sasprog\CRD1023_CAEP.sas (April 7, 2023 (14:41). Data Cutoff Date: 03FEB2023 Data Snapshot Date: 17FEB2023)

[1] P-value calculated by two one-sided T- test (TOST) for informational purpose only

The mean slope, through the origin, from this population was 0.94 ± 0.07. The 95% confidence interval for the mean slope was (0.80, 1.08), which fell within the 35% equivalence margin (0.65, 1.35) (p = <0.001). Hence, the null hypothesis is rejected, and it is concluded that the secondary effectiveness endpoint was met.

6. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: gender, age, and comorbidities.

Poolability by Site Category

Table 16 through **Table 18** present the primary endpoint poolability analysis results by Site Category. There were no statistically significant differences at the 0.15 significance level among the three site categories for any endpoint.

Table 16: Poolability by Site Category - Primary Safety Endpoint

	Number of Subjects Without Complication (n)	Number of Subjects in the Site Category(N)	3-Month CFR (n/N)*100%	P-value[1]
Large (# of Subjects > 10)	97	109	89.0%	0.5712
Medium (5 < # of Subjects ≤ 10)	82	88	93.2%	
Small (# of subjects ≤ 5)	92	103	89.3%	

Source: S:\SHRDATA\AMD\AVG\CRD_1023 LEADLESS DR\Regulatory Reports\PMA\3M\Sasprog\CRD1023_POOL.sas (December 1, 2022 (6:26). Data Cutoff Date: 26OCT2022 Data Snapshot Date: 28OCT2022)

[1] P-Value is calculated by Fisher's exact test and to be compared with 0.15 significance level.

Table 17: Poolability by Site Category - Primary Effectiveness Endpoint #1

	Number of Subjects Meeting Success Criteria (n)	**Number of Subjects in the Site Category(N)**	**3-Month Success Rate (n/N) *100%**	**P-value[1]**
Large (# of Subjects > 10)	99	106	93.4%	0.3071
Medium (5 < # of Subjects ≤ 10)	73	84	86.9%	
Small (number of subjects ≤5	91	100	91.0%	
Source: S:\SHRDATA\AMD\AVG\CRD_1023 LEADLESS DR\Regulatory Reports\PMA\3M\Sasprog\CRD1023_POOL.sas (December 1, 2022 (6:26). Data Cutoff Date: 26OCT2022 Data Snapshot Date: 28OCT2022)				

[1] P-Value is calculated by Fisher's exact test and to be compared with 0.15 significance level.

Table 18: Poolability by Site Category - Primary Effectiveness Endpoint #2

	Number of Subjects Meeting Success Criteria (n)	Number of Subjects in the Site Category (N)	3 Month AV Synchrony Success Rate (n/N)*100%	P-value[1]
Large (#of Subjects >10)	101	104	97.1%	0.6347
Medium (5<# of Subjects ≤10)	77	78	98.7%	
Small (# of subjects ≤5	94	95	98.9%	
Source: S:\SHRDATA\AMD\AVG\CRD_1023 LEADLESS DR\Regulatory Reports\PMA\3M\Sasprog\CRD1023_POOL.sas (December 1, 2022 (6:26). Data Cutoff Date: 26OCT2022 Data Snapshot Date: 28OCT2022)				

[1] P-Value is calculated by Fisher's exact test and to be compared with 0.15 significance level.

Since there were no statistically significant differences among the site categories, poolability by site enrollment is verified.

Descriptive summaries and 95% confidence intervals for the primary safety and effectiveness endpoints were presented across (1) gender, (2) age, and (3) comorbidities.

For all subgroup analyses, the primary safety endpoint and primary effectiveness endpoint #2 calculations were based on the same evaluable populations used for the study endpoint analyses (n=300 and n=277, respectively). The subgroup analyses for primary effectiveness endpoint #1 were based on subjects with 3-month data available for evaluation only (n=290). Unlike the study endpoint analysis which used multiple imputation, missing data was excluded for the subgroup analyses.

Consistency of results was examined using the Fisher's exact test for informational purposes. The comparisons between the subgroups are not powered for hypothesis testing and are exploratory in nature only.

Table 19 presents the subgroup analysis for the primary safety and two effectiveness endpoints by gender. There were no statistically significant differences observed at the 0.05 significance levels between males and females for all three endpoints.

Table 19: Subgroup Analysis by Gender

Variable	Male % (n/N) 95% CI	Female % (n/N) 95% CI	P-value[1]
Primary Safety Endpoint (3-Month CFR)	88.2% (165/187) [82.7%, 92.5%]	93.8% (106/113) [87.7%, 97.5%]	0.1573
Primary Effectiveness Endpoint #1 (3-Month Success Rate)	91.2% (165/181) [86.0%, 94.9%]	89.9% (98/109) [82.7%, 94.9%]	0.8351
Primary Effectiveness Endpoint #2 (3-Month AV Synchrony Success Rate)	97.1% (168/173) [93.4%, 99.1%]	100% (104/104) [96.5%, 100%]	0.1607

[1] P-values are calculated using a Fisher's exact test
Note: All p-values displayed are two-tailed and not from pre-specified hypothesis testing and are displayed for information only

Table 20 presents the subgroup analysis above and below the median age of 72 years old at the time of enrollment. There were no statistically significant differences observed at the 0.05 significance levels across age for the two effectiveness endpoints. However, the overall complication free rate was higher in those subjects younger than 72 years compared with those who were 72 years of age or older, with borderline significance ($p = 0.05$). Nevertheless, even subjects above the median age of 72 years of age had a complication free rate of 86.8% that exceeded the assumed success rate of 85%.

Upon closer examination of the types of complications between the older and younger populations in the DR study, the complication reported with the highest frequency that was exclusive to the older cohort was urinary retention (2.0% (3/152)).

In the Leadless II – Phase 2 study, the same subgroup exploratory analysis was conducted to evaluate the impact of age on the implantation of a single-chamber Aveir VR device. The analysis showed no statistically significant differences in the 6-week complication free rates between confirmatory cohort subjects less than and greater than the median age of 77 years, which was 95.7% and 96.2%, respectively. Urinary retention was not observed within the entire confirmatory cohort in the Leadless II-Phase 2 study.

Higher rates of urinary retention in the older cohort of the DR study may be explained by a longer procedure time compared with the VR implant, which is a known risk factor for post-operative urinary retention. Other contributory factors may include the method and duration of anesthesia, age, and history of benign prostatic hyperplasia (BPH)[14]. In fact, all subjects with urinary retention had a

history of BPH, and the investigators attributed at least two of these events to anesthesia.

Table 20: Subgroup Analysis by Age

Variable	Age < 72 Years (Median) % (n/N) 95% CI	Age >= 72 Years (Median) % (n/N) 95% CI	P-value[1]
Primary Safety Endpoint (3-Month CFR)	93.9% (139/148) [88.8%, 97.2%]	86.8% (132/152) [80.4%, 91.8%]	0.0498
Primary Effectiveness Endpoint #1 (3-Month Success Rate)	93.1% (134/144) [87.6%, 96.6%]	88.4% (129/146) [82.0%, 93.1%]	0.2251
Primary Effectiveness Endpoint #2 (3-Month AV Synchrony Success Rate)	97.8% (134/137) [93.7%, 99.5%]	98.6% (138/140) [94.9%, 99.8%]	0.6818

[1] P-values are calculated using a Fisher's exact test
Note: All p-values displayed are two-tailed and not from pre-specified hypothesis testing and are displayed for information only

After enrollment was completed, only those comorbidities thought to be associated with dual-chamber leadless pacemaker complications or effectiveness were selected for analysis based on the opinions of the Principal and Co-Principal Investigators, without any knowledge of the trial results. Among this subset, only those comorbidities with sufficient representation, occurring in approximately 25% or more of the full analysis population, were considered for the univariate subgroup analyses. These included: abnormal body mass index (BMI)[1], non-ventricular arrhythmia history[2], and tricuspid valve disease. Subjects taking anticoagulation or antiplatelet drug therapies[3] were also included as a subgroup since this condition met these criteria.

Since the specific comorbidity subgroup analyses were not derived from a pre-specified hypothesis, they were not powered with a minimal sample size to detect an effect. Therefore, the p-values presented are for informational or exploratory use only.

Table 21 represents a univariate subgroup analyses for each of these pre-determined baseline comorbidities or conditions.

[1] Abnormal BMI is > 30 kg/m^2 or < 20 kg/m^2
[2] Includes history of atrial fibrillation, atrial flutter, atrial tachycardia, and supraventricular tachycardia
[3] Subjects on anticoagulation or antiplatelet therapies who did not suspend both therapies earlier than 1 day prior to procedure date

Table 21: Subgroup Analyses by Comorbidities

Abnormal BMI			
Variable	**BMI Normal % (n/N) 95% CI**	**BMI Abnormal % (n/N) 95% CI**	**P-value[1]**
Primary Safety Endpoint (3-Month CFR)	90.0% (99/110) [82.8%, 94.9%]	90.5% (172/190) [85.4%, 94.3%]	>0.9999
Primary Effectiveness Endpoint #1 (3-Month Success Rate)	89.7% (96/107) [82.3%, 94.8%]	91.3% (167/183) [86.2%, 94.9%]	0.6793
Primary Effectiveness Endpoint #2 (3-Month AV Synchrony Success Rate)	99.0% (102/103) [94.7%, 100%]	97.7% (170/174) [94.2%, 99.4%]	0.6541
[1]P-values are calculated using a Fisher Exact Note: All P-values displayed are two-tailed and not from pre-specified hypothesis testing and are displayed for information only			
Tricuspid Valve Disease			
Variable	**With History of TVD % (n/N) 95% CI**	**No History of TVD % (n/N) 95% CI**	**P-value[1]**
Primary Safety Endpoint (3-Month CFR)	91.8% (67/73) [83.0%, 96.9%]	89.9% (204/227) [85.2%, 93.5%]	0.8203
Primary Effectiveness Endpoint #1 (3-Month Success Rate)	87.5% (63/72) [77.6%, 94.1%]	91.7% (200/218) [87.3%, 95.0%]	0.3482
Primary Effectiveness Endpoint #2 (3-Month AV Synchrony Success Rate)	95.7% (67/70) [88.0%, 99.1%]	99.0% (205/207) [96.6%, 99.9%]	0.1045
[1]P-values are calculated using a Fisher Exact Note: All P-values displayed are two-tailed and not from pre-specified hypothesis testing and are displayed for information only			
Non-Ventricular (Supraventricular) Arrhythmia History			
Variable	**With History of NVA % (n/N) 95% CI**	**No History of NVA % (n/N) 95% CI**	**P-value[1]**
Primary Safety Endpoint (3-Month CFR)	87.4% (118/135) [80.6%, 91.2%]	92.7% (153/165) [87.6%, 96.2%]	0.1684
Primary Effectiveness Endpoint #1 (3-Month Success Rate)	85.7% (114/133) [78.6%, 91.2%]	94.9% (149/157) [90.2%, 97.8%]	0.0084
Primary Effectiveness Endpoint #2 (3-Month AV Synchrony Success Rate)	99.2% (126/127) [95.7%, 100%]	97.3% (146/150) [93.3%, 99.3%]	0.3792
Source: S:\SHRDATA\AMD\AVG\CRD_1023 LEADLESS DR\Regulatory Reports\PMA\3M\Sasprog\CRD1023_SUBGRP.sas (December 1, 2022 (10:48). Data Cutoff Date: 26OCT2022 Data Snapshot Date: 28OCT2022) [1]P-values are calculated using a Fisher Exact Note: All P-values displayed are two-tailed and not from pre-specified hypothesis testing and are displayed for information only			

Anticoagulant/Antiplatelet Therapy			
Variable	**Anticoagulant or Antiplatelet Therapy Until Procedure % (n/N) 95% CI**	**Suspended/No Anticoagulant/Antiplatelet Therapy % (n/N) 95% CI**	**P-value[1]**
Primary Safety Endpoint (3-Month CFR)	89.5% (170/190) [84.2%, 93.5%]	91.8% (101/110) [85.0%, 96.2%]	0.5504
Primary Effectiveness Endpoint #1 (3-Month Success Rate)	87.3% (158/181) [81.5%, 91.8%]	96.3% (105/109) [90.9%, 99.0%]	0.0114
Primary Effectiveness Endpoint #2 (3-Month AV Synchrony Success Rate)	99.4% (171/172) [96.8%, 100%]	96.2% (101/105) [90.5%, 99.0%]	0.0701
[1]P-values are calculated using a Fisher Exact Note: All P-values displayed are two-tailed and not from pre-specified hypothesis testing and are displayed for information only			

There were no statistically significant differences observed at the 0.05 significance level among any of the primary endpoints for subjects with normal or abnormal BMI and for subjects with or without a history of tricuspid valve disease. However, there was a statistically higher rate of failure for the primary effectiveness endpoint #1, which evaluated Atrial LP pacing and sensing, observed for subjects with non-ventricular (i.e., supraventricular) arrhythmia history and those who were on anti-coagulation or antiplatelet therapy prior to the procedure.

Substrate modification or atrial remodeling following catheter ablation were hypothesized to have an impact on P-wave amplitudes in the LP sensing vector. However, among the subjects with non-ventricular (i.e., supraventricular) arrhythmia history, 53% (10/19) of those who failed the effectiveness endpoint and 45% (52/115) of those who passed the endpoint had a prior history of ablation or any form of right atrial tissue modification (e.g., Cox Maze, bypass cannulation).

Given this unclear relationship with the only hypothesized variable that could have a direct impact on atrial sensing, a multivariable logistic regression was done to help understand the relationship between effectiveness endpoint #1 and other patient characteristics that could impact the endpoint's success. The covariates included were based on those determined by the Principal and Co-Principal Investigators to have a biologically plausible effect on right atrial size or tissue characteristics, without regard to a 25% representation threshold or knowledge of the trial results. These included history non-ventricular arrhythmias, tricuspid valve disease, and congestive heart failure. Subjects who were the median age or older and on anti-coagulation or antiplatelet therapy were also included as covariates since they had the lowest effectiveness endpoint #1 success rate among the remaining covariates explored in the univariate subgroup analysis above.

Table 22 shows the results of the multivariable logistic regression model. When these covariates are adjusted, there are no statistically significant differences

observed at the 0.05 significance level among this set of predictors for failing the primary effectiveness endpoint #1.

Table 22: Primary Effectiveness Endpoint #1 Multivariable Analysis

Effect	P-value[1]	Odds Ratio Estimate	95% Wald Confidence Limits for Odds Ratio
Age >= 72 Years (Median)	0.2879	1.58	(0.68, 3.67)
History of Congestive Heart Failure	0.1864	1.99	(0.72, 5.53)
History of Non-Ventricular Arrhythmias	0.1007	2.14	(0.86, 5.34)
History of Tricuspid Valve Disease	0.8335	1.10	(0.45, 2.73)
Anticoagulant or Antiplatelet Therapy Until Procedure	0.1448	2.38	(0.74, 7.64)

Source: S:\SHRDATA\AMD\AVG\CRD_1023 LEADLESS DR\Regulatory Reports\PMA\3M\Sasprog\CRD1023_PE1EPMV.sas (December 20, 2022 (10:04). Data Cutoff Date: 26OCT2022 Data Snapshot Date: 28OCT2022)

[1]From Wald Chi-Square Test

7. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 143 investigators of which none were full-time or part-time employees of the sponsor and three (3) had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 3
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

A. Device Electrical Measurements – PMA Cohort

Table 23 summarizes the critical device electrical measurements for each LP among the implanted population (n=298). The measurements reflect the mean capture thresholds, sensing amplitudes, and impedance values from implant and during each study visit through 6 months post-implant. The capture thresholds were measured at a median 0.4 ms pulse width.

Table 23: Device Electrical Measurements (Implanted Population)

	Ventricular LP			Atrial LP		
Visit Type	**Capture Threshold [V] Mean ± SD (n) (Min, Median, Max)**	**R-Wave Amplitude [mV] Mean ± SD (n) (Min, Median, Max)**	**Impedance [Ω] Mean ± SD (n) (Min, Median, Max)**	**Capture Threshold [V] Mean ± SD (n) (Min, Median, Max)**	**P-Wave Amplitude [mV] Mean ± SD (n) (Min, Median, Max)**	**Impedance [Ω] Mean ± SD (n) (Min, Median, Max)**
Implant	0.79 ± 0.60 (298) (0.25, 0.50, 3.75)	8.71 ± 3.96 (291) (<1.00, 7.90, 18.00)	784.06 ± 355.56 (298) (230.00, 695.00, 2000.00)	2.57 ± 1.56 (295) (0.25, 2.25, 6.00)	1.95 ± 1.17 (290) (<1.00, 1.50, 7.50)	331.41 ± 68.34 (297) (200.00, 320.00, 710.00)
Pre-Discharge	0.57 ± 0.44 (296) (0.00, 0.50, 3.75)	10.06 ± 3.94 (284) (2.00, 9.60, 18.00)	764.51 ± 239.48 (296) (310.00, 710.00, 2000.00)	1.22 ± 1.05 (290) (0.25, 0.75, 6.00)	2.71 ± 1.70 (291) (<1.00, 2.40, 10.00)	375.88 ± 87.40 (295) (200.00, 370.00, 810.00)
1-Month	0.60 ± 0.53 (293) (0.00, 0.50, 5.00)	11.66 ± 4.24 (283) (2.90, 11.40, 18.00)	646.70 ± 192.30 (294) (310.00, 620.00, 2000.00)	0.91 ± 0.90 (283) (0.25, 0.50, 6.00)	3.50 ± 1.87 (281) (<1.00, 3.20, 10.00)	328.46 ± 53.81 (293) (200.00, 320.00, 600.00)
3-Month	0.63 ± 0.57 (293) (0.00, 0.50, 4.50)	12.00 ± 4.17 (281) (3.50, 12.10, 18.00)	594.74 ± 150.29 (293) (300.00, 570.00, 1070.00)	0.82 ± 0.70 (287) (0.25, 0.50, 5.25)	3.58 ± 1.88 (286) (<1.00, 3.30, 10.00)	315.40 ± 44.77 (291) (210.00, 310.00, 500.00)
6-Month	0.68 ± 0.60 (287) (0.25, 0.50, 5.50)	11.72 ± 4.11 (279) (2.90, 11.60, 18.00)	593.96 ± 144.65 (288) (220.00, 580.00, 1020.00)	0.86 ± 0.72 (276) (0.25, 0.50, 5.50)	3.55 ± 1.96 (279) (<1.00, 3.30, 10.00)	307.19 ± 41.48 (286) (200.00, 300.00, 430.00)

Note: De novo subjects with both Atrial and Ventricular LPs implanted are included
Note: R-wave/P-wave Amplitudes smaller than 1 mV are recorded and displayed as < 1 mV by the device. 1 mV was used for this statistical summary.
Note: R-wave/P-wave Amplitudes greater than > 18 mV/10 mV respectively are recorded and displayed as maximum mV by the device. 18 mV/10 mV were used for this statistical summary.
Note: Ventricular/Atrial Impedance greater 2000 [ ] respectively are recorded and displayed as > 2000 [ ] by the device. 2000 [ ] was used for this statistical summary

Overall, the capture threshold and R-wave amplitude of the Ventricular LP demonstrated appropriate behavior and stability through the 3-month visit that was consistent with the electrical measures exhibited by the physically equivalent Aveir VR LP in the Leadless II-Phase 2 study. The impedance trends of the Ventricular LP were also similar to those observed in the Aveir VR LP.

For the Atrial LP, the mean capture threshold remained below the 3.0V threshold, and the mean sensing amplitude remained above the 1.0 mV threshold identified in the study protocol for the primary effectiveness endpoint #1 during each study visit.

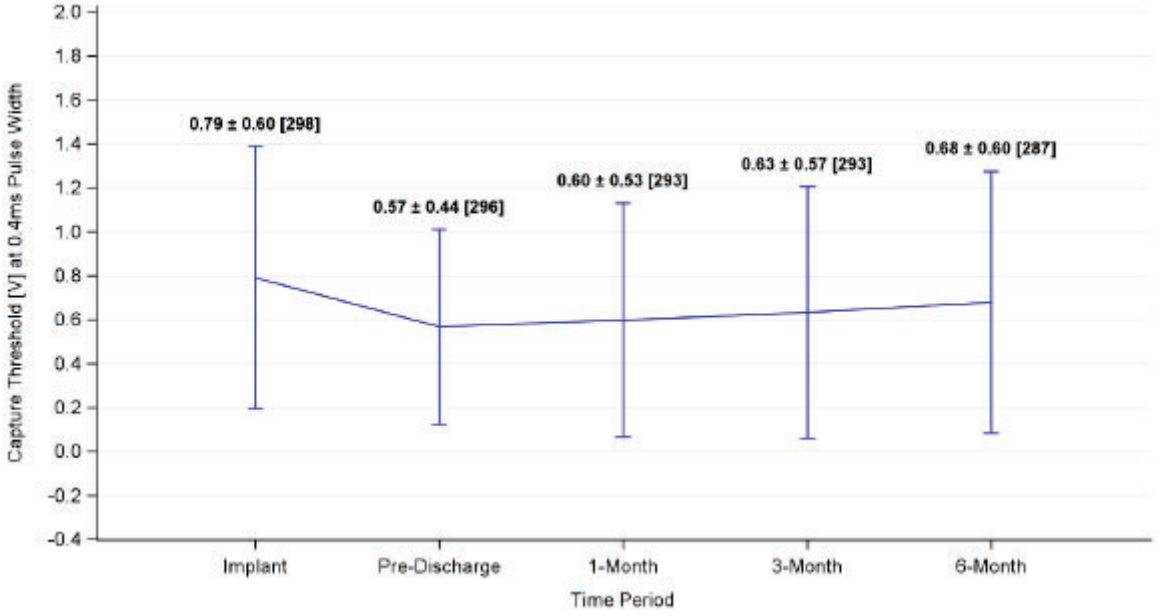
Figure 5 through **Figure 10** visualize the trends of these parameters through the 6-month post-implant visit.

For the Atrial LP, the mean capture threshold began at 2.57 ± 1.56 V post-implant and decreased to 1.22 ± 1.05 V at discharge, with continued decline at 1-month and 3-month visits. The mean P-wave amplitude was 1.95 ± 1.17 mV at implant and increased to 2.71±1.70 mV at discharge, with continued increase in amplitude at 1-month and 3-month visits. Both measures continued to stabilize with minor variations at the 6-month visit.

The mean atrial impedance was 331.41 ± 68.34 Ω at implant that acutely rose to 375.88 ± 87.40 Ω at discharge and progressively declined until it reached a mean impedance of 307.19 ± 41.48 at 6 months.

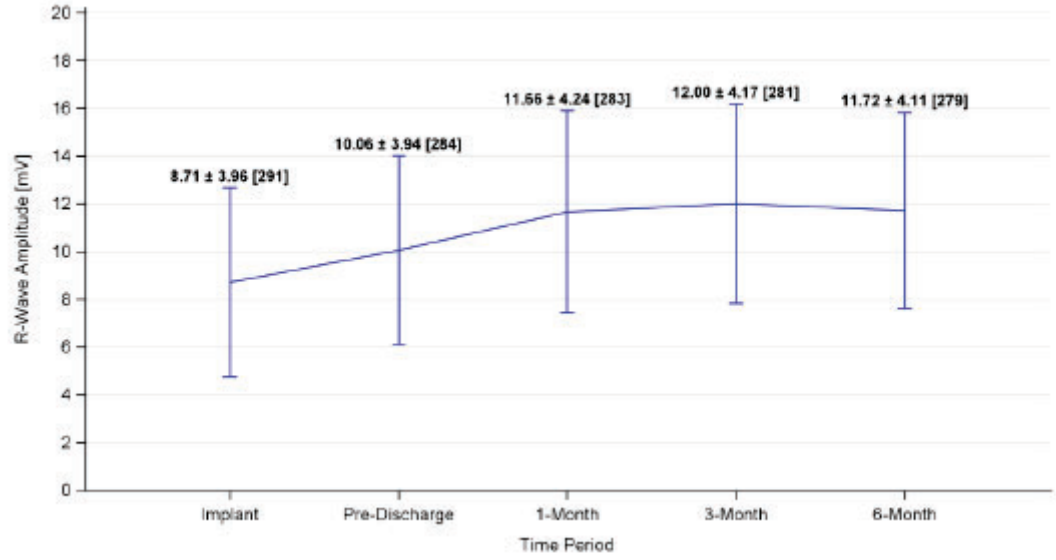
Ventricular LP Electrical Measurements

Figure 5: Device Measurements Summary- Ventricular LP Capture Threshold (Implanted Population)



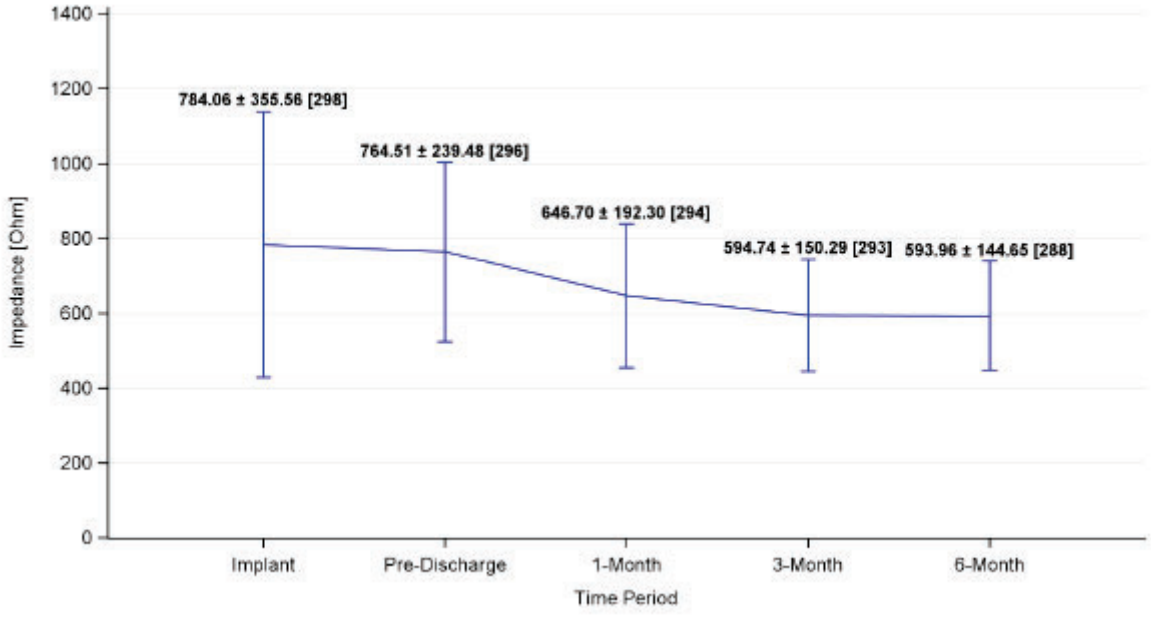
Mean ± STD is shown

Figure 6: Device Measurements Summary- Ventricular LP R-Wave Amplitude (Implanted Population)



Mean ± STD is shown

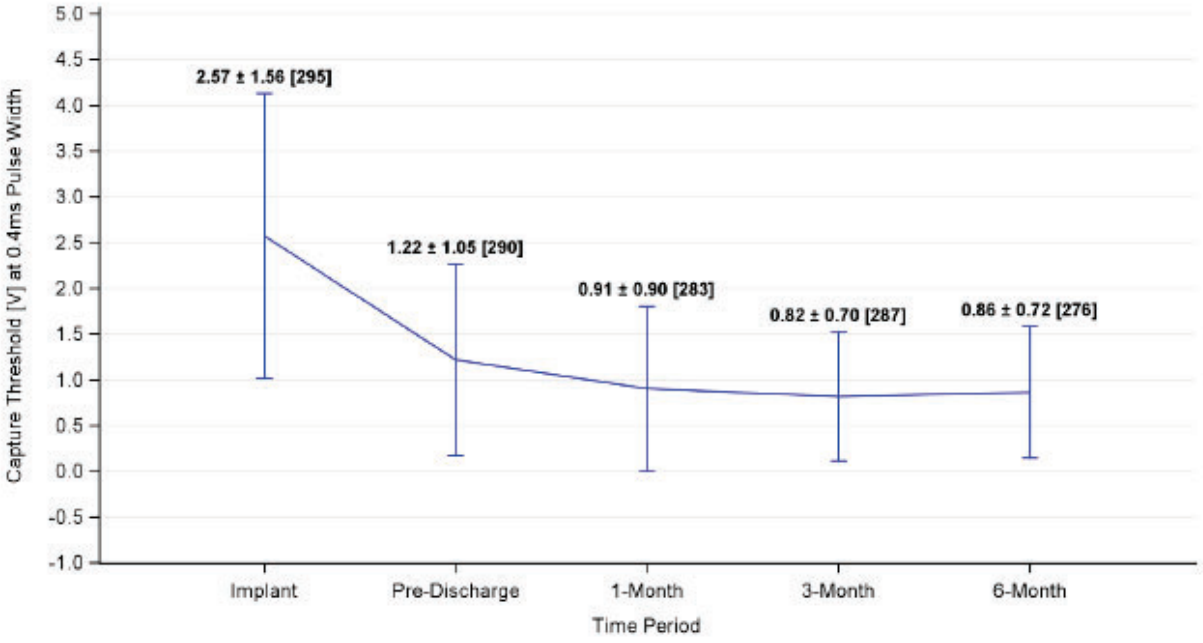
Figure 7: Device Measurements Summary- Ventricular LP Impedance (Implanted Population)



Mean ± STD is shown

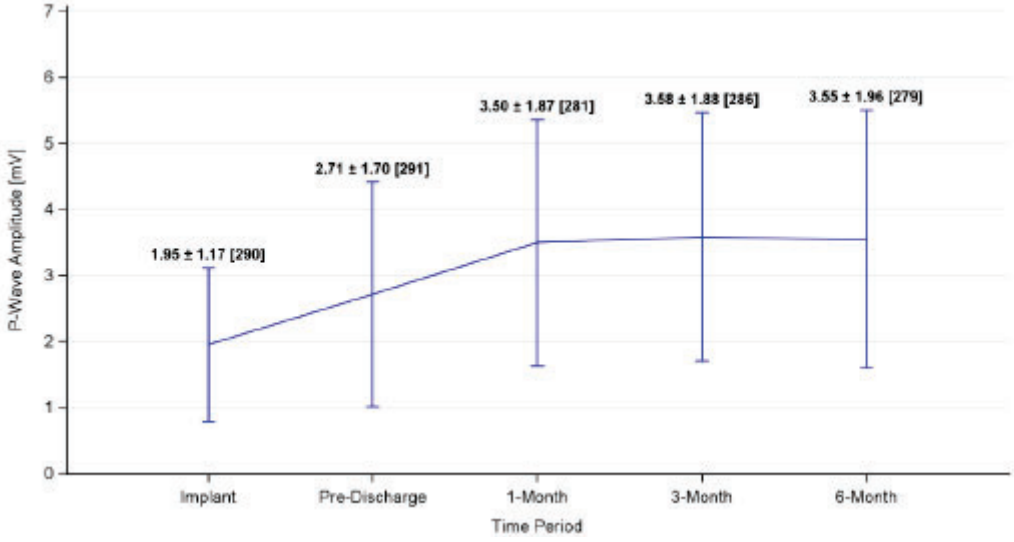
Atrial LP Electrical Measurements

Figure 8: Device Measurements Summary- Atrial LP Capture Threshold (Implanted Population)



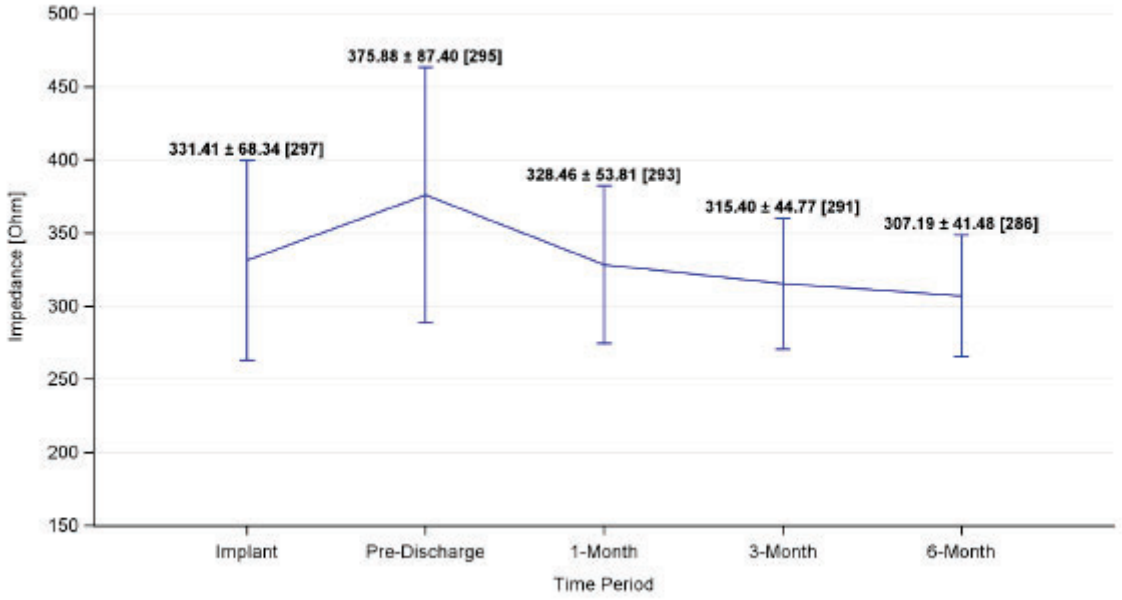
Mean ± STD is shown

Figure 9: Device Measurements Summary- Atrial LP P-Wave Amplitude (Implanted Population)



Mean ± STD is shown

Figure 10: Device Measurements Summary- Atrial LP Impedance (Implanted Population)



Mean ± STD is shown

B. <u>Projected Remaining Device Longevity at the 6-Month Visit</u>

Table 24 shows the mean remaining battery longevities for the Ventricular LP and Atrial LP among the implanted population from the 6-month visit. Longevities were excluded if the 6-month device interrogation captured less than 1 month of follow-up data.

Table 24: Projected Remaining Longevity at 6 Months All Pacing Modes (Implanted Population)

	Summary
Projected Remaining Longevity at 6-Month Follow-up Visit (Years)	
Ventricular LP	
Mean ± SD (n)	10.5 ± 4.9 (270)
(Min, Median, Max)	(2.0, 9.5, 25.0)
[95% Confidence Interval]	[9.9, 11.1]
Atrial LP	
Mean ± SD (n)	5.1 ± 3.2 (267)
(Min, Median, Max)	(0.5, 4.6, 25.0)
[95% Confidence Interval]	[4.7, 5.5]

Source: S:\SHRDATA\AMD\AVG\CRD_1023 LEADLESS DR\Regulatory Reports\PMA\6M\Sasprog\CRD1023_BATTERY.sas (March 31, 2023 (10:30). Data Cutoff Date: 03FEB2023 Data Snapshot Date: 17FEB2023)

Table 25 through 27 show the mean remaining battery longevities in the Ventricular LP and/or Atrial LP at the 6-month visit among different sub-populations that are stratified by the pacing mode of the device presented at the 6-month visit. Subjects in dual-chamber modes included those in DDD, DDDR, DDI, DDIR, or VDD modes. Subjects in a

Ventricular LP single-chamber mode included those in VVI or VVIR modes. Subjects in an Atrial LP single-chamber mode included those in AAI or AAIR modes.

Table 25: Projected Remaining Longevity at 6 Months- Dual-Chamber Modes (Implanted Population)

	Summary
Projected Remaining Longevity at 6-Month Follow-up Visit (Years)	
Ventricular LP	
Mean ± SD (n)	9.4 ± 3.2 (250)
(Min, Median, Max)	(2.0, 9.3, 22.5)
[95% Confidence Interval]	[9.0, 9.8]
Atrial LP	
Mean ± SD (n)	4.9 ± 2.8 (249)
(Min, Median, Max)	(0.5, 4.5, 25.0)
[95% Confidence Interval]	[4.6, 5.3]
Source: S:\SHRDATA\AMD\AVG\CRD_1023 LEADLESS DR\Regulatory Reports\PMA\6M\Sasprog\CRD1023_BATTERY.sas (March 31, 2023 (10:30). Data Cutoff Date: 03FEB2023 Data Snapshot Date: 17FEB2023)	

Table 26: Projected Remaining Longevity at 6 Months Ventricular LP Single Chamber Modes (Implanted Population)

	Summary
Projected Remaining Longevity at 6-Month Follow-up Visit (Years)	
Ventricular LP	
Mean ± SD (n)	17.9 ± 8.0 (4)
(Min, Median, Max)	(6.7, 19.9, 25.0)
[95% Confidence Interval]	[5.2, 30.5]
Source: S:\SHRDATA\AMD\AVG\CRD_1023 LEADLESS DR\Regulatory Reports\PMA\6M\Sasprog\CRD1023_BATTERY.sas (March 31, 2023 (10:30). Data Cutoff Date: 03FEB2023 Data Snapshot Date: 17FEB2023)	

Table 27: Projected Remaining Longevity at 6 Months Atrial LP Single Chamber Modes (Implanted Population)

	Summary
Projected Remaining Longevity at 6-Month Follow-up Visit (Years)	
Atrial LP	
Mean ± SD (n)	6.7 ± 3.3 (16)
(Min, Median, Max)	(0.5, 6.5, 16.3)
[95% Confidence Interval]	[5.0, 8.5]
Source: S:\SHRDATA\AMD\AVG\CRD_1023 LEADLESS DR\Regulatory Reports\PMA\6M\Sasprog\CRD1023_BATTERY.sas (March 31, 2023 (10:30). Data Cutoff Date: 03FEB2023 Data Snapshot Date: 17FEB2023)	

The projected longevities shown above were based on the value displayed by the programmer based on delivered therapy, programmed settings, percent pacing, and measured pacing impedance.

These longevity measures were predominantly obtained prior to a software update intended to improve the projected longevity accuracy by accounting for additional pacing events under specific conditions.

An analysis found that the lowest 5th percentile of these projected longevities can be attributed to programmed settings. All subjects in the lowest 5th percentile had either higher i2i strength settings in both directions (6/7-7/7) or a composite of parameters that contribute to higher pacing current output. Higher i2i strength settings are intended to improve bidirectional LP communication by employing higher amplitude and/or longer pulse-width communication pulses. However, these higher settings require increased energy consumption. Higher current output for pacing, which also requires more energy from the battery, is primarily modulated by pulse amplitude, pulse-width, pacing rate, and load resistance.

There have been no reports of premature battery depletion for any device.

C. Upgrades from the Aveir VR LP to the Aveir DR LP System

There were 25 subjects with a pre-existing Aveir VR who had an attempted upgrade to an Aveir DR system through the period that the full analysis population was enrolled, specifically, through August 5, 2022.

Among the 25 subjects with an attempted upgrade from a pre-existing Aveir VR to an Aveir DR system, 92% (23/25) were successfully implanted with an Aveir Atrial LP. The Aveir VR was successfully programmed to a dual-chamber pacing mode in all successfully implanted subjects.

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Cardiovascular Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

However, a general issues panel meeting for the class of leadless pacemakers was held on February 18, 2016. The panel was asked to discuss and provide recommendations on the acute adverse event rates noted in available clinical trial information, post approval study design considerations, device labeling, and indications for use for leadless pacemakers. The panel recommended the following:

- Expectations of cardiac perforation rates should be consistent with rates of transvenous systems.
- No subgroups need to be excluded from receiving a leadless pacemaker.

- Implanting physicians should be adequately trained/informed about adverse events and patient selection.
- Acute and long-term events should be captured via a post approval study.
- Post approval study sample size is acceptable to be 1741 patients, with at least 500 followed for 9 years.
- Data from a total of 200 end-of-life cases, including device removal/extraction experience, where applicable, should be collected.
- Labeling should be device-specific and incorporate device experience, noting limitations of knowledge gaps, where appropriate.
- Indications for use of transvenous, single chamber pacemakers apply to this class of devices and AHA/ACC/HRS guidelines are already applicable.

These recommendations were considered in the course of this review as they applied to leadless pacemakers in general. The panel meeting transcript can be found at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/CirculatorySystemDevicesPanel/UCM489547.pdf.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The clinical results demonstrate a reasonable assurance of effectiveness for the Aveir DR Leadless System. In the clinical study, both primary effectiveness endpoints were met. The primary effectiveness endpoint #1 Atrial LP pacing and sensing 3-month composite success rate among 297 evaluable subjects was 90.8%, of which the one-sided 97.5% LCB, 87.5%, exceeded the performance goal of 82.5% with statistical significance ($p<0.0001$). A 6-month primary effectiveness #1 analysis was consistent with the 3-month results. The primary effectiveness endpoint #2 AV Synchrony success rate among 277 evaluable subjects was 98.2%, of which the one-sided 97.5% LCB, 96.6%, exceeded the performance goal of 83% with statistical significance ($p<0.0001$).

The rate response assessment for the secondary effectiveness endpoint demonstrated an appropriate and proportional rate response during graded exercise testing. The mean slope of the normalized increase in sensor-indicated rate versus normalized CAEP workload for each subject among 18 analyzable subjects was 0.94 ± 0.07 with a 95% confidence interval (0.80, 1.08), which fell within the pre-specified success criterion of a 35% equivalence margin (0.65, 1.35), with statistical significance ($p=<0.001$).

Among the 25 subjects with an attempted upgrade from a pre-existing Aveir VR to an Aveir DR system, 92% (23/25) were successfully implanted with an Aveir Atrial LP. The Aveir VR was successfully programmed to a dual-chamber pacing mode in all successfully implanted subjects.

B. Safety Conclusions

The risks of the Aveir DR Leadless System are based on data collected in nonclinical laboratory and animal studies as well as data collected in the Aveir DR i2i Study conducted to support PMA approval. Non-clinical testing performed, including biocompatibility, mechanical, electrical, simulated and MRI testing, demonstrates that the Aveir DR Leadless System is designed to be safe for its intended use.

In the clinical study, the primary safety endpoint was met as the 3-month complication free rate (CFR) among 300 evaluable subjects in the full analysis population was 90.3%, of which the one sided 97.5% lower confidence bound (or the lower bound of the two-sided 95% confidence interval) for the CFR was 87.0% and exceeded the performance goal of 78% ($p<0.0001$). The secondary safety endpoint was also met, as the 3-month Atrial LP related complication-free rate (CFR_A) among the full analysis population was 91.3%, of which the one sided 97.5% lower confidence bound for the CFR_A was 88.1% and exceeded the performance goal of 84% ($p=0.0003$). A 6-month primary safety analysis and 6-month secondary safety analysis were consistent with the 3-month results.

C. Benefit-Risk Determination

The Aveir DR system is indicated for use in patients with bradyarrhythmias and is intended to provide pacing therapy. The device has been shown as effective for achieving this purpose and benefit. The product and its therapies are well understood, and the labeling is consistent with the medical understanding of the product.

The use of the product itself and failure modes of the product are tracked for their health affect. Adverse effects of patient health, including effects with no product allegation, are summarized above. The serious adverse events for use with the product are less than the adverse events without use of the product. Based on this, the benefit of the product use outweighs the risk for this benefit risk assessment.

The Aveir DR system, and its indications for use and intended purpose, is similar to traditional dual chamber pacemakers in the medical landscape.

The product performs with a positive benefit to risk assessment. The product also performs in a manner that is consistent with other current medical treatments. Based on the individual and aggregate residual risks and product performance in context with other current medical therapies, there is a positive benefit / risk analysis with an acceptable overall residual risk for the Aveir DR system.

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above.

1. Patient Perspective
   This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the PMA for this device.

In conclusion, given the available information above, the data support that for the safety and effectiveness of the Aveir DR Leadless Pacemaker system for dual chamber pacing indications, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

The Aveir DR i2i Study met the pre-specified performance goals for both the safety (freedom from serious adverse device effects) and effectiveness (acceptable Atrial LP pacing and sensing, AV Synchrony) endpoints. These results showed that the Aveir Dual Chamber Leadless Pacemaker System is safe and effective for DDD(R) pacing, and the Aveir Atrial LP is safe and effective for AAI(R) pacing. Finally, the results from the upgrade cohort supported the upgradeability of the Aveir VR LP to an Aveir DR LP system for subjects indicated for DDD(R) pacing.

The totality of the evidence provided in this PMA demonstrates a reasonable assurance of the safety and effectiveness of the Aveir DR LP system and provides valid scientific evidence to conclude that the probable benefit to health from the use of the Aveir DR LP outweighs any probable risk or injury.

XIV. CDRH DECISION

CDRH issued an approval order on 6/29/2023. The final clinical conditions of approval cited in the approval order are described below.

The Aveir DR Real-World Evidence Study will be conducted as per protocol dated January 9, 2023, Version A. The purpose of this post-approval study (PAS) is to evaluate the long-term safety of the dual-chamber Aveir™ Leadless Pacemaker device (DR LP) using real-world evidence methods. A sample size of 1,805 patients is required to provide estimates of adverse events to a specific resolution with confidence intervals. All de novo patients who had an implant of the Aveir DR LP device, met inclusion/exclusion criteria, and has linked to Medicare FFS claims will be included in the analysis of this endpoint. Acute and long-term safety of the Aveir™ DR LP will be evaluated in terms of 30-day and 5-years post implant complication-free rates. The frequency of PAS reports is every 6 months for the first 2 years and yearly thereafter.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.