September 6, 2024
Medical Device Evaluation Division
Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Report on the Deliberation Results

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Implantable leadless cardiac pacemaker
Brand Name	Aveir LP
Applicant	Abbott Medical Japan LLC
Date of Application	October 12, 2023 (Application for partial change approval)

Results of Deliberation

In its meeting held on September 6, 2024, the Committee on Medical Devices and *In-vitro* Diagnostics reached the following conclusion, and decided that this conclusion should be presented to the Pharmaceutical Affairs Council.

The product is designated as a medical device subject to a use-results survey. The product is not classified as a biological product or a specified biological product.

The use-results survey period should be 5 years and 6 months. The product should be approved with the following conditions.

Approval Conditions

1. The applicant is required to work with the related academic society to set qualification criteria for medical institutions and healthcare professionals to ensure that the treatment with the Aveir LP and MRI scanning be provided at medical institutions with assured safety and by healthcare professionals with adequate product knowledge. To this end, necessary measures including training provision should be taken.
2. The applicant is required to give patients thorough education on the conditions for MRI scanning and establish a sufficient support system to assure safety.

Review Report

August 15, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following medical device submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Implantable leadless cardiac pacemaker
Brand Name	Aveir LP
Applicant	Abbott Medical Japan LLC
Date of Application	October 12, 2023 (Application for partial change approval of a medical device)
Reviewing Office	Office of Medical Devices I

Review Results

August 15, 2024

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Implantable leadless cardiac pacemaker
Brand Name	Aveir LP
Applicant	Abbott Medical Japan LLC
Date of Application	October 12, 2023 (Application for partial change approval of a medical device)

Results of Review

The Aveir LP is an implantable leadless cardiac pacemaker system that provides periodic electric stimuli to the heart to treat bradycardia. The Aveir LP consists of leadless pacemakers (LPs), delivery catheters, and accessories. The LP, a generator with a built-in electrode, is inserted into the femoral vein percutaneously using the delivery catheter and implanted in the right heart by the helix fixation mechanism at the LP tip.

The Aveir LP has already been approved as a ventricular LP (hereinafter referred to as Aveir Ventricular LP). The present application for partial change approval (the present partial change application) has been submitted for the atrial LP (hereinafter referred to as Aveir Atrial LP) added to the existing Aveir LP, aiming to broaden the system's indication to atrial pacing, or dual chamber pacing that physiologically allows atrioventricular synchrony (AV synchrony). During dual chamber pacing, the Aveir Atrial LP and the Aveir Ventricular LP synchronize with each other via beat-to-beat "i2i communication" to provide physiological heart beats.

The applicant submitted nonclinical data supporting the physicochemical properties, electric safety, electromagnetic compatibility, biological safety, durability, performance, and directions for use of the Aveir LP. There was no particular problem in the data submitted.

The applicant submitted clinical data of the Aveir LP from the Aveir DR i2i study, a global (including Japan), multicenter, prospective, single-arm study in patients for whom dual chamber pacing is indicated. The efficacy and safety hypotheses for the Aveir LP were evaluated in a pivotal cohort consisting of 300 patients overseas (overseas pivotal cohort). The possibility of extrapolation of the overseas data to Japan was assessed in a sub-cohort consisting of 24 Japanese patients (Japanese cohort).

"Composite success rate based on atrial pacing thresholds and P wave amplitudes at 3 months post-implantation," the primary efficacy endpoint 1, was 90.8% in the overseas pivotal cohort. The lower limit of the 95% confidence interval (87.5%) exceeded the predefined performance goal (82.5%) ($P <$

0.0001). The composite success rate was 91.7% in the Japanese cohort, showing consistency with the overseas pivotal cohort.

"The sitting/resting AV synchrony success rate at 3 months post-implantation," the primary efficacy endpoint 2, was 98.2% in the overseas pivotal cohort. The lower limit of the 95% confidence interval (96.6%) exceeded the predefined performance goal (83%) ($P < 0.0001$). The AV synchrony success rate was 95.7% in the Japanese cohort, which was consistent with the result in the overseas pivotal cohort.

"Freedom rate from serious adverse device effects (SADEs) at 3 months post-implantation," the primary safety endpoint, was 90.3% in the overseas pivotal cohort. The lower limit of the 95% confidence interval (87.0%) exceeded the predefined performance goal (78%) ($P < 0.0001$). The Japanese cohort showed a freedom rate of 79.2% that exceeded the predefined performance goal, which was considered consistent with that in the overseas pivotal cohort. However, an additional analysis was performed to identify a contributing factor to the lower rate in the Japanese cohort than in the overseas pivotal cohort. The propensity score matching analysis was performed with age as an adjusting factor, with attention to older population of the Japanese cohort compared to the overseas pivotal cohort. The analysis yielded a freedom rate of 85.4% in the overseas pivotal cohort, which was comparable with the result of the Japanese cohort. This suggests that the imbalanced age distributions contributed to the gap in the freedom rates between the 2 cohorts. The SADEs in the Japanese cohort were not specific to Japanese patients, and the safety profile of the Aveir LP in Japanese patients is considered acceptable. Nevertheless, the eligibility of patients for the Aveir LP must be carefully and comprehensively assessed, weighing the benefits of the leadless system against the risk of dislodgement, risks specific to the atrium (e.g., myocardial injury and atrial arrhythmia), the number of devices implantable, battery life, limited retrieval experience, the age, characteristics, and life-style of patients, etc. It is important that this advice be reflected in the related academic society's statement and followed, with the comments from the Expert Discussion taken into account.

The appropriateness of post-marketing safety measures including product training and the statement-based eligibility criteria for the Aveir LP should be verified through a use-results survey. The clinical outcomes of the Aveir LP in Japan should be assessed through the survey, and additional risk reduction measures should be taken as necessary.

As a result of its review, PMDA has concluded that the Aveir LP may be approved for the intended use shown below with the following approval conditions, and that the results should be presented to the Committee on Medical Devices and *In-vitro* Diagnostics for further deliberation. The underlines denote changes in the present partial change application.

Intended Use

The Aveir LP is an implantable cardiac pacemaker system with built-in electrodes to be placed in the right ventricle or/and the right atrium percutaneously using a catheter. The leadless pacemakers are MRI-conditional, thus MRI scanning is allowed only under specific conditions.

Approval Conditions

1. The applicant is required to work with the related academic society to set qualification criteria for medical institutions and healthcare professionals so as to ensure that the Aveir LP treatment and MRI scanning be performed at medical institutions with assured safety and by healthcare professionals with adequate product knowledge. To this end, appropriate measures including training provision should be taken.
2. The applicant is required to give patients thorough education on the conditions for MRI scanning and establish a sufficient support system to assure safety.

Review Report

August 15, 2024

Product for Review

Classification	Instrument & Apparatus 7, Organ Function Replacement Device
Term Name	Implantable leadless cardiac pacemaker
Brand Name	Aveir LP
Applicant	Abbott Medical Japan LLC
Date of Application	October 12, 2023 (Application for partial change approval of a medical device)
Proposed Intended Use	The Aveir LP is an implantable cardiac pacemaker system with built-in electrodes to be placed in the right ventricle or/and the right atrium percutaneously using a catheter. The leadless pacemakers are MRI-conditional, thus MRI scanning is allowed only under specific conditions.

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List of Abbreviations

ACC	American College of Cardiology
ACE	Angiotensin Converting Enzyme
ADE	Adverse Device Effect
AHA	American Heart Association
BMI	Body Mass Index
CRT	Cardiac Resynchronization Therapy
EC	Ethics Committee
EMC	Electro Magnetic Compatibility
EMI	Electro Magnetic Interference
EN	European Norm
ESC	European Society of Cardiology
HRS	Heart Rhythm Society
IEC	International Electrotechnical Commission
IRB	Institutional Review Board
ISO	International Organization for Standardization
LP	Leadless Pacemaker
MRI	Magnetic Resonance Imaging
PM	Pacemaker
RAO	Right Anterior Oblique position
RF	Radio Frequency
RRT	Recommended Replacement Time
SADE	Serious Adverse Device Effect

I. Product Overview

The Aveir LP is an implantable leadless cardiac pacemaker system that provides periodic electric stimuli to the heart to treat bradycardia. The Aveir LP consists of leadless pacemakers (LPs), delivery catheters, and accessories (Figure 1).

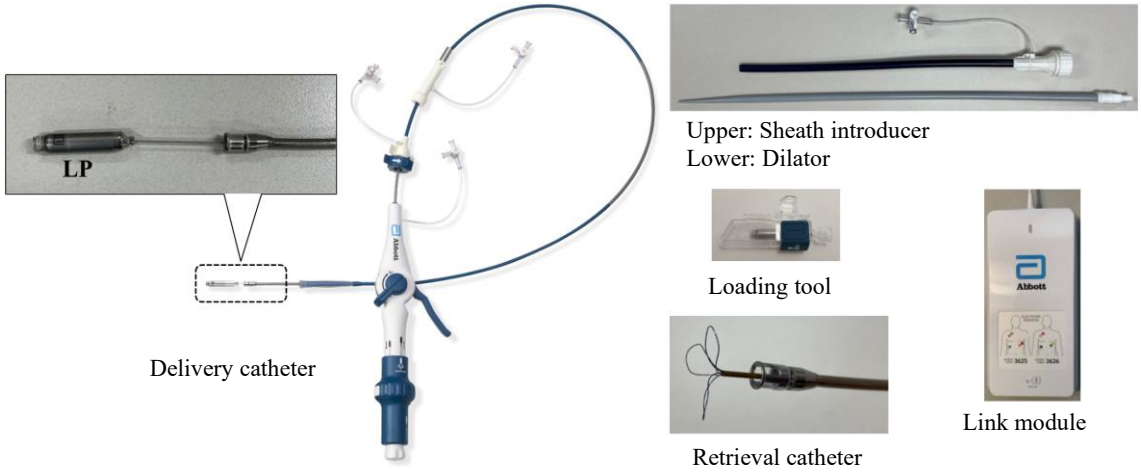


Figure 1. Appearance of the Aveir LP

The LP, a generator with a built-in electrode, is inserted into the femoral vein using the delivery catheter percutaneously and implanted in the right heart using the helix fixation mechanism at the LP tip. The electrode nested in the titanium capsule detects cardiac electrical activities and paces the heart. Once detecting bradycardia, the LP starts pacing therapy based on preset parameters. The blood temperature sensor built into the LP adjusts the pacing rate in response to patient's physical activities. Patients with the Aveir LP can undergo a magnetic resonance imaging (MRI) scanning under specific conditions.

The Aveir LP has already been approved as ventricular LP (hereinafter referred to as Ventricular LP) (Approval number: 30400BZX00287000). The present application for partial change approval (partial change application) was submitted to add an atrial LP (hereinafter referred to as Aveir Atrial LP) to the existing Aveir LP with the intention to expand its indication to atrial pacing (hereinafter atrial or ventricular pacing is referred to as single chamber pacing), or "dual chamber pacing," which physiologically allows atrioventricular synchrony (AV synchrony) (Figure 2). During dual chamber pacing, the Aveir Atrial LP and the Aveir Ventricular LP synchronize with each other via beat-to-beat "i2i communication" to provide physiological heart beats. The Aveir LP is designed to allow pacing mode change (upgrade) to the dual chamber mode employing i2i communication by adding either Atrial or Ventricular LP. This enables patients who have been on single chamber pacing with either Ventricular or Atrial LP but need dual chamber pacing due to disease progression, etc. to have dual chamber pacing.

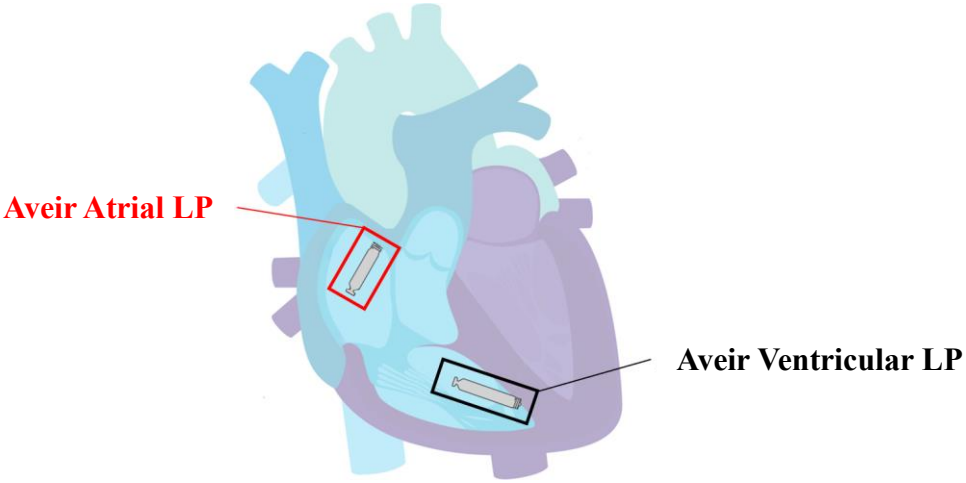
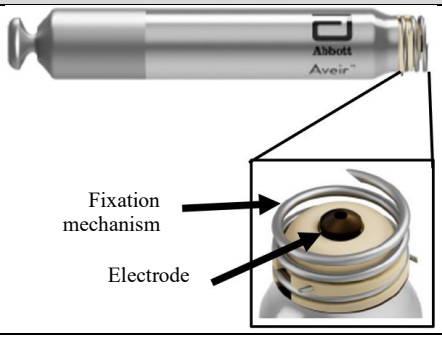
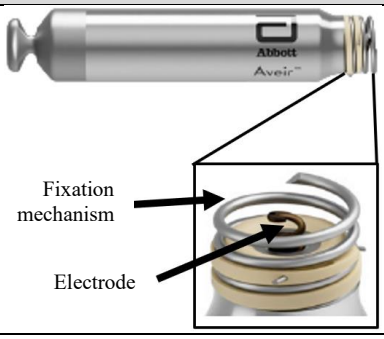


Figure 2. Image of the LPs implanted in the heart

The ventricle and the atrium differ in size and the ventricular and atrial walls have different anatomical characteristics. The Aveir Atrial LP, therefore, is shorter in electrode length than the Aveir Ventricular LP and has a different shape (Table 1).

Table 1. Main shape and structure of the Aveir Ventricular LP and the Aveir Atrial LP

		Aveir Ventricular LP	Aveir Atrial LP
Appearance			
Size	Outside diameter	6.5 mm	
	Length	38.0 mm	32.2 mm
	Weight	2.4 g	2.1 g
	Volume	1.1 mL	1.0 mL
Fixation mechanism		Helix	
Electrode		Chip	Helix
Expected battery life*		Single chamber mode: 9.9 years Dual chamber mode: 7.3 years	Single chamber mode: 6.8 years Dual chamber mode: 5.0 years

* Rate 60 min^{-1}, pulse width 0.4 ms, voltage 2.5 V, impedance 600 Ω, pacing rate 100%

The present partial change application also includes DR Delivery Catheter that has been modified from the approved delivery catheter (VR Delivery Catheter) to improve its manipulability (Table 2). The DR Delivery Catheter can be used with the Aveir Ventricular LP and the Aveir Atrial LP. The Aveir Ventricular LP comes in the following models: A model that is used with the DR Delivery Catheter (DR model) and the approved model that is used with the VR Delivery Catheter (VR model). Both models have the same configurable parameters.

Table 2. List of constituent parts (those added in the partial change application are shaded)

Constituent part		Outline
LP	Aveir Ventricular LP (VR model)	Used in combination with the VR Delivery Catheter.
	Aveir Ventricular LP (DR model)	Used in combination with the DR Delivery Catheter.
	Aveir Atrial LP (DR model)	Used in combination with the DR Delivery Catheter.
Delivery catheter	VR Delivery Catheter	Deploys the Aveir Ventricular LP (VR model) to the implantation site.
	DR Delivery Catheter	Deploys the Aveir Ventricular LP (DR model) or Aveir Atrial LP (DR model) to the implantation site.
Accessories	Retrieval catheter	Used to retrieve the LP percutaneously.
	Introducer kit	Consists of a sheath introducer and a dilator. It is used to secure the vascular insertion sites of the delivery catheter and retrieval catheter.
	Link module	An external communication device that is attached to a special programmer (not included in the Aveir LP) and used to communicate with the LP. It can also acquire a patient's electrocardiographic waveform.
	Loading tool	Used to connect the LP to the delivery catheter.

II. Summary of the Data Submitted and Outline of the Review Conducted by the Pharmaceuticals and Medical Devices Agency

The data submitted by the applicant with the present application and the applicant's responses to the inquiries from the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined below.

The expert advisors present during the Expert Discussion on the Aveir LP declared that they did not fall under the Item 5 in Chapter 3 of the Rules for Convening Expert Discussions, etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1. History of Development, Use in Foreign Countries, and Other Information

1.A Summary of the data submitted

1.A.(1) History of development

Conventional implantable cardiac pacemakers are designed so that the lead is implanted in the right side of the heart via the subclavian vein, with the generator that is to be connected to the lead implanted in the subcutaneous pocket in the chest (hereinafter a conventional implantable cardiac pacemaker is referred to as transvenous pacemaker [PM]). Those transvenous PMs are associated with lead-related complications (e.g., lead break) and subcutaneous pocket-related complications (e.g., infection). Lead deployment may be difficult in some cases due to anatomical obstacles. Lead implantation via the subclavian vein is difficult or inadvisable in some patients including those who need to reserve the subclavian vein for dialysis, and the implantation of generator in a subcutaneous pocket is inadvisable in patients with a history of infection, etc.[1]

The LP was developed to solve the above-mentioned issues with the transvenous PMs. The LP is designed so that the electrode and generator can be implanted all together in the heart without a transvenous lead. In Japan, a ventricular LP for single chamber pacing "Micra Transcatheter Pacing System" (Approval number: 22900BZX00047000, hereinafter referred to as Micra) was approved in February 2017. Single chamber pacing is a non-physiological pacing modality that is independent from spontaneous atrial beats. Since most patients eligible for pacemaker therapy require dual chamber pacing, dual-chamber transvenous PMs are commonly used in clinical practice.[2] Patients who require dual chamber pacing and are ineligible for a transvenous PM for any of the reasons mentioned above, etc. had no choice but choose dual chamber pacing with a transvenous PM or single chamber pacing with a

ventricular LP. A new model of Micra, approved in July 2021, is the ventricular LP that detects spontaneous atrial beats by itself, allowing synchronization with its ventricular pacing. This model, however, has no atrial pacing function.

With the above background, the present partial change application was submitted to add the Aveir Atrial LP as a constituent part of the Aveir LP to allow dual chamber pacing.

1.A.(2) Use in and outside Japan

Table 3 presents the information regarding the use of the Aveir LP as of the end of March 2024 in major foreign countries and Japan.

Table 3. Use of the Aveir LP in major foreign countries and Japan

Country/ region	LP	Approved/ certified in	Intended use	Sales quantity
US	VR model	March 2022	Same in Japan	Aveir Ventricular LP: [redacted]
	DR model	June 2023		Aveir Ventricular LP: [redacted], Aveir Atrial LP: [redacted]
Europe*	VR model	July 2023	Same in Japan	Aveir Ventricular LP: [redacted]
Japan	VR model	December 2022	-	Aveir Ventricular LP: [redacted]
Others	-	-	-	Aveir Ventricular LP: [redacted]
Total	-	-	-	Aveir Ventricular LP: [redacted], Aveir Atrial LP: [redacted]

* The DR model was certified in Europe in June 2024 (not sold yet as of the end of June 2024).

1.A.(3) Malfunctions and adverse events in and outside Japan

Table 4 and Table 5 present malfunctions and adverse events, respectively, of the VR model reported in and outside Japan as of the end of March 2024. Neither malfunction nor adverse event of the DR model has been reported as of the present application.

Table 4. Malfunctions of the VR model reported in and outside Japan

Malfunction	Japan		Foreign countries	
	Number of malfunctions	Incidence	Number of malfunctions	Incidence
Helix distortion	[redacted]	1.41%	[redacted]	0.68%
Material distortion		0.81%		0.03%
Positioning difficulty or delay		0.81%		0.17%
Unintended release		0.59%		0.40%
Increased threshold		0.44%		1.03%
Release failure		0.37%		0.23%
Pacing failure		0.30%		0.04%
Device dislocation or dislodgement		0.30%		0.55%
Rotation failure of the main body		0.22%		0.02%
Docking difficulty		0.22%		0.11%
Unstable telemetry		0.15%		0.16%
Abnormal resistance		0.07%		0.39%
Insertion difficulty		0.07%		0.01%
Sensing problem		0%		0.23%
Breakage		0%		0.15%
Display error/artifact		0%		0.09%
Inappropriate or unexpected reset		0%		0.04%
Premature battery depletion		0%		0.01%
Use of wrong control/therapy settings		0%		0.01%

Table 5. Adverse events of the VR model reported in and outside Japan

Event	Japan		Foreign countries	
	Number of events	Incidence	Number of events	Incidence
Re-surgery	[redacted]	0.81%	[redacted]	0.77%
Cardiac perforation		0.59%		0.53%
Pericardial effusion		0.52%		0.27%
Haemorrhage		0.37%		0.00%
Modification of surgical procedure (procedure cancelled)		0.30%		0.04%
Arrhythmia		0.30%		0.29%
Surgical procedure delay		0.22%		1.17%
Cardiac tamponade		0.22%		0.09%
Pain		0.22%		0.03%
Infection		0.15%		0.02%
Syncope, loss of consciousness		0.07%		0.03%
Hospitalization or prolonged hospitalization		0.07%		0.00%
Ventricular fibrillation		0.07%		0.04%
Cardiac arrest		0.07%		0.07%
Embolism		0.07%		0.20%
Tricuspid valve insufficiency/regurgitation		0.07%		0.04%
Susceptibility to contusion (facial contusion)		0.07%		0.00%
Hypotension, hypertension		0%		0.28%
Dizziness		0%		0.05%
Myocardial infarction		0%		0.03%
Cardiac failure/cardiac failure congestive		0%		0.03%
Asystole		0%		0.03%
Pneumothorax		0%		0.02%
Discomfort		0%		0.02%
Sepsis		0%		0.02%
Unwanted nerve stimulation		0%		0.01%
Pleural effusion		0%		0.01%
Tissue injury		0%		0.01%
Fall		0%		0.01%

2. Design and Development

2.(1) Performance and safety specifications

2.(1).A Summary of the data submitted

In association with the present partial change application, parameters for atrial pacing and dual chamber pacing were added to the specifications for the LP.

2.(1).B Outline of the review conducted by PMDA

PMDA reviewed the proposed performance and safety specifications of the Aveir LP, and concluded that there was no particular problem.

2.(2) Physicochemical properties

2.(2).A Summary of the data submitted

To support the physicochemical properties of the DR Delivery Catheter, the applicant submitted the results of corrosion resistance tests. The test results met the prespecified acceptance criteria, showing that there was no problem in the physicochemical properties of the Aveir LP. The Aveir Atrial LP and the Aveir Ventricular LP (DR model) were not tested because their materials are the same as those of the approved Aveir Ventricular LP (VR model).

2.(2).B Outline of the review conducted by PMDA

PMDA reviewed the data on the physiochemical properties and concluded that there was no particular problem.

2.(3) Biological safety

2.(3).A Summary of the data submitted

To support the biological safety of the Aveir LP, the applicant submitted the results of biological safety studies conducted in accordance with the International Organization for Standardization (ISO) 10993-1.

The Aveir Atrial LP was tested for cytotoxicity, sensitization potential, intradermal reaction, acute systemic toxicity, pyrogenicity, and genotoxicity. These tests showed no remarkable findings. The Aveir Atrial LP was also tested for embedding, sub-acute systemic toxicity, sub-chronic systemic toxicity, and chronic systemic toxicity in animal studies described later in Section 2.(8).A.3). The Aveir Ventricular LP (DR model) was not tested for biological safety because its housing is the same for the VR model and the DR model.

The DR Delivery Catheter was tested for cytotoxicity, sensitization potential, intradermal reaction, acute systemic toxicity, pyrogenicity, and blood compatibility. These tests showed no remarkable findings.

2.(3).B Outline of the review conducted by PMDA

PMDA reviewed the data on the biological safety and concluded that there was no particular problem.

2.(4) Electrical safety and electromagnetic compatibility

2.(4).A Summary of the data submitted

To support the electrical safety and electromagnetic compatibility of the Aveir Atrial LP, the applicant submitted the results of the following tests conducted in accordance with ISO 14708-2:2019 or European Norm (EN) 45502-2-1:2003: Leakage currents, protection from harm to the patient caused by heat, issues regarding surgical diathermy (electrical scalpel), defibrillation, protection from changes caused by miscellaneous medical treatments, protection from mechanical forces (vibrations and shocks), protection from damage caused by atmospheric pressure changes, protection from damage caused by temperature changes, conducted electromagnetic interference (EMI)/electromagnetic compatibility (EMC), and radiated EMI/EMC. The test results met the specifications, assuring the electrical safety and electromagnetic compatibility of the Aveir Atrial LP.

2.(4).B Outline of the review conducted by PMDA

PMDA reviewed the data on the electrical safety and electromagnetic compatibility and concluded that there was no particular problem.

2.(5) Conformity to IEC 62304

2.(5).A Summary of the data submitted

The applicant submitted the data showing that Aveir LP meets the international standards that define the software life-cycle process of medical device software (International Electrotechnical Commission [IEC] 62304:2006+Amd. 1:2015).

2.(5).B Outline of the review conducted by PMDA

PMDA reviewed the data on the conformity to IEC 62304 and concluded that there was no particular problem.

2.(6) Stability and durability

2.(6).A Summary of the data submitted

The applicant omitted the submission of the stability data of the Aveir LP and instead submitted a self-declaration stating that the shelf-life of the Aveir LP was determined based on the results of necessary stability evaluation in accordance with the "Handling of stability studies related to the determination of the shelf life in the application for marketing approval (certifications) of medical devices (in Japanese)" (PFSB/ELD/OMDE Notification No. 1227-5, dated December 27, 2012).

To support the durability of the Aveir LP, the applicant submitted the results of durability tests of the helix electrode of the Aveir Atrial LP ([redacted]). The durability of its fixation mechanism was not tested because it has the same structure as that of the Aveir Ventricular LP.

2.(6).B Outline of the review conducted by PMDA

PMDA reviewed the data on the stability and durability and concluded that there was no particular problem.

2.(7) Directions for use

2.(7).A Summary of the data submitted

To support the directions for use of the Aveir LP, the applicant submitted the results of the following MRI compatibility tests in accordance with ISO/TS 10974: Radio frequency (RF)-induced heat, RF rectified electric current, pulse inhibition by RF-conducted magnetic field, RF magnetic field-induced damage, gradient magnetic field-induced rectification, gradient magnetic field-induced function, mixed magnetic field-induced function, and safety of implantation of multiple LPs within the same cardiac chamber. Gradient magnetic field-induced heat, vibration, magnetostatic field-induced displacement force, magnetostatic field-induced rotation force, and image artifacts were not tested with the Aveir LP because the Aveir Atrial LP has a smaller surface area, weight, and magnetic substance volume than those of the approved Aveir Ventricular LP.

2.(7).B Outline of the review conducted by PMDA

PMDA reviewed the data on the directions for use concluded that there was no particular problem.

2.(8) Performance

2.(8).A Summary of the data submitted

To support the performance of the Aveir LP, the applicant submitted the results of tests in accordance with ISO 14708-2:2019 and EN 45502-2-1:2003 (pulse width, pulse interval, escape interval, sensing refractory period, pacing refractory period, pulse rate, pulse amplitude, sensing threshold, and input impedance), tests on bi-directional i2i communication, operation checks with the programmer, and

verification tests of configurable parameters. The test results met the prespecified acceptance criteria, assuring the performance of the Aveir LP.

To support the performance of the DR Delivery Catheter, the applicant submitted the results of tests on tip-butting load, docking holding force, and loading of the LP on the delivery catheter. The test results met the prespecified acceptance criteria, assuring the performance of the Aveir LP. No other tests were conducted with the delivery catheter of the Aveir LP because the DR Delivery Catheter is the same as the approved VR Delivery Catheter in terms of its structure other than the tether.

To support the performance and safety of the implantation and retrieval procedures of the LPs, the applicant submitted the results of tests on implantation of the Aveir Atrial LP, implantation of both the Aveir Atrial LP and the Aveir Ventricular LP, retrieval of the Aveir Atrial LP, and side-by-side implantation. The major test results are provided on the following sections.

2.(8).A.1) Implantation of the Aveir Atrial LP

The Aveir Atrial LP was implanted in 9 sheep to investigate its manipulability, electrical performance, dislodgement, communication with the programmer, pathology, cardiac perforation, pulmonary embolism, and damage to the Aveir Atrial LP at implantation and 91 days post-implantation.

Manipulation during implantation was acceptable for all test samples as assessed by the operator. Basic electrical performance as a LP, including pacing, and communication with the programmer were verified. There were no dislodgements, tissue injuries (myocardium, tricuspid valve, and tendinous cord), significant blood loss or fatal cardiovascular perforation, pulmonary thromboembolism, or damage to the Aveir Atrial LP that might affect its function (e.g., erosion) during the test period or necropsy.

2.(8).A.2) Implantation of both the Aveir Atrial LP and the Aveir Ventricular LP

Both the Aveir Atrial LP and the Aveir Ventricular LP were implanted in 9 sheep to investigate its manipulability, electrical performance, dislodgement, communication with the programmer, pathology, cardiac perforation, pulmonary embolism, damage to the LPs, and i2i communication at implantation and 91 days post-implantation.

Manipulation during implantation was acceptable for all test samples as assessed by the operators. Basic electrical performance as a LP, including pacing, and communication with the programmer were verified. There were no dislodgements, tissue injuries (myocardium, tricuspid valve, and tendinous cord), significant blood loss or fatal cardiac perforation, pulmonary thromboembolism, or damage to the LPs that might affect its function (e.g., erosion) during the test period or necropsy. The i2i setting level, which is a parameter that adjust signal strength on a 7-point scale (higher levels create stronger signals but consume more battery), was maintained low throughout the test while i2i throughput (i2i communication success rate) was maintained (Table 6).

Table 6. Time course of i2i setting levels and i2i throughputs*

	Aveir Atrial LP → Aveir Ventricular LP		Aveir Ventricular LP → Aveir Atrial LP	
	i2i setting level (1-7)	**i2i throughput (%)**	**i2i setting level (1-7)**	**i2i throughput (%)**
At implantation	5.4 ± 1.3 (4.0, 5.0, 7.0)	97.0 ± 5.3 (85, 100, 100)	4.9 ± 1.5 (2.0, 5.0, 7.0)	100 ± 0 (100, 100, 100)
3 days post-implantation	5.4 ± 1.3 (4.0, 5.0, 7.0)	85.9 ± 17.5 (57.0, 91.0, 100)	4.9 ± 1.5 (2.0, 5.0, 7.0)	91.6 ± 8.7 (72.0, 96.0, 100)
14 days post-implantation	2.6 ± 0.7 (2.0, 2.0, 4.0)	92.8 ± 12.1 (62.0, 97.0, 99.0)	4.4 ± 1.5 (2.0, 4.0, 7.0)	93.8 ± 10.8 (67.0, 98.0, 99.0)
30 days post-implantation	2.8 ± 1.1 (1.0, 3.0, 5.0)	98.2 ± 1.4 (95.0, 99.0, 99.0)	3.7 ± 1.0 (2.0, 4.0, 5.0)	99.0 ± 0 (99, 99, 99)
42 days post-implantation	2.8 ± 1.3 (1.0, 3.0, 4.0)	97.8 ± 1.7 (94.0, 99.0, 99.0)	3.0 ± 1.1 (2.0, 3.0, 5.0)	98.3 ± 1.3 (95.0, 99.0, 99.0)
91 days post-implantation	3.0 ± 0.9 (2.0, 3.0, 4.0)	98.9 ± 0.3 (98.0, 99.0, 99.0)	4.0 ± 0.9 (3.0, 4.0, 5.0)	98.3 ± 1.7 (94.0, 99.0, 99.0)
91 days post-implantation (at anesthesia)	2.9 ± 1.1 (1.0, 3.0, 4.0)	93.8 ± 12.7 (61.0, 99.0, 100)	3.8 ± 1.3 (1.0, 4.0, 5.0)	95.1 ± 12.4 (62.0, 99.0, 100)

* The figures in the table represent means ± standard deviations (SDs) (minimum, median, and maximum).

2.(8).A.3) Retrieval of the Aveir Atrial LP

The Aveir Atrial LP was implanted in 7 sheep to investigate the retrieval of the Aveir Atrial LP using the retrieval catheter of the Aveir LP at 91 days post-implantation.

The Aveir Atrial LP was successfully retrieved in all animals. Manipulation during retrieval was acceptable as assessed by the operators. It took 2 to 28 minutes for the operator to insert and retrieve the retrieval catheter. Necropsy showed no clear pericardial effusions-related myocardial injury. Gross observation revealed no tissue injuries (myocardium, tricuspid valve, and tendinous cord) or pulmonary thromboembolism.

The Aveir Atrial LP was implanted in 10 sheep to investigate the retrieval of the Atrial LP using the retrieval catheter of the Aveir LP at 182 days post-implantation in 9 animals that received successful implantation. The remaining 1 animal was excluded from the study because the dislodgement of the Aveir Atrial LP occurred during the implantation procedure, resulting in pulmonary embolism.

Of the 9 animals with successful implantation, 1 animal required the use of another retrieval catheter because the snare of the first retrieval catheter could not be opened and closed during the procedure. The Aveir Atrial LP was successfully retrieved in all animals. Manipulation during retrieval was acceptable as assessed by the operators. It took 1 to 8 minutes for the operator to insert and retrieve the retrieval catheter. Clinical observation and haematology performed to assess the health conditions of sheep throughout 182 days showed no clinically significant findings. Histopathological examination showed no LP-related pulmonary thromboembolism. Pathology of organs (heart, lungs, lymph nodes, liver, kidneys, spleen, femoral vein, and inferior vena cava) revealed no retrieval procedure- or device-related clinically significant event.

Causal analyses of the above malfunctions that occurred in this study are described below.

- The cause for the 1 case of the dislodgement of the Aveir Atrial LP during the implantation procedure was the introducer size not matching the diameter of the femoral vein of the sheep. The introducer damaged the femoral vein. Tissue fragments of the femoral vein attached to the fixation mechanism

of the Aveir Atrial LP and prevented the Aveir Atrial LP from being fully fixed on the right atrial appendage.

- An analysis of the retrieval catheter that caused 1 malfunction (failure to open and close the snare) showed no manufacturing failure. The most likely cause for the malfunction was a snare breakage resulting from repeated opening and closing of the device, approximately 90 times. Peri-operative images showed an angle between the implanted Aveir Atrial LP and the retrieval catheter that cannot happen in humans. In addition, the snare is not expected to be opened and closed 90 times in clinical practice. For these reasons, this malfunction does not raise any clinical efficacy or safety concerns of the Aveir LP.

2.(8).A.4) Side-by-site implantation

One each of the Aveir Atrial LP and the Aveir Ventricular LP were implanted in 5 sheep, followed by implantation of another 1 each of the Aveir Atrial LP and the Aveir Ventricular LP 36 days later. The animals were followed up until 42 days after the implantation of the second LPs to investigate the performance and safety of the implantation of the 2 LPs within a cardiac chamber (atrium or ventricle).

With 2 LPs implanted in a cardiac chamber, the programmer successfully communicated with each LP, stopped the first LP, switched the first LP to the second LP, and activated the second LP in the presence of the first LP that had been stopped. Pathology showed no remarkable findings in any animal.

2.(8).B Outline of the review conducted by PMDA

PMDA's view:

The applicant's causal analyses of the malfunctions observed in the retrieval test of the Aveir Atrial LP were reasonable. No similar event occurred in the clinical study described later. These malfunctions were acceptable. The aforementioned nonclinical studies confirmed the basic efficacy and safety of the Aveir LP during atrial pacing and dual chamber pacing using the Aveir LP. Nevertheless, the Aveir Atrial LP has never been used in clinical practice. Thus, a comprehensive assessment of the data, including the clinical results later described, is necessary for atrium-specific risks and the tendency for i2i communication to improve over time, which were reported from the above-mentioned animal study.

3. Conformity to the Requirements Specified in Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices

3.A Summary of the data submitted

The applicant submitted a declaration of conformity declaring that the Aveir LP meets the standards for medical devices as stipulated by the Minister of Health, Labour and Welfare in accordance with Paragraph 3 of Article 41 of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (hereinafter referred to as "the Essential Principles") (MHLW Public Notice No. 122, 2005).

3.B Outline of the review conducted by PMDA

PMDA reviewed the conformity of the Aveir LP to the Essential Principles.

(1) PMDA's view on the conformity of the Aveir LP to Article 1, which stipulates preconditions, etc. for designing medical devices (particularly requirements for users, such as the expected level of technical knowledge and experience, and the expected level of education and training for users):
As described later in Section "6.B Outline of the review conducted by PMDA," user training, patient selection in accordance with the statement jointly created with the related academic society, and compliance with the requirements for medical institutions and surgeons are important to maintain a risk-benefit balance of the Aveir LP. To this end, the approval conditions will be attached to ensure that necessary measures are taken.

(2) PMDA's view on the conformity of the Aveir LP to Article 2, which stipulates requirements for risk management throughout the product life cycle of medical devices:
As described later in Sections "6.B Outline of the review conducted by PMDA" and "7.B Outline of the review conducted by PMDA," the efficacy and safety of the Aveir LP should be evaluated in clinical practice in Japan because the clinical efficacy and safety data of the Aveir LP are limited. Additional risk reduction measures should be taken as necessary. PMDA instructed the applicant to conduct a use-results survey.

(3) PMDA's view on the conformity of the Aveir LP to Article 3, which stipulates requirements for the performance and functions of medical devices, and to Article 6, which stipulates the efficacy of medical devices:
As described later in Section "6.B Outline of the review conducted by PMDA," the clinical study submitted demonstrated the efficacy and safety of the Aveir LP in eligible patients selected based on the characteristics of the Aveir LP. The Aveir LP conforms to Articles 3 and 6.

(4) PMDA's view on the conformity of the Aveir LP to Article 17, which stipulates requirements for publicizing information including precautionary advice or the communication of information to users via instructions for use, etc. (the Information on Precautions etc.):
As described later in Section "6.B Outline of the review conducted by PMDA," physicians with expert knowledge about arrhythmia treatment must select eligible patients for the Aveir LP therapy and users must use the Aveir LP after fully understanding its characteristics to maintain its risk-benefit balance. To this end, information should be provided through the Information on Precautions, etc., statement by the academic society, training, and other measures.

PMDA comprehensively reviewed the conformity of the Aveir LP to the Essential Principles and concluded that there was no particular problem.

4. Risk Management

4.A Summary of the data submitted

The applicant submitted a summary of risk management, the risk management system, and its progress in accordance with ISO 14971:2019 "Medical devices – Application of risk management to medical devices."

4.B Outline of the review conducted by PMDA

PMDA comprehensively reviewed the document on risk management taking into account the discussion presented earlier in Section "3.B Outline of the review conducted by PMDA" and concluded that there was no particular problem.

5. Manufacturing Process

5.A Summary of the data submitted

The applicant submitted data on the sterilization method for the Aveir LP (sterilization validation) and the results of bacterial endotoxin tests of the DR Delivery Catheter. The model added in the partial change application was not tested for residual ethylene oxide gas concentration because this new model has the same sterilization parameters, and comparable shape/structure, raw materials, and surface area as those of the approved model. The Aveir Atrial LP was not tested for bacterial endotoxins because it has the comparable materials as those of the approved Aveir Ventricular LP.

5.B Outline of the review conducted by PMDA

PMDA reviewed the data on the manufacturing process and concluded that there was no particular problem.

6. Clinical Data or Alternative Data Accepted by the Minister of Health, Labour and Welfare

The applicant submitted clinical data of the Aveir LP from the results of the Aveir DR i2i study, which was a global clinical study (the i2i study). The applicant also submitted the reference data from the long-term results (up to 12 months post-implantation) of the i2i study.

6.A Summary of the data submitted

The i2i study was a global, multicenter, prospective, single-arm study to evaluate the efficacy and safety of dual chamber pacing with the Aveir LP in patients eligible for pacemaker therapy with a DDD mode, which synchronizes the atrium and ventricle to pace both the atria and ventricles, at 38 study sites in the US, 12 study sites in Europe, 5 study sites in Canada, and 4 study sites in Japan.

The original plan for this global i2i study included Japan. Their participation was, however, delayed because of the situation of the COVID-19 pandemic in Japan during the enrollment period. The primary analysis was performed in a cohort consisting of overseas sites only (hereinafter referred to as overseas pivotal cohort). The Japanese sites participated in a cohort that was separately created to assess the possibility of extrapolation of the overseas data to Japan (hereinafter referred to as Japanese cohort). Accordingly, in the present partial change application, the applicant submitted evaluation data from the study results at 3 months post-implantation (primary evaluation) and 6 months post-implantation in the overseas pivotal cohort, and the study results at 3 months post-implantation (primary evaluation) in the Japanese cohort. The applicant also submitted reference data from study results up to 12 months post-implantation in each cohort.

Outside Japan, a separate cohort was created to exclusively assess the possibility of upgrading to the dual chamber mode with the Aveir Atrial LP in patients who had already been with the Aveir Ventricular

LP (VR model) (hereinafter referred to as overseas upgrade cohort). The inclusion and exclusion criteria for the overseas upgrade cohort were the same as those for the overseas pivotal cohort and the Japanese cohort.

Since the overseas pivotal cohort planned to use the Aveir Atrial LP for the first time in humans, an adaptive design, which allows for a change in the original plan based on the results of an interim analysis, was used for this study. An interim analysis for sample size determination was planned.

Table 7 presents an outline of the overseas pivotal cohort and Japanese cohort in the i2i study.

Table 7. Outline of the overseas pivotal cohort and the Japanese cohort

	Overseas pivotal cohort	Japanese cohort
Study objective	To evaluate the efficacy and safety of dual chamber pacing with the Aveir LP in patients eligible for DDD mode	
Study population	Patients eligible for DDD mode	
Study design	Prospective, single-arm, multicenter, global study	
Sample size	300	24
Enrollment period	February 2022 to August 2022	November 2022 to March 2023
Primary endpoints	Primary efficacy endpoint 1 Composite success rate based on atrial pacing thresholds and P wave amplitudes at 3 months post-implantation Definition of success The following 2 criteria must be met: • Pacing threshold voltage: ≤3.0 V at a pulse width of 0.4 ms • P-wave amplitude: ≥1.0 mV Primary efficacy endpoint 2 Sitting/resting AV synchrony success rate at 3 months post-implantation Definition of success AV interval* of ≤300 ms in ≥70% of the cardiac cycles within collected Holter electrocardiography data as evaluated by the Core Lab Primary safety endpoint Freedom rate from serious adverse device effects (SADEs) at 3 months post-implantation	
Inclusion criteria	1. Subject who must have at least one of the clinical indications for device implant in adherence with ACC/AHA/HRS/ESC dual chamber pacing guidelines. 2. Subject aged ≥18 years or age of legal consent, whichever age is greater 3. Subject with a life expectancy of at least 1 year 4. Subject who is willing to comply with study procedures and agrees to return to clinic for all required follow-up visits, tests, and examinations. 5. Subject who has been informed of the nature of the study, agrees to its provisions, and has provided a signed written informed consent, approved by the IRB/EC.	
Exclusion criteria	1. Subject who is currently participating in another clinical study that may confound the results of this study as determined by the sponsor. 2. Subject who is pregnant or nursing and those who plan pregnancy during the follow-up period of the study. 3. Subject who 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 study device and/or implant procedure, limit the subject's ability to participate in the study or to comply with follow-up requirements of the study 4. Subject who has a known allergy or hypersensitivity to <1 mg of dexamethasone sodium phosphate or any blood or tissue contacting material listed in the operating instructions 5. Subject with an implanted vena cava filter or mechanical tricuspid valve prosthesis. 6. Subject with pre-existing, permanent endocardial pacing or defibrillation leads (does not include lead fragments) 7. Subject who has current implantation of either conventional or subcutaneous implantable cardioverter defibrillator or cardiac resynchronization therapy (CRT) device 8. Subject with current implantation of leadless cardiac pacemaker (except for an Aveir Ventricular LP) 9. Subject who has current implantation of an electrically-active implantable medical device with stimulation capabilities (such as neurological or cardiac stimulators), excluding medical devices with no known impact to the Aveir LP 10. Subject who is unable to read or write.	
Follow-up period	Baseline, at implantation, before discharge, 1, 3, 6, and 12 months post-implantation	

* AV interval: An interval from paced or sensed atrial beat to a paced or sensed ventricular beat

The following 3 primary endpoints were selected for the i2i study: Pacing and sensing performance of the Aveir Atrial LP (primary efficacy endpoint 1), synchrony performance of the Aveir Atrial LP and the Aveir Ventricular LP (primary efficacy endpoint 2), and complications associated with implantation of both LPs (primary safety endpoint). Table 8 presents the performance goal of each endpoint and its rationale.

Table 8. Definitions and performance goals of the primary endpoints

Primary efficacy endpoints		Definition of success and its rationale	Performance goal and its rationale
1	Composite success rate based on atrial pacing thresholds and P wave amplitudes at 3 months post-implantation	**Definition of success:** The following 2 criteria must be met: • Pacing threshold voltage: ≤3.0 V at a pulse width of 0.4 ms • P-wave amplitude: ≥1.0 mV **Rationale** Safety margins of 2 and 4 times the configurable ranges for pacing threshold and P wave amplitude, respectively	**Performance goal:** 82.5% **Rationale:** The performance goals (85% at 6 months post-implantation, [3] 80% at 12 months post-implantation[4]) in the clinical study of the Aveir Ventricular LP, and the performance goal (80% at 6 months post-implantation) in the clinical study of Micra[5]
2	Sitting/resting AV synchrony success rate at 3 months post-implantation	**Definition of success:** AV interval of ≤300 ms in ≥70% of the cardiac cycles within collected Holter electrocardiography data as evaluated by the Core Lab **Rationale:** The definition of AV synchrony success in the clinical study of Micra VDD mode* (MARVEL 2 study[6])	**Performance goal:** 83% **Rationale:** The lower limit (82%) of the 95% confidence interval of the study outcome (95%) in the MARVEL 2 study[6]
Primary safety endpoint		**Performance goal and its rationale**	
Freedom rate from serious adverse device effects (SADEs) at 3 months post-implantation		**Performance goal:** 78% **Rationale:** The incidence of complications of the dual chamber transvenous PM was estimated to be 14.7% from the results of prospective, multicenter clinical research in 1,517 patients implanted with transvenous PMs (approximately 30% for single chamber, approximately 70% for dual chamber) (FOLLOWPACE study[7]). The performance goal of 78% was determined based on the sum of this estimated incidence and a margin of 1.5 times the incidence (22.05%).	

* VDD mode: A mode that detects spontaneous atrial beats and synchronizes ventricular pacing with them

Upgrade failure in the overseas upgrade cohort was defined as the "failure to complete the upgrade procedure in patients implanted with the Aveir Ventricular LP because of difficulty in implanting the Aveir Atrial LP or failure to switch to the dual chamber mode."

6.A.(1) Disposition of enrolled subjects

Figure 3 presents the disposition of enrolled subjects in the overseas pivotal cohort.

Of 300 subjects who underwent LP implantation in the overseas pivotal cohort, 2 subjects received only the Aveir Ventricular LP alone because of an implantation failure of the Aveir Atrial LP (implantation difficulty due to pericardial effusion for both cases). The remaining 298 subjects had successful implantation of the Aveir Atrial LP and the Aveir Ventricular LP. Four subjects did not return for the 3-month follow-up visit for evaluation of the primary endpoints because of death in 3 subjects (not causally related to the Aveir LP) and LP retrieval for therapy change to cardiac resynchronization therapy (CRT) in 1 subject. Table 9 presents the analysis populations for the primary endpoints pre-specified in the statistical analysis plan.

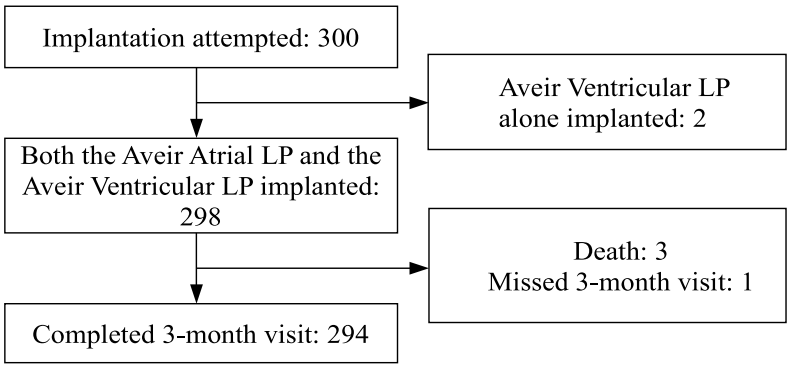


Figure 3. Disposition of enrolled subjects in the overseas pivotal cohort

Table 9. Analysis populations for the primary endpoints in the overseas pivotal cohort

Primary endpoints	Analysis population
Primary efficacy endpoint 1	A total of 7 subjects, including those who died, failed to return for the 3-month follow-up visit, and had missing data, were included in the analysis population by multiple imputation. A total of 297 subjects were included in the analysis population for primary efficacy endpoint 1, and the remaining 3 subjects who received the Aveir Ventricular LP alone (not because of the pacing and sensing failure of the Aveir Atrial LP) and had no measurable data because of atrial tachycardia were excluded.
Primary efficacy endpoint 2	A total of 277 subjects were included in the analysis population for primary efficacy endpoint 2, and the remaining 23 subjects who received the Aveir Ventricular LP alone (not because of AV synchrony failure) and deviations from the programming protocol (e.g., a preset AV interval of >250 ms) were excluded.
Primary safety endpoint	All 300 subjects in whom implantation was attempted were included in the primary safety endpoint.

The Japanese cohort (24 subjects) had neither failed LP implantation nor lost to follow-up. The analysis populations for the primary endpoints in the Japanese cohort were also pre-specified in the statistical analysis plan. All subjects were included in the analyses of the primary efficacy endpoint 1 and the primary safety endpoint. One subject who had missing data was excluded from the analysis population for primary efficacy endpoint 2.

Figure 4 presents the disposition of enrolled subjects in the overseas upgrade cohort.

In the overseas upgrade cohort (26 subjects), 1 subject was excluded from the analysis of the upgrade success rate because the existing Aveir Ventricular LP (VR model) had been implanted inappropriately (the proximal end of the Aveir Ventricular LP protruding from the tricuspid valve) and was exchanged for a new one. Also, 2 subjects had a failed implantation of the Aveir Atrial LP (fixation failure of the Aveir Atrial LP in 1 subject and cardiac tamponade in 1 subject).

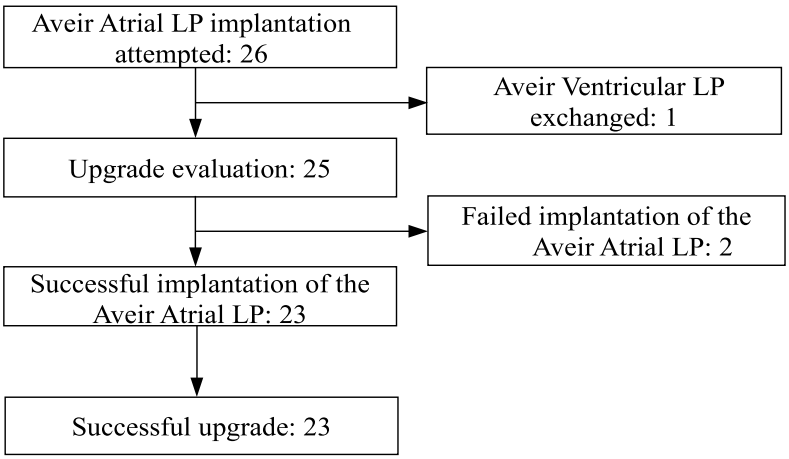


Figure 4. Disposition of enrolled subjects in the overseas upgrade cohort

6.A.(2) Patient characteristics

Table 10 presents the key patient characteristics in the i2i study.

Table 10. Key patient characteristics in the i2i study

	Overseas pivotal cohort (N = 300)	Japanese cohort (N = 24)	Overseas upgrade cohort (N = 26)
Sex			
Male	62.3% (187/300)	45.8% (11/24)	65.4% (17/26)
Female	37.7% (113/300)	54.2% (13/24)	34.6% (9/26)
Age (years)			
Mean ± SD (n)	69.2 ± 13.5 (300)	77.9 ± 7.7 (24)	67.0 ± 14.4 (26)
(minimum, median, maximum)	(20.0, 72.0, 90.0)	(61.0, 78.0, 92.0)	(28.0, 69.0, 92.0)
Height (cm)			
Mean ± SD (n)	171.6 ± 10.1 (300)	157.2 ± 10.9 (24)	175.2 ± 12.7 (26)
(minimum, median, maximum)	(140.0, 172.7, 195.6)	(136.0, 157.8, 176.0)	(154.9, 173.9, 198.0)
Body weight (kg)			
Mean ± SD (n)	82.9 ± 19.1 (300)	57.9 ± 9.2 (24)	82.6 ± 20.5 (26)
(minimum, median, maximum)	(43.5, 81.7, 163.3)	(42.6, 59.5, 73.0)	(52.4, 84.4, 124.0)
BMI (kg/m2)			
Mean ± SD (n)	28.1 ± 5.6 (300)	23.5 ± 3.5 (24)	26.6 ± 4.5 (26)
(minimum, median, maximum)	(15.1, 27.5, 49.7)	(17.8, 23.6, 32.8)	(19.8, 26.3, 35.1)
Common pacemaker indications			
Sinus node dysfunction	63.3% (190/300)	41.7% (10/24)	50.0% (13/26)
Atrioventricular block	33.3% (100/300)	54.2% (13/24)	46.2% (12/26)
Grade 1	11.0% (11/100)	0.0% (0/13)	25.0% (3/12)
Grade 2, type 1	14.0% (14/100)	7.7% (1/13)	8.3% (1/12)
Grade 2, type 2	34.0% (34/100)	15.4% (2/13)	8.3% (1/12)
Grade 3	41.0% (41/100)	76.9% (10/13)	58.3% (7/12)
Conduction disorder with 1:1 atrioventricular conduction	1.3% (4/300)	0.0% (0/24)	0.0% (0/26)
Vasovagal syncope	2.0% (6/300)	4.2% (1/24)	3.8% (1/26)
History of ablation	19.7% (59/300)	12.5% (3/24)	34.6% (9/26)
Atrioventricular node	1.7% (1/59)	0.0% (0/3)	0.0% (0/9)
Atrial fibrillation/atrial flutter	79.7% (47/59)	66.7% (2/3)	77.8% (7/9)
Ventricular tachycardia	10.2% (6/59)	0.0% (0/3)	0.0% (0/9)
Others	11.9% (7/59)	33.3% (1/3)	22.2% (2/9)
Tricuspid valve disease	24.3% (73/300)	12.5% (3/24)	23.1% (6/26)
Coronary artery disease	34.0% (102/300)	25.0% (6/24)	19.2% (5/26)
Hypertension	66.7% (200/300)	79.2% (19/24)	50.0% (13/26)
Drug therapy			
Anti-arrhythmic (Class I)	5.0% (15/300)	0.0% (0/24)	3.8% (1/26)
Anti-arrhythmic (Class III)	9.7% (29/300)	4.2% (1/24)	7.7% (2/26)
Anti-coagulant	31.0% (93/300)	29.2% (7/24)	42.3% (11/26)
Anti-platelet	39.0% (117/300)	33.3% (8/24)	26.9% (7/26)
ACE inhibitor	22.0% (66/300)	12.5% (3/24)	7.7% (2/26)
Angiotensin II receptor blocker	23.0% (69/300)	29.2% (7/24)	19.2% (5/26)
β blocker	23.3% (70/300)	16.7% (4/24)	23.1% (6/26)
Previous retrieval of a lead or LP			
Transvenous lead	8.0% (24/300)	4.2% (1/24)	15.4% (4/26)
LP	0.7% (2/300)	0.0% (0/24)	7.7% (2/26)

6.A.(3) Study results

A scheduled interim analysis was performed by an independent analysis committee when 150 subjects enrolled in the overseas pivotal cohort completed the 3-month follow-up visit. The analysis showed that no additional subject was necessary. The planned sample size of 300 was used for evaluations as originally planned.

6.A.(3).1) Efficacy

(a) Overseas pivotal cohort

The composite success rate based on atrial pacing thresholds and P wave amplitudes at 3 months post-implantation, the primary efficacy endpoint 1, was 90.8% in the overseas pivotal cohort (7 subjects with missing data included by multiple imputation. The lower limit of the one-sided 97.5% confidence interval was 87.5%.), which exceeded the predefined performance goal (82.5%) ($P < 0.0001$).

The sitting/resting AV synchrony success rate at 3 months post-implantation, the primary efficacy endpoint 2, was 98.2% (272 of 277 subjects; the lower limit of the one-sided 97.5% confidence interval was 96.6%.), which exceeded the predefined performance goal (83%). The mean AV synchrony rate as determined by Holter electrocardiography was 98.0% (minimum 3.6%, median 100%, maximum 100%).

(b) Japanese cohort

The result of the primary efficacy endpoint 1 was 91.7% (22 of 24 subjects) in the Japanese cohort. Fisher's exact test to assess the possibility of extrapolation of the data from this cohort to the overseas pivotal cohort showed $P > 0.9999$, which exceeded the predefined performance goal ($P = 0.15$).

The result of the primary efficacy endpoint 2 was 95.7% (22 of 23 subjects). Fisher's exact test to assess the possibility of extrapolation of the data from this cohort to the overseas pivotal cohort showed $P = 0.3829$, which exceeded the predefined performance goal ($P = 0.15$). The mean AV synchrony rate as determined by Holter electrocardiography was 95.8% (minimum 16.7%, median 100%, maximum 100%).

(c) Overseas upgrade cohort

The upgrade success rate was 92.0% (23 of 25 subjects). The 2 subjects with failed upgrade had a failed implantation of the Aveir Atrial LP. The upgrade success rate in subjects with successful implantation of the Aveir Atrial LP was 100% (23 of 23 subjects).

Table 11 presents time course of electrical parameters of the Aveir Atrial LP, including the pacing threshold, from the follow-up results up to 12 months post-implantation submitted as reference data.

Table 11. Time course of electrical parameters of the Aveir Atrial LP up to 12 months post-implantation in the i2i study*

	Cohort	At implantation	Before discharge	1 month post-implantation	3 months post-implantation	6 months post-implantation	12 months post-implantation
Pacing threshold (V)	(a)	2.57 ± 1.56	1.22 ± 1.05	0.91 ± 0.90	0.82 ± 0.70	0.86 ± 0.72	0.83 ± 0.62
	(b)	2.22 ± 1.44	0.97 ± 0.84	0.73 ± 0.54	0.72 ± 0.44	0.67 ± 0.44	0.75 ± 0.49
	(c)	2.51 ± 1.71	1.33 ± 1.47	1.17 ± 1.58	1.18 ± 1.56	1.09 ± 1.41	0.76 ± 0.58
P-wave amplitude (mV)	(a)	1.95 ± 1.17	2.71 ± 1.70	3.50 ± 1.87	3.58 ± 1.88	3.55 ± 1.96	3.51 ± 1.87
	(b)	1.94 ± 0.94	2.58 ± 1.26	3.20 ± 1.26	3.32 ± 1.50	3.25 ± 1.45	3.01 ± 1.44
	(c)	1.96 ± 0.89	3.65 ± 2.55	4.70 ± 2.81	4.73 ± 2.63	4.69 ± 2.71	4.58 ± 2.75
Impedance (Ω)	(a)	331.41 ± 68.34	375.88 ± 87.40	328.46 ± 53.81	315.40 ± 44.77	307.19 ± 41.48	311.73 ± 48.12
	(b)	327.08 ± 36.53	407.17 ± 160.59	313.75 ± 56.48	297.50 ± 41.10	291.25 ± 35.91	292.50 ± 36.98
	(c)	330.00 ± 50.27	381.30 ± 91.12	343.48 ± 53.14	324.09 ± 38.13	314.78 ± 43.16	321.22 ± 46.55

(a) Overseas pivotal cohort
(b) Japanese cohort
(c) Overseas upgrade cohort
* The figures in the table represent means ± SDs.

6.A.(3).2) Safety

(a) Overseas pivotal cohort

A freedom rate from serious adverse device effects (SADEs) at 3 months post-implantation, the primary safety endpoint, was 90.3% (271 of 300 subjects) in the overseas pivotal cohort. The lower limit of the one-sided 97.5% confidence interval was 87.0%, which exceeded the predefined performance goal

(78%) ($P < 0.0001$). The freedom rate from of SADEs at 6 months post-implantation was 89.1% (262 of 294 subjects). The lower limit of the 95% confidence interval was 85.6%. Table 12 presents SADEs reported by 6 months post-implantation.

(b) Japanese cohort

The result of the primary safety endpoint was 79.2% (19 of 24 subjects) in the Japanese cohort. Fisher's exact test to assess the possibility of extrapolation of the data from this cohort to the overseas pivotal cohort showed $P = 0.1548$, which exceeded the predefined performance goal ($P = 0.15$). The freedom rate from SADEs at 3 months post-implantation was 79.2% (19 of 24 subjects). Table 13 presents SADEs reported by 3 months post-implantation.

(c) Overseas upgrade cohort

The result of the primary safety endpoint was 88.5% (23 of 26 subjects) in the overseas upgrade cohort. The freedom rate from SADEs at 6 months post-implantation was 88.5% (23 of 26 subjects). Table 14 presents SADEs reported by 6 months post-implantation.

Table 12. SADEs reported by 6 months post-implantation in the overseas pivotal cohort

Event	Number of events	Incidence*1	Procedure-related (number of events)	Aveir Ventricular LP-related (number of events)	Aveir Atrial LP-related (number of events)	Ventricular LP Catheter-related (number of events)*2	Atrial LP Catheter-related (number of events)*3
Arrhythmia-atrial fibrillation	9	3.0% (9/300)	8	0	7	0	1
Post-implantation device dislodgement	5	1.7% (5/300)	0	0	5	0	0
Urinary retention	3	1.0% (3/300)	3	0	0	0	0
Inappropriate fixation without LP dislocation during implantation (peri-procedural dislodgement)	3	0.7% (2/300)	3	0	1	0	2
Inappropriate fixation with LP dislocation during implantation (peri-procedural dislodgement)	2	0.7% (2/300)	2	1	1	0	0
Increased threshold	2	0.7% (2/300)	0	1	1	0	0
Pericardial effusion or friction murmur	2	0.7% (2/300)	2	0	2	0	0
False magnet mode	1	0.3% (1/300)	0	0	1	0	0
Syncope	1	0.3% (1/300)	0	0	1	0	0
Intermittent capture	1	0.3% (1/300)	0	1	0	0	0
Intermittent or complete loss of i2i communication	1	0.3% (1/300)	0	1	0	0	0
Oversensing	1	0.3% (1/300)	0	1	0	0	0
Presyncope	1	0.3% (1/300)	0	1	0	0	0
Puncture site haemorrhage	1	0.3% (1/300)	1	0	0	0	0
Cardiac failure	1	0.3% (1/300)	1	0	0	0	0
Haematoma (including retroperitoneal haematoma/haemorrhage)	1	0.3% (1/300)	1	0	0	0	0
Pain	1	0.3% (1/300)	1	0	0	0	0
Pleural effusion	1	0.3% (1/300)	1	0	0	0	0
Pulmonary embolism	1	0.3% (1/300)	1	0	0	0	0
Physically caused device dislodgement (interference with the LP by the echo catheter in the cardiac cavity during the procedure)	1	0.3% (1/300)	1	0	0	0	0
Atrioventricular block complete	1	0.3% (1/300)	1	0	0	1	0
Total	**40**	**11.0% (33/300)**	**26**	**6**	**19**	**1**	**3**

*1 Some subjects experienced multiple events.
*2 Adverse events related to the delivery catheter during implantation of the Aveir Ventricular LP
*3 Adverse events related to the delivery catheter during implantation of the Aveir Atrial LP

Table 13. SADEs reported by 3 months post-implantation in the Japanese cohort

Event	Number of events	Incidence*1	Procedure-related (number of events)	Aveir Ventricular LP-related (number of events)	Aveir Atrial LP-related (number of events)	Ventricular LP Catheter-related (number of events)*2	Atrial LP Catheter-related (number of events)*3
Cardiac failure	1	4.2% (1/24)	0	1	0	0	0
Increased threshold	1	4.2% (1/24)	0	1	0	0	0
Arteriovenous fistula	1	4.2% (1/24)	1	0	0	0	0
Arrhythmia-atrial fibrillation	1	4.2% (1/24)	1	0	1	0	0
Arterial laceration	1	4.2% (1/24)	1	0	0	0	0
Cardiac arrest	1	4.2% (1/24)	1	0	0	0	0
Cardio-respiratory arrest	1	4.2% (1/24)	0	1	0	0	0
Total	**7**	**20.8% (5/24)**	**4**	**3**	**1**	**0**	**0**

*1 Some subjects experienced multiple events.
*2 Adverse events related to the delivery catheter during implantation of the Aveir Ventricular LP
*3 Adverse events related to the delivery catheter during implantation of the Aveir Atrial LP

Table 14. SADEs reported by 6 months post-implantation in the overseas upgrade cohort

Event	Number of events	Incidence*1	Procedure-related (number of events)	Aveir Ventricular LP-related (number of events)	Aveir Atrial LP-related (number of events)	Ventricular LP Catheter-related (number of events)*2	Atrial LP Catheter-related (number of events)*3
Atrial fibrillation	1	3.8% (1/26)	1	0	0	0	0
Pleural effusion	1	3.8% (1/26)	1	0	0	0	0
Respiratory failure	1	3.8% (1/26)	1	0	0	0	0
Cardiac tamponade	1	3.8% (1/26)	1	0	1	0	0
Inappropriate fixation without LP dislocation during implantation	1	3.8% (1/26)	1	0	1	0	0
Total	**5**	**11.5% (3/26)**	**5**	**0**	**2**	**0**	**0**

*1 Some subjects experienced multiple events.
*2 Adverse events related to the delivery catheter during implantation of the Aveir Ventricular LP
*3 Adverse events related to the delivery catheter during implantation of the Aveir Atrial LP

Tables 15, 16, and 17 present malfunctions reported in each cohort of the i2i study.

Table 15. Malfunctions reported by 6 months post-implantation in the overseas pivotal cohort

Malfunction	Number of subjects with malfunction (N = 300)	Number of malfunctions of each constituent part
i2i communication problem*[1]	86	Aveir Atrial LP: 102 Aveir Ventricular LP: 83 Programmer: 1
Improper display of RRT flag*[2]	24	Aveir Atrial LP: 19 Aveir Ventricular LP: 8
Programmer, link module, or software problem	14	Aveir Atrial LP: 1 Aveir Ventricular LP: 4 Programmer: 8 Link Module: 1
LP release difficulty	10	Aveir Atrial LP: 1 Aveir Ventricular LP: 1 Delivery Catheter: 10
Noise reversion	12	Aveir Atrial LP: 12
Treatment switch due to i2i problem*[3]	7	Aveir Atrial LP: 7 Aveir Ventricular LP: 2
Device dislodgement	9	Aveir Atrial LP: 7 Aveir Ventricular LP: 1 Delivery Catheter: 1
Helix distortion	8	Aveir Atrial LP: 7 Aveir Ventricular LP: 2
Failure to establish communication between the programmer and the Aveir Atrial LP	7	Aveir Atrial LP: 8
Undersensing	5	Aveir Atrial LP: 5
Change in battery life	3	Aveir Atrial LP: 2 Aveir Ventricular LP: 2
Magnet response problem*[4]	4	Aveir Atrial LP: 4
Delivery catheter flexion/kink	3	Delivery Catheter: 3
False magnet mode*[5]	3	Aveir Atrial LP: 3
Capture loss/increased threshold of the Aveir Ventricular LP	3	Aveir Ventricular LP: 3
Tether mode expansion problem*[6]	3	Delivery Catheter: 3
Oversensing	2	Aveir Atrial LP: 2
Impossible battery diagnosis	2	Aveir Atrial LP: 1 Aveir Ventricular LP: 1
LP fixation difficulty	2	Aveir Atrial LP: 2
Electrogram storage problem	2	Aveir Ventricular LP: 2
Failure to establish communication between the programmer and the Aveir Ventricular LP	2	Aveir Ventricular LP: 2
Introducer/dilator problem	2	Introducer: 2 Dilator: 0
LP backup/reset problem	2	Aveir Atrial LP: 2
Transition to backup mode of LP*[7]	2	Aveir Atrial LP: 1 Aveir Ventricular LP: 1
Capture loss/increased threshold of the Aveir Atrial LP	2	Aveir Atrial LP: 2
Capture test operation problem	1	Aveir Atrial LP: 1
Clinical symptoms related to automatic mode switch	1	Aveir Atrial LP: 1
Delivery catheter flexion problem	1	Delivery Catheter: 1
The Aveir Atrial LP dislodgement due to interference by the ultrasonic catheter in the cardiac cavity	1	Aveir Atrial LP: 1
Inappropriate mounting of the LP to the delivery catheter during LP implantation	1	Delivery Catheter: 1
Intermittent capture	1	Aveir Ventricular LP: 1
Procedural mistake	1	Delivery Catheter: 1
Leakage from protective sleeve*[8]	1	Delivery Catheter: 1
Retrieval catheter deployment problem	1	Retrieval Catheter: 1
Tether dislocation*[9]	1	Delivery Catheter: 1
Total	**156**	**339**

*1 Unexpected i2i communication-related activities or less-than-expected i2i throughput
*2 Improper recommended replacement time (RRT) was displayed.
*3 Although proper AV synchrony was not achieved because of some i2i communication problem, transient re-programming or reset restored AV synchrony.
*4 When a magnetic programmer device was attached to the chest to assess the battery condition, it did not trigger the transition to a special mode (magnetic mode).

*5 Transition to the magnetic mode occurred because of device malfunction.
*6 Malfunction of a part (tether) of the delivery catheter, which is used to connect the LP
*7 The transition to the backup mode of the LP (safety feature to ensure safe LP reset) occurred during communication with the programmer.
*8 A leakage from the protective sleeve, a part of the delivery catheter
*9 Inappropriate tether position found when the delivery catheter was removed from its package

Table 16. Malfunctions reported by 3 months post-implantation in the Japanese cohort

Event	Number of subjects with malfunction (N = 24)	Number of malfunctions of each constituent part
Impossible battery diagnosis	2	Aveir Atrial LP: 1 Aveir Ventricular LP: 2
LP operating with parameters other than those preset	1	Aveir Atrial LP: 1 Aveir Ventricular LP: 1
Failure to establish communication between the programmer and the Aveir Atrial LP	1	Aveir Atrial LP: 1
Elongation or damage of LP helix	1	Aveir Ventricular LP: 1
Capture loss/increased threshold	1	Aveir Ventricular LP: 1
Leakage from protective sleeve	1	Delivery Catheter: 1
i2i communication problem	1	Aveir Atrial LP: 1
Total	**6**	**10**

Table 17. Malfunctions reported by 6 months post-implantation in the overseas upgrade cohort

Event	Number of subjects with malfunction (N = 26)	Number of malfunctions of each constituent part
i2i communication problem	5	Aveir Atrial LP: 5 Aveir Ventricular LP: 2
Elongation or damage of LP helix	3	Aveir Atrial LP: 3
Programmer, link module, or software problem	2	Programmer: 1 Link Module: 1
Improper display of RRT flag	2	Aveir Atrial LP: 2
Impossible battery diagnosis	1	Aveir Atrial LP: 1
Clinical symptoms related to automatic mode switch	1	Aveir Atrial LP: 1
Device dislodgement	1	Aveir Atrial LP: 1
Noise reversion	1	Aveir Atrial LP: 1
Unintended LP release	1	Delivery Catheter: 1
Tether mode expansion problem	1	Delivery Catheter: 1
Total	**11**	**20**

6.B Outline of the review conducted by PMDA

6.B.(1) Clinical positioning

PMDA's view on the clinical positioning of the Aveir LP:

The Aveir LP is a device intended for atrial and ventricular pacing and used in patients eligible for single chamber pacing and dual chamber pacing, as with transvenous PMs. Two types of ventricular LPs are commercially available (the Aveir Ventricular LP and Micra). Micra has a VDD mode that detects spontaneous atrial beats and synchronizes ventricular pacing with them. No LP that has a DDD mode that synchronizes the atrium and ventricle to enable both atrial and ventricular pacing currently exists. The Aveir LP is a new technology that offers a DDD mode. For patients eligible for the DDD mode, the LP therapy that is not associated with risks of transvenous PM-specific complications (e.g., lead breakage and subcutaneous pocket infection) is beneficial. In particular, the LP therapy has a high clinical usefulness in patients who have difficult lead venous access (e.g., patients on dialysis) and patients who are at high risk of infection (e.g., patients with a medical history of recurrent device infection).

As described later, the Aveir LP is associated with some risks due to the thin atrial walls, including LP dislocation or dislodgement, pericardial effusion, cardiac tamponade, and the possibility for the implanted Aveir Atrial LP to interfere with other treatment that is performed through the atrial septum. There is only limited long-term efficacy and safety data of the Aveir Atrial LP available. Those risks must be appropriately considered in selecting eligible patients for this therapy. For the following reasons, age must also be carefully determined in patient selection as with conventional LPs:

- The structure and size of the atrium limit the number of the Aveir Atrial LPs that can be implanted to not more than 2.
- The mean expected battery life of the Aveir Atrial LP used in the dual chamber mode was 5.7 years (Table 18, sum of an estimated remaining battery life of 4.7 years at 1 year post-implantation and an implantation period of 1 year) in the overseas pivotal cohort and 5.8 years (Table 18, sun of an estimated remaining battery life of 4.8 years at 1 year post-implantation and an implantation period of 1 year) in the Japanese cohort in the i2i study.
- There is only limited experience with retrieval of the Aveir Atrial LP.

Table 18. Estimated remaining battery life in the i2i study (year)* (1 year post-implantation)

	Overseas pivotal cohort Dual chamber mode (N = 235)	**Japanese cohort Dual chamber mode (N = 21)**
Aveir Atrial LP	4.7 ± 2.5 (0.3, 4.3, 19.3) [4.3, 5.0]	4.8 ± 1.2 (2.0, 5.0, 6.5) [4.3, 5.4]
Aveir Ventricular LP	8.8 ± 3.1 (1.4, 8.8, 23.7) [8.4, 9.2]	9.0 ± 2.3 (5.3, 9.8, 13.1) [8.0, 10.1]

* The figures in the table represent means ± SDs (minimum, medians, and maximum) [95% confidence interval].

Taking into consideration the comments from the Expert Discussion, PMDA has concluded that the Aveir LP is of clinical significance as a new treatment option and that it is necessary to inform healthcare professionals of the importance of fully understanding the characteristics of the Aveir LP to select eligible patients for this therapy. The criteria for eligible patients for the Aveir LP therapy are described in Section 6.B.(6).

6.B.(2) Design of the i2i study

PMDA's view on the appropriateness of the design of the i2i study:

Treatment of bradycardia with pacemaker has been established in Japan. Multiple transvenous PMs, LPs, and other pacemakers have already been approved and yielded data. Evaluation of the efficacy and safety of the Aveir LP in a single-arm study was appropriate provided that appropriate primary endpoints and performance goals are used.

Primary efficacy endpoints 1 and 2 are appropriate for evaluation of the electrical performance and AV synchrony of a LP, as a pacemaker that provides dual chamber pacing, at some point after implantation. The performance goals were selected for the study in accordance with the appropriate rationales as described in Table 8.

The primary safety endpoints, which were set based on the justifiable rationales as described in Table 8 to assess device- or procedure-related complications, are appropriate. For the following reasons, however, safety evaluation should be conducted at 6 months post-implantation in addition to the primary

safety endpoint (3 months post-implantation), as with the Aveir Ventricular LP: (1) The Aveir LP comprises Japan's first LP to be implanted in the atrium; (2) the data suggested potential risks specific to the Aveir Atrial LP; and (3) no clinical data supporting the long-term safety of the Aveir LP are currently available. The present partial change application included the study results at 6 months post-implantation in the overseas pivotal cohort as evaluation data and the study results at 3 months post-implantation in the Japanese cohort as reference data. The validity of these data is described later in Section 6.B.(3).

6.B.(3) Extrapolation of overseas data to Japan

As described above, the applicant submitted the results at 3 month post-implantation (as primary endpoint) as well as data at 6 months post-implantation from the preceding overseas pivotal cohort. From the Japanese cohort, the results at 3 months post-implantation were submitted to assess the possibility of extrapolation of the overseas data to Japan.

PMDA asked the applicant to explain reasons for the conclusion that the safety of the Japanese cohort would be evaluable based on the results at 3 months post-implantation, while submitting the results at 6 months post-implantation in the overseas pivotal cohort.

The applicant's explanation:

The study result in the Japanese cohort met the performance goal, with a higher incidence of SADEs than that in the overseas pivotal cohort. A comparison of the patient characteristics between the Japanese cohort and the overseas pivotal cohort for causal analysis showed significant differences in body mass index (BMI) and age (the Japanese cohort had a lower mean BMI by approximately 5 kg/m^2 and a higher mean age by approximately 8 years). A propensity score matching analysis was performed with those parameters as adjusting factors.

The analysis suggested no relationship with BMI. The primary safety endpoint adjusted for age in the overseas pivotal cohort (85.4%, 82 of 96 subjects) was lower than that before the adjustment (90.3%, 271 of 300 subjects) and consistent with that in the Japanese cohort (79.2%, 19 of 24 subjects).

Based on the above, the analysis suggested that the age difference between the 2 cohorts might have contributed to the difference in the study result. The differences in medical environment or body build between the 2 regions had no influence on the safety results. Currently, there is no evidence of a higher incidence of SADEs particularly in Japanese population.

Since the safety profile of the Aveir LP did not differ between Japanese and non-Japanese subjects, the clinical outcome at 6 months post-implantation in Japan is evaluable based on the results at 6 months post-implantation in the overseas pivotal cohort and the results at 3 months post-implantation in the Japanese cohort.

PMDA's view:

The applicant submitted only the results at 3 months post-implantation from the Japanese cohort. The results of primary efficacy endpoint 1 at 3 months (90.8%) and 6 months (90.8%) in the overseas pivotal

cohort, and at 3 months (91.7%) in the Japanese cohort were all comparable. Taking the above findings and the pacing principle for bradycardia treatment into consideration, the Japanese cohort can be expected to have similar results at 6 months post-implantation to those in the overseas pivotal cohort. Comparisons of the point estimates of the primary safety endpoint at 3 months post-implantation (90.3%) and 6 months post-implantation (89.1%) in the overseas pivotal cohort, and 3 months post-implantation (79.2%) in the Japanese cohort showed differences in freedom rate from events. Three events (increased threshold, false magnetic mode, and oversensing) were reported between 3 and 6 months post-implantation in the overseas pivotal cohort. The incidence of these events is very unlikely to increase over time only in Japanese patients. PMDA concluded that it was possible to make a comprehensive evaluation of the clinical outcome at 6 months post-implantation in Japan based on the results at 6 months post-implantation in the overseas pivotal cohort and the results at 3 months post-implantation in the Japanese cohort. The primary safety endpoint at 6 and 12 months post-implantation in the Japanese cohort, submitted as reference data, was 79.2%, which was consistent with that at 3 months post-implantation (Table 19).

Table 19. Freedom rate from SADEs in the overseas pivotal cohort and the Japanese cohort

Freedom rate from SADEs	3 months post-implantation	6 months post-implantation	12 months post-implantation
Overseas pivotal cohort	90.3%	89.1%	88.6%*
Japanese cohort	79.2%	79.2%*	79.2%*

* Reference data

6.B.(4) Efficacy

PMDA's view on the efficacy of the Aveir LP:

The primary endpoints exceeded the predefined performance goals in the overseas pivotal cohort, showing the efficacy of dual chamber pacing and atrial pacing with the Aveir LP. Primary efficacy endpoints were consistent between the overseas pivotal cohort and the Japanese cohort to a certain extent, verifying the possibility to extrapolate the efficacy results to Japan. The follow-up results up to 12 months post-implantation in each cohort submitted as reference data showed the stability of the electrical parameters, including the pacing threshold (Table 11). Those findings suggest the long-term efficacy of the Aveir LP.

Upgrading from the single chamber mode to the dual chamber mode was not successful in 2 subjects (failed implantation of the Aveir Atrial LP) because of procedure-related complications (inappropriate fixation without LP dislocation during implantation or cardiac tamponade). The upgrade failures were not related to the existing Aveir Ventricular LP. PMDA concluded that upgrade was possible provided that peri-procedural complications (described later in Section 6.B.[5]), which are safety issues associated with the Aveir LP, are clinically acceptable.

6.B.(5) Safety

PMDA's view on the safety of the Aveir LP:

As described above, the primary safety endpoint met the predefined performance goal both in the overseas pivotal cohort and the Japanese cohort. Nevertheless, the following information should be provided to healthcare professionals to ensure that they carefully perform the implantation procedure: The Japanese cohort tended to have a higher incidence of SADEs than the overseas pivotal cohort; the

Japanese cohort experienced SADEs during the implantation procedure or in the acute phase after implantation; and the details of each SADE reported in the study.

The safety of the Aveir LP should be evaluated based not only on the incidence of SADEs (the primary safety endpoint), but also adverse events more common with the Aveir Atrial LP than with the Aveir Ventricular LP, potential risks specific to the Aveir Atrial LP, and malfunctions of the i2i communication, which enables the Aveir LP's unique AV synchrony. PMDA should evaluate those issues, and reviews as shown below.

6.B.(5).1) Adverse events more common with the Aveir Atrial LP than with the Aveir Ventricular LP (atrial fibrillation and the Aveir Atrial LP dislodgement)

As shown in Tables 12 and 13, the SADEs more common in the atrium than in the ventricle in the i2i study (6 ventricular events and 19 atrial events in the overseas pivotal cohort, 3 ventricular events and 1 atrial event in the Japanese cohort).

PMDA asked the applicant to explain the reason that the above Aveir Atrial LP-related SADEs were clinically acceptable.

The applicant's explanation:
The incidence of adverse events differed between the ventricle and the atrium because atrial fibrillation and the Aveir Atrial LP dislodgement more commonly occurred in the atrium. Below is the reason that each event was considered clinically acceptable:

Atrial fibrillation

- The Aveir Atrial LP, which delivers direct stimuli to the atrium unlike the Aveir Ventricular LP, is potentially associated with atrial fibrillation compared with the Aveir Ventricular LP to some extent.
- The incidence of atrial fibrillation, one of SADEs in the i2i study (3.0%, 9 of 300 subjects up to 6 months post-implantation), was consistent with that reported with dual chamber transvenous PMs (5%-6% up to 6 months post-implantation).[8]

The Aveir Atrial LP dislodgement

- In general, dislodgement more commonly occurs in the right atrium than the right ventricular because of the thinner myocardium of the right atrium.
- The incidence of the Aveir Atrial LP dislodgement in the i2i study (1.7% up to 6 months post-implantation) was consistent with that reported with conventional transvenous atrial leads (1.9% up to 2 months post-implantation).[7,9] The Aveir Atrial LPs that were dislodged could be retrieved without causing complications (Table 20).

Table 20. Summary of the Aveir Atrial LP dislodgement (the overseas pivotal cohort, 6 months post-implantation)

Event No.	Number of days from implantation to onset	Finding associated with dislodgement	Implantation site*	Location of the dislodged Aveir Atrial LP	Retrieval success or failure	Retrieval-related complication
Peri-procedural dislodgement						
1	-	-	Unknown	Left ventricle	Success	None
2	-	-	Unknown	Right atrium	Success	None
3	-	-	Unknown	Right atrium	Success	None
4	-	-	Unknown	Right atrium	Success	None
Physically caused peri-procedural device dislodgement (interference with the Aveir Atrial LP by the echo catheter in the cardiac cavity during the procedure)						
5	-	-	Right auricular base	Right atrium	Success	None
Post-implantation dislodgement						
6	Immediately after procedure	Capture loss	Mid to deep part of the right auricle	Right atrium	Success	None
7	19	Shortness of breath, fatigue, palpitations	Mid to deep part of the right auricle	Pulmonary artery	Success	None
8	32	Capture loss	Mid to deep part of the right auricle	Right ventricle	Success	None
9	39	Right ventricular capture (asymptomatic)	Right auricular base	Right ventricle	Success	None
10	40	Persistent dizziness	Right auricular base	Right ventricle	Success	None

* The site of peri-procedural dislodgement is unknown because only the information about the final implantation site was collected.

It is critical to adhere to the selection criteria for the appropriate implantation site shown below to reduce the risk of the Aveir Atrial LP dislodgement because the risk of dislodgment differs between LPs and transvenous leads.

The i2i study demonstrated a lower incidence of dislodgement of the Aveir Atrial LP up to 6 months post-implantation in the right auricular base (1.1%, 2 of 181 subjects) than in the mid to deep part of the right auricle (4.4%, 3 of 68 subjects). This tendency appears to be associated with the thicker cardiac wall of the right auricular base than that of the mid to deep part of the right auricle. Since dislodgement commonly occurs in the mid to deep part of the right auricle, the right auricular base should be recommended as an implantation site. This recommendation and information about implantation procedures that ensure an appropriate fixation (e.g., deflection test, current of injury check, and impedance check) should be provided in training at the time of introducing the Aveir LP to Japan. The anatomical factors of the right auricular base limit the number of the Aveir Atrial LPs that can be implanted to not more than 2.

PMDA's view on the Aveir Atrial LP-related adverse events:

Atrial fibrillation

Although implantation of transvenous PMs is associated with the risk of atrial fibrillation because it involves intracardiac manipulations, etc., implantation of the Aveir LP carries higher risks since the Aveir Atrial LP, which is larger than a transvenous lead, is implanted in the atrium via the delivery catheter with the LP pressed to the myocardium, and therefore requires careful caution. The literature report on dual chamber transvenous PMs[8] referenced by the applicant in the present application is not appropriate for a comparison with the i2i study since this report has no assessment data on peri-procedural atrial fibrillation. However, atrial fibrillation reported as SADE by 6 months post-implantation in the overseas pivotal cohort occurred during the procedure in all of the subjects, except for 1 subject, and was intervened and resolved during the procedure in all of the subjects, and the 1

subject who experienced the event after implantation recovered after a medical change. The event was clinically acceptable. The applicant is, therefore, required to provide information about the atrial fibrillation cases in the i2i study and collect relevant information (e.g., persistency of atrial fibrillation) in the use-results survey described later.

The Aveir Atrial LP dislodgement

As shown in Table 20, dislodgement may cause the dislocation of LP from the intended site, posing a risk different from that posed by transvenous lead dislodgement and leading to serious adverse events. There is a potential risk of adverse events during the retrieval of the dislodged LP, and the location or positioning of the dislodged LP can affect the feasibility of transcutaneous retrieval. As explained above by the applicant, the risk of dislodgement is higher in the atrium than the ventricle because of the anatomical difference. However, in the i2i study, the incidence of dislodgement of the Aveir Atrial LP was consistent with that of the transvenous atrial leads, and the dislodged LPs were retrieved successfully without causing complications. The risk of the Aveir Atrial LP dislodgement is thus clinically acceptable. Prior to the introduction of the Aveir LP to Japan, the applicant needs to provide information including recommended implantation site, a method to anatomically locate the base of the right atrial appendage accurately, a procedure to confirm appropriate fixation, and the occurrence of dislodgement cases in the i2i study. The collection of safety information and discussion about risk reduction measures should be continued in the post-marketing setting through the use-results survey and post-marketing malfunction reports mentioned later.

6.B.(5).2) Myocardial injury

For the risk of myocardial injury associated with implantation of LPs, death within 1 month post-implantation, which is rare with the transvenous PMs, was continuously reported after the use of the Aveir Ventricular LP in Japan, and the related academic society has warned about myocardial injury, including Micra and the Aveir Ventricular LP. Generally, the atrium has a thinner myocardium than the ventricular, which is associated with a higher risk of myocardial injury, and more thorough discussion is required for myocardial injury in the atrium.

Table 21 presents the information about myocardial injury reported in the i2i study.

Table 21. Myocardial injury reported in the i2i study

	Overseas pivotal cohort	Japanese cohort	Overseas upgrade cohort
SADE	2/300 (atrium in 2 subjects,[a] ventricle in 0 subjects)	0/24	1/26 (atrium in 1 subject,[c] ventricle in 0 subjects)
ADE	3/300 (atrium in 2 subjects,[a] unknown onset site in 1 subject[b])	0/24	0/26

* SADE = serious adverse device effect
ADE = adverse device effect
a Pericardial effusion for all cases
b Pericardial effusion whose onset site was unknown because it occurred after implantation
c Cardiac tamponade

The overseas pivotal cohort had myocardial injury with an incidence of 1.7% (5 of 300 subjects) by 6 months post-implantation; 1.0% (3 of 300 subjects) as adverse device effects (ADEs) and 0.7% (2 of 300 subjects) as SADEs. All cases were pericardial effusion in the atrium, except for 1 ADE whose

onset site was unknown. For the SADEs in 1 subject, i2i communication was found insufficient during interrogation after implantation of the Aveir Atrial LP and the Aveir Ventricular LP and pericardial effusion was observed during retrieval of the Aveir Atrial LP. The event resolved after pericardial paracentesis at 15 days post-implantation. The remaining SADE in 1 subject was the Aveir Atrial LP-related pericardial effusion that occurred on the following day of implantation. It resolved after thoracic paracentesis at 4 days post-implantation.

The Japanese cohort experienced no myocardial injury. The overseas upgrade cohort had no ADE of myocardial injury but an SADE of myocardial injury (atrial cardiac tamponade) in 1 of 26 subjects. This subject had a high pacing threshold of the Aveir Atrial LP, and 3 Aveir Atrial LPs were repeatedly attempted to be implanted. Pericardial effusion was observed during the implantation of the third Aveir Atrial LP. The subject received pericardial drainage, transfusion, and vasopressor therapy, and was discharged from the hospital at 3 days post-implantation.

PMDA asked the applicant to explain the reason that the above myocardial injury cases were clinically acceptable.

The applicant's explanation:
The incidence of the SADEs of myocardial injury (total of the overseas pivotal cohort, Japanese cohort, and overseas upgrade cohort, 3 of 350 subjects, 0.86%) was lower than the incidence (1.5%) of myocardial injury (cardiac tamponade in all cases) at 6 weeks post-implantation in the clinical study of the Aveir Ventricular LP (phase 2 of the Leadless II study, 200 subjects).[3] The instructions for use included caution to avoid unnecessary re-implantation after LP implantation, and check whether electrical parameters (sensing threshold, pacing threshold, impedance, and intracardiac potential) measured with the LP touching the endocardium are within their respective acceptable ranges, in order to reduce the risk of cardiac perforation and pericardial effusion.

PMDA's view on the risk of myocardial injury associated with the Aveir LP:
As explained by the applicant, the onset trends of myocardial injury in the i2i study is acceptable based on the results from the study of the Aveir Ventricular LP. In order to avoid unnecessary re-implantation, the applicant should provide the following information: Thorough measurements of the electrical parameters prior to implantation, as advised in the instructions for use, and the recommended implantation site and the recommended distance between the 2 LPs as described in Sections 6.B.(5).1) and 6.B.(5).6). Information about myocardial injury cases in the i2i study should also be provided since LP implantation in the atrium, which has a thin myocardium, requires more caution. The supplicant should collect further information in the use-results survey described later and provide new findings, if any, to healthcare professionals.

6.B.(5).3) Difference in time required for implantation between the Aveir Ventricular LP and the Aveir Atrial LP

Table 22 presents the time required for implantation of each LP (from insertion of each delivery catheter until its removal). It took ≥10 minutes longer to implant the Aveir Atrial LP than the Aveir Ventricular LP in both the overseas pivotal cohort and the Japanese cohort.

Table 22. Time required for implantation of the Aveir Ventricular LP and the Aveir Atrial LP (min)*

	Overseas pivotal cohort	Japanese cohort
Aveir Ventricular LP	24.2 ± 16.1 (3.0, 19.0, 157.0)	34.6 ± 26.9 (11.0, 24.5, 120.0)
Aveir Atrial LP	40.2 ± 22.6 (9.0, 34.0, 162.0)	46.3 ± 35.4 (18.0, 35.5, 163.0)

* The figures in the table represent means ± SDs (minimum, medians, and maximum).

PMDA asked the applicant to explain the reason for the longer time to implant the Aveir Atrial LP than the Aveir Ventricular LP and difficulty of the implantation procedure specific to the Aveir Atrial LP.

The applicant's explanation:

The implantation procedure of the Aveir Atrial LP is as difficult as that of the Aveir Ventricular LP for the following reasons.

- The Aveir Atrial LP is the world's first atrial LP. The level of surgeons' experience with implantation differs between the Aveir Ventricular LP and the Aveir Atrial LP. The time to implant the Aveir Atrial LP may be shortened as their experience increases.
- The atrium has a thinner myocardium than the ventricle and a smooth myocardial surface. These anatomical factors of the atrium make it more prone to re-implantation.
- There is no specific recommendation on the order of implantation of the Aveir Atrial LP and the Aveir Ventricular LP. It takes at least 5 minutes to check peri-implantation i2i communication, which is performed during implantation of a following LP. In the i2i study, more subjects had the Aveir Ventricular LP implanted first, followed by the Aveir Atrial LP (88.7% in the overseas pivotal cohort, 100% in the Japanese cohort), which is considered to affect the time required for implantation.
- In the overseas pivotal cohort, the manipulability of the Aveir Ventricular LP and the Aveir Atrial LP during implantation were rated similar by surgeons using a 4-point scale (Table 23).

Table 23. Manipulability of the Aveir Ventricular LP and the Aveir Atrial LP during implantation in the overseas pivotal cohort

		Assessment			
		Easy	Acceptable	Poor	Not applicable*
Passability in the introducer	Aveir Ventricular LP	94.7% (284/300)	5.3% (16/300)	0% (0/300)	0% (0/300)
	Aveir Atrial LP	94.7% (284/300)	5.3% (16/300)	0% (0/300)	0% (0/300)
Manipulability in a vein	Aveir Ventricular LP	92.7% (278/300)	6.3% (19/300)	0.3% (1/300)	0.7% (2/300)
	Aveir Atrial LP	93.7% (281/300)	5.7% (17/300)	0% (0/300)	0.7% (2/300)
Easiness of LP implantation	Aveir Ventricular LP	81.3% (244/300)	16.0% (48/300)	2.7% (8/300)	0% (0/300)
	Aveir Atrial LP	82.7% (248/300)	15.3% (46/300)	2.0% (6/300)	0% (0/300)
Easiness of delivery system removal	Aveir Ventricular LP	92.0% (276/300)	6.0% (18/300)	0.7% (2/300)	1.3% (4/300)
	Aveir Atrial LP	92.3% (277/300)	6.3% (19/300)	0.7% (2/300)	0.7% (2/300)

* The procedure was not attempted or data were missing.

PMDA's view:

The difference in time required for implantation procedure between the Aveir Ventricular LP and the Aveir Atrial LP was mainly because of the anatomical differences between the ventricle and the atrium and the influence of the checking order of the i2i communication. Taking into account the results of the manipulability assessment (Table 23), the Aveir Atrial LP could be implanted properly provided that surgeons with expert knowledge in arrhythmia treatment receive appropriate product training described later.

6.B.(5).4) Risk of the implanted Aveir Atrial LP interfering with procedures via the atrial septum or tricuspid valve

PMDA asked the applicant to explain the risk of the implanted Aveir Atrial LP interfering with procedures via the atrial septum or tricuspid valve (e.g., left atrium ablation and tricuspid valvuloplasty).

The applicant's explanation:

Risk of interfering with procedures via the atrial septum

- Implantation of the Aveir Atrial LP in the atrial septum is not recommended for the following reasons:
  - Delivery of the Aveir Atrial LP is difficult.
  - The tissue is smooth.
  - The implanted LP may interfere with future transseptal treatment.
  - The foramen ovale occupies a large part of the atrial septum. The tissue is thin and not suitable for electric conduction.
- Considering the anatomical characteristics of the atrium and the size of the Aveir Atrial LP, its implantation in the right auricular base (★ in Figure 5), the recommended implantation site, is very unlikely to interfere with access to a foramen ovale (● in Figure 5).

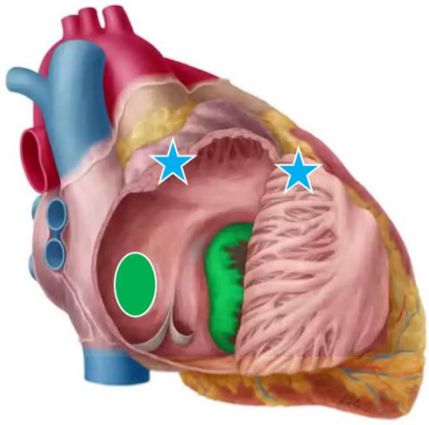


Figure 5. Recommended implantation site of the Aveir Atrial LP and the atrial septum

Risk of interfering with procedures via the tricuspid valve

- The proximal end of the Aveir Atrial LP may come close to the tricuspid annulus. Considering the anatomical factors and the size of Aveir Atrial LP, there should be enough space between the LP and the tricuspid valve.
- In the i2i study, the subjects who had the Aveir Atrial LP implanted first, followed by the Aveir Ventricular LP (34 subjects in the overseas pivotal cohort, 0 subjects in the Japanese cohort), experienced no interference with the implanted Aveir Atrial LP by any device used to implant the Aveir Ventricular LP.

PMDA's view:

There was no particular problem in the applicant's view about the risk of the implanted Aveir Atrial LP interfering with procedures via the atrial septum or tricuspid valve. Nevertheless, the overseas pivotal

cohort had 1 event of dislodgement during the procedure (not via the atrial septum or tricuspid valve) caused by an echo catheter in the cardiac cavity hitting the implanted Aveir Atrial LP. Caution should be taken to prevent other devices from interfering with the LPs during procedures in the LP-implanted heart. This information should be provided to healthcare professionals. The applicant should collect further information about adverse events, if any, associated with interference with the LPs by other devices in the use-results survey described later.

6.B.(5).5) Retrieval of the Aveir Atrial LP

PMDA's view on retrieval of the Aveir Atrial LP:
While Micra is not intended to be retrieved, the Aveir LP is designed so that it can be retrieved (helix fixation mechanism at the distal end).

At the time of approval of the Aveir Ventricular LP, the clinical study results of its former generation were submitted. The retrieval outcome during the chronic phase was "successful" in 87.4% (195 of 223) of subjects over the average implantation duration up to retrieval of 34.4 months. The longest implantation duration in subjects with successful retrieval was 86.7 months. The success rate did not depend on the implantation duration. In principle, however, the Aveir LP should not be retrieved once it is implanted, although it is within the scope of expectation. The retrieval cannot always be successful depending on the degree of adhesion to the tissue and associated risk of myocardial injury. The instructions for use give cautions about possible challenging cases of Ventricular LP retrieval and urge careful assessment of the necessity for retrieval.

The Aveir Ventricular LP and the Aveir Atrial LP have the same fixation mechanism at their distal ends. However, the differences in anatomical characteristics between the atrium and ventricle should also be considered. There were 8 cases of the Aveir Atrial LP retrieval in the i2i study, which occurred on the day of implantation for 1 case and after the day of implantation for 7 cases. The Aveir Atrial LP was retrieved on the day of implantation due to dislodgement, and after the day of implantation due to dislodgement in 5 cases (19, 38, 46, 63, and 81 days post-implantation), therapy change to CRT in 1 case (109 days post-implantation), and increased threshold in 1 case (154 days post-implantation). Retrieval was successful in all of the 8 cases. In 6 of them, the Aveir Atrial LP was retrieved due to dislodgement. There was limited experience with retrieval of the implanted Aveir Atrial LP, 2 cases (109 and 154 days post-implantation). Its retrieval performance is unknown after tissue adhesion increases over time.

Based on the above, the Aveir Atrial LP requires the same cautions as those for the Aveir Ventricular LP, and the applicant should provide the following information appropriately through training, etc. and collect detailed information about each case of retrieval in the use-results survey described later: The details of the Aveir Atrial LP retrieval cases in the i2i study; the higher risk of myocardial injury during retrieval of the Aveir Atrial LP because of the thinner tissue of the atrium than the ventricle; and the limited availability of data on retrieval of the Aveir Atrial LP and no availability of long-term data.

6.B.(5).6) i2i communication-related malfunctions

The following i2i communication-related malfunctions (term of the malfunction, "i2i communication problem") were reported in the i2i study:

- A total of 178 events in 26.3% (79 of 300) of subjects by 3 months post-implantation in the overseas pivotal cohort
- A total of 186 events in 28.7% (86 of 300) of subjects by 6 months post-implantation in the overseas pivotal cohort
- One event in 4.2% (1 of 24) of subjects by 3 months post-implantation in the Japanese cohort
- One event in 3.8% (1 of 26) of subjects by 6 months post-implantation in the overseas upgrade cohort

PMDA asked the applicant to explain reasons for these malfunctions and measures to address those problems since i2i communication is the function responsible for AV synchrony of the Aveir LP.

The applicant's explanation about i2i communication settings, safety mechanisms, and the definition of malfunctions, as well as the results of causal analyses and measures to address the problems:
These malfunctions were clinically acceptable.

Settings of i2i communication

The condition of i2i communication is assessed by checking the i2i throughput via the programmer.

When the i2i throughput is assessed as insufficient, it can be improved by increasing the i2i setting level, which adjusts the pulse strength for i2i communication of the sending side and the sensitivity of the receiving side to control communication strength on a 7-point scale. The higher i2i setting levels consume more battery (the level 7 consumes battery faster by approximately 40% than the level 4 [nominal]). In addition, when the i2i setting level is unnecessarily high, the receiving LP may not be able to identify signals as i2i signals. For these reasons, the i2i setting level needs to be adjusted for each patient.

Safety mechanisms against poor i2i communication

The safety mechanisms against poor i2i communication are roughly classified into the following 2 categories:

- Mechanism for keeping a mode for a certain time period after mode change
  When the prespecified number (nominal, [redacted]) of communications errors occur due to external noise, etc., noise reversion is activated during [redacted] cardiac cycles (to stop i2i communication and switches to the single chamber pacing mode with the Aveir Ventricular LP).
- Mechanism for switching back to the original mode once i2i communication is successful
  Choice in mode switching has been predetermined based on the original mode, the direction of i2i communication (Atrial LP to Ventricular LP, Ventricular LP to Atrial LP, or bidirectional), and the number of communication errors. The original mode is restored once i2i communication is successful.

Definition of the malfunction term "i2i communication problem"

The malfunction of "i2i communication problem" was defined as unexpected i2i communication-related activities or less-than-expected i2i throughput. The i2i communication system is the Aveir LP-specific

new technology. The appropriate reference value of i2i throughput remains unclear, and no specific reference value for “unexpected” or “less-than-expected” throughput has been established. This particular malfunction was investigated to collect extensive information about possible i2i communication-related malfunctions as felt by surgeons. When poor i2i communication led to a mode or system change in the study, it was separately reported as the adverse event of “intermittent or complete loss of i2i communication.”

Occurrence of intermittent or complete loss of i2i communication

Intermittent or complete loss of i2i communication occurred as an SADE in 1 subject and as ADEs in 12 subjects by 6 months post-implantation in the overseas pivotal cohort, and as an ADE in 1 subject by 6 months post-implantation in the overseas upgrade cohort. This event was not reported by 3 months post-implantation in the Japanese cohort.

For SADE in the overseas pivotal cohort, 1 subject had poor i2i communication at the 1-month follow-up visit, which led to a change to the single chamber mode. The subject experienced bradycardia 3 days later and the Aveir Ventricular LP was exchanged with a new one with the intention to improve i2i communication at approximately 3 months post-implantation. This case was reported as a serious event. The Aveir Ventricular LP was exchanged without complications. After the LP exchange, the dual chamber mode was used.

For ADE in the overseas pivotal cohort, 12 subjects had poor i2i communication by the 3-month follow-up visit, which prevented the use of the dual chamber mode. The mode could be changed to the dual chamber mode at 3-month follow-up visit in all of these subjects, and these cases were reported as non-serious event. One subject in the overseas upgrade cohort had the ADE of poor i2i communication, which prevented the use of the dual chamber mode, and continued the treatment in the single chamber mode.

Causes and measures to be taken for poor i2i communication

Causes and measures to be taken for poor i2i communication are as follows:

Cause 1

Noises are more easily mistaken as i2i signals because of the software.

Measure 1

The software was updated during the subject enrollment period for the overseas pivotal cohort.

Prior to the study, the frequency of noise reversion was not included in the endpoints. After this measure was taken, this variable was collected whenever possible for investigation. The mean frequency of noise reversion up to approximately 1 month post-implantation was 15,565 times (18 subjects) in the group without the software update and 70 times (29 subjects) in the group with the software update, showing a substantial improvement.

Cause 2

The i2i study demonstrated that good i2i communication could be established by maintaining a certain relative angle or distance between the implantation sites of the Aveir Atrial LP and the Aveir Ventricular LP. More specifically, the data suggested that subjects with a relative angle between the LPs of <40° or a distance between the proximal ends of both LPs of less than 2 Aveir Ventricular LPs (approximately 70 mm) on the right anterior oblique position (RAO) 30° view were more likely to reduce an i2i throughput of <70% (● in the graph) (Figure 6).

Measure 2

Controlling the distance between the LPs is easier than controlling their relative angle during the implantation. It is recommended that the LPs be implanted so that the distance between their proximal ends is less than 2 Aveir Ventricular LPs (approximately 70 mm).

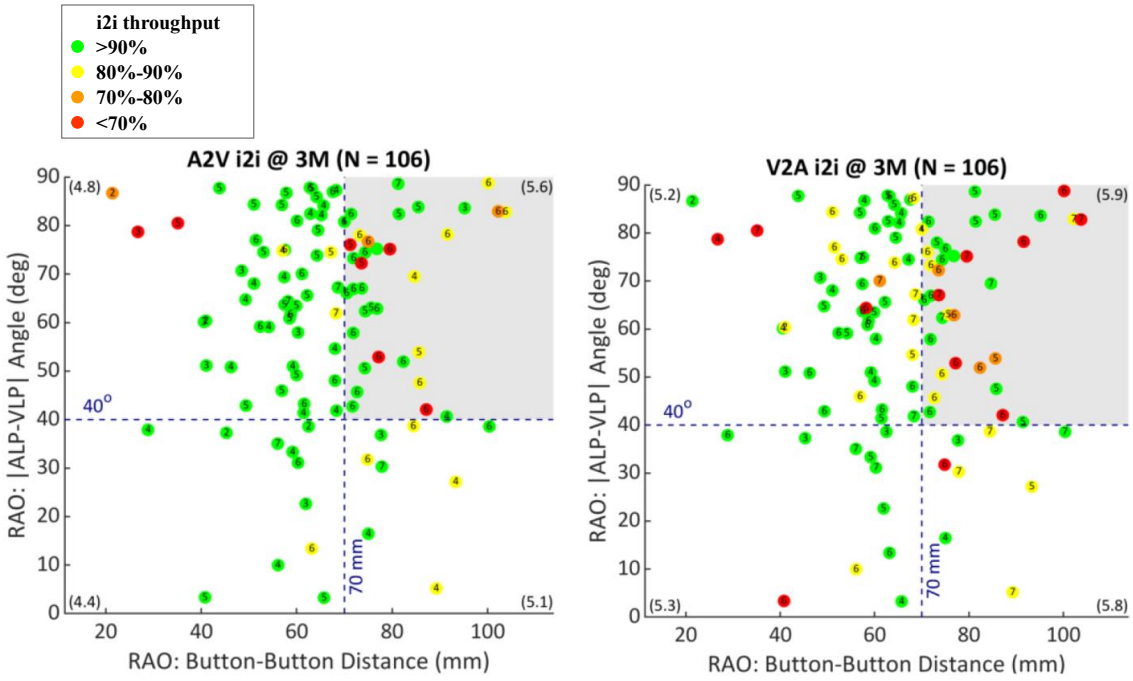


Figure 6. Distribution of i2i throughput at 3 months post-implantation versus the relative angle (vertical axis) and distance (horizontal axis) between the Aveir Ventricular LP and the Aveir Atrial LP (Left graph, i2i communication from the atrium to the ventricle; Right graph, i2i communication from the ventricle to the atrium)

* The numbers in dots represent i2i setting levels (1-7).

Cause 3

The i2i study demonstrated that i2i communication could improve over time (Figure 7).

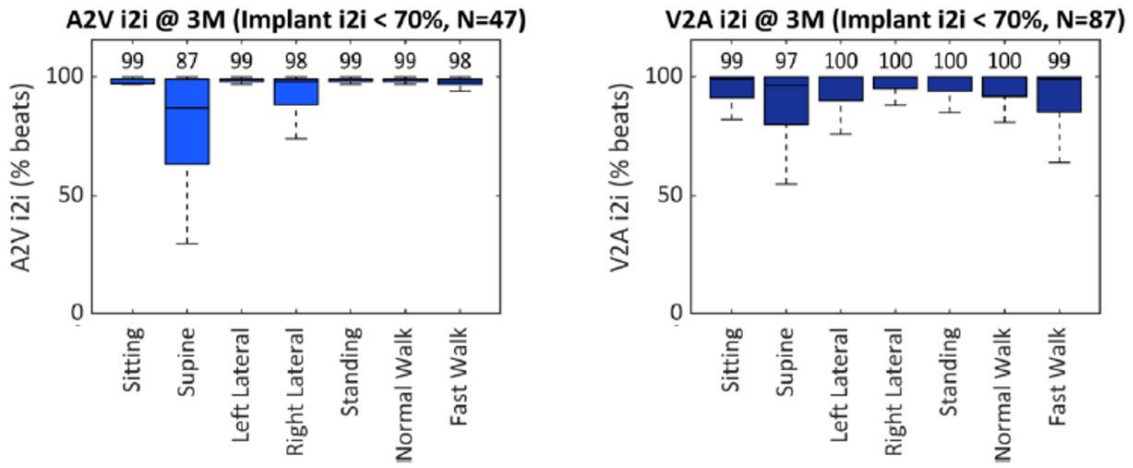


Figure 7. i2i throughput (%) for each body position at 3 months post-implantation in subjects with a peri-implantation i2i throughput of <70%
(Left graph, i2i communication from the atrium to the ventricle; Right graph, i2i communication from the ventricle to the atrium)

Measure 3

With the expectation that i2i throughput will improve with time, surgeons will be advised to complete the procedure even when the peri-implantation i2i throughput is low. This will reduce the risk of damage to the Aveir LP or myocardial injury during the re-implantation procedure. The following factors likely contribute to the mechanism of overtime improvement:

- The throughput has been shown to be lowest in a supine position, and thus low throughput is expected in the acute phase, i.e., during the procedure or hospitalization.
- Interactions between the tissue and the Aveir LP on the boundary surface (e.g., the formation of fibrous scar tissue or the shrinkage of the tissue surrounding the LP in the healing phase from 4 to 6 weeks post-implantation) may contribute to the overtime improvement.

Reason that the "i2i communication problems" reported in the i2i study were considered clinically acceptable

As described above, the device transiently switches to non-AV synchrony mode during transient poor i2i communication so that the ventricular pacing is maintained. The device then switches back to the original mode once i2i communication is successful. In the study, 96% of the cases of i2i communication loss resolved in a short time period (<6 seconds). This likely explains the results in the i2i study, i.e., the sitting/resting AV synchrony success rate at 3 months post-implantation (primary efficacy endpoint 2) that was as high as 98.2% (272 of 277 subjects) in the overseas pivotal cohort and 95.7% (22 of 23 subjects) in the Japanese cohort.

PMDA's view:

The i2i communication-related malfunctions were expected to occur less commonly in the post-marketing setting than the i2i study for the following reasons:

- The Aveir LP will be introduced to the Japanese market after the above measures are taken.
- A total of 186 malfunctions were reported as "i2i communication problem" in 28.7% (86 of 300) of subjects by 6 months post-implantation in the overseas pivotal cohort. However, no clear criteria were set for reporting "i2i communication problem" so that extensive data would be gathered on

possible malfunctions as judged by individual surgeons. “Intermittent or complete loss of i2i communication,” reported as an adverse event when poor i2i communication led to a mode or system change in the study, occurred in a small number of subjects (13 events, 1 SADE and 12 ADEs).

- The Japanese cohort, which received the Aveir LP therapy after the above measures 1 to 2 were taken, had, by 3 months post-implantation, the malfunction of “i2i communication problem” in 4.2% (1 of 24) of subjects and the adverse event of “intermittent or complete loss of i2i communication” in 0 subjects. Their incidence was less than that in the overseas pivotal cohort, suggesting that measures 1 and 2 improved the i2i communication to a certain extent.
- A total of [redacted] units of Aveir Atrial LPs have been sold outside Japan without any serious malfunctions/adverse events reported.

However, whether it is appropriate to complete the procedure based on the assumption that i2i communication will improve over time, as suggested by the applicant in measure 3, warrants careful discussion for the following reasons;

- This measure is grounded on the presumed mechanisms and limited data.
- The i2i throughputs largely vary in a supine position and during fast walk (“Supine” and “Fast Walk” in Figure 7).
- The AV synchrony success rate (primary efficacy endpoint 2) was assessed in a sitting position but not in a supine position.
- There is no clear standard for i2i throughput necessary in clinical use.

Taking account of comments from the Expert Discussion, PMDA has concluded that the following information should be provided regarding patients who have low peri-implantation i2i throughput after the measures 1 and 2 are taken:

- Although the i2i throughput may improve over time, an originally intended pacing mode may not be used until the i2i throughput improves.
- The i2i throughput can be improved by increasing the i2i setting level, which however shortens the battery life. Switching to a conventional transvenous PM should also be considered depending on the age, medical history, lifestyle, etc. of each patient.
- Patients who have a low i2i throughput at the completion of procedure require more frequent outpatient follow-up than those who do not for i2i setting adjustment.
- Although there is no clear standard for peri-implantation i2i throughput, the information about peri-implantation i2i throughput in the groups with and without “intermittent or complete loss of i2i communication” and i2i setting levels over time is helpful in judging the sufficiency of i2i throughput.
- Despite that the i2i communication is responsible for AV synchrony of the Aveir LP, there is no adequate technical knowledge about it (e.g., unknown mechanism of how i2i throughput improves over time is unclear; the low i2i throughput tendency in a supine position or during fast walk).

6.B.(6) Post-marketing safety measures

The applicant’s explanation about post-marketing safety measures for the Aveir LP:

To introduce the Aveir Atrial LP to Japan, the details of training that should be provided, in addition to the existing training for the Aveir Ventricular LP, are being discussed. When Micra was approved as the Japan first LP, the Japanese Heart Rhythm Society issued requirements for medical institutions and

surgeons to use the LPs,[10] as well as a related statement.[11] The necessity of revising the statement, etc. is being discussed with the Japanese Heart Rhythm Society.

PMDA's view on the post-marketing safety measures of the Aveir LP:
The Aveir Atrial LP has the same basic structure and directions for use as those of the approved Aveir Ventricular LP. Some of the safety measures taken for the Aveir Ventricular LP can be applied for the Aveir Atrial LP. However, this is the Japan first LP intended for implantation in the atrium. As described earlier in Section 6.B.(5), the atrium-specific risks, recommended implantation site, i2i communication-related precautions, battery life, etc. must also be considered. It is essential for physicians to fully understand the characteristics of the Aveir LP and then select eligible patients for the therapy. The Aveir LP should be carefully used by physicians with expert knowledge about arrhythmia treatment after they receive appropriate training on the Aveir Atrial LP at medical institutions responsive to various possible complications.

To this end, taking account of comments from the Expert Discussion, PMDA instructed the applicant to provide information required by PMDA in Section 6.B.(5) through the instructions for use, training, the statement, etc. and collect further information through a use-results survey and post-marketing malfunction reports. The applicant agreed with this. The training should be provided under the supervision of the related academic society, and the contents of the statement, etc. should also be discussed with the related academic society. As proposed, these requirements should be attached as an approval condition.

7. Plan for Post-marketing Surveillance, etc. Stipulated in Paragraph 1 of Article 2 of Ministerial Ordinance on Good Post-marketing Study Practice for Medical Devices

7.A Summary of the data submitted

Table 24 presents a summary of the use-results survey plan (draft) of the Aveir LP.

Table 24. Summary of the use-results survey plan (draft)

Objective	To evaluate the safety and efficacy of the Aveir LP in clinical practice
Target sample size	• Total number of newly enrolled patients: up to 280 Dual chamber (new implantation of both LPs): 194 Aveir Atrial LP alone: up to 50 Upgrade: up to 36 • Number of patients enrolled from the Japanese cohort of the i2i study: up to 24
Planned number of study sites	Up to 15
Survey period	5 years and 6 months (preparation, 9 months; registration, 1 year and 3 months; follow-up, 3 years*; analysis, 6 months)
Key survey item	Serious adverse device effect (SADEs) of the Aveir LP (Aveir Atrial or Ventricular LP) by 3 years post-implantation
Survey items	• Patient characteristics and procedural information • Follow-up information (e.g., electrical parameters including i2i throughput and battery life) and information on system change (e.g., retrieval) • Adverse events, death, and device malfunctions

* From LP implantation until completion of the follow-up period

The applicant's explanation about the rationale for the plan:
The target sample size of 194, who receive the dual chamber therapy (new implantation of both LPs), was determined from the incidence of SADEs by 12 months post-implantation in patients newly

implanted with both LPs from the i2i study (both the overseas pivotal cohort and the Japanese cohort) and the incidence of complications associated with the dual chamber pacemakers in the large-scale clinical research of transvenous PMs, the FOLLOWPACE study.[7] The primary evaluation will use data from the dual chamber (new implantation of both LPs) population. The sample sizes for the sub-populations, up to 50 subjects for the Aveir Atrial LP alone population and up to 36 subjects for the upgrade population, are feasible to be achieved within the registration period. By including these sub-populations, information can be collected from a more variety of patients. In addition, subjects from the Japanese cohort of the i2i study (up to 24 subjects) will be enrolled separately in this survey to collect the long-term results of the Aveir LP therapy in Japanese subjects.

7.B Outline of the review conducted by PMDA

PMDA's view:

It is important to assess the post-marketing safety measures including product training, and the appropriateness of the proposed criteria for eligible patients for this therapy based on the statement by the academic society in the post-marketing use-results survey since there is limited experience with using the Aveir LP in Japan. Additional risk reduction measures should be taken as necessary. The use-results survey plan (draft) proposed by the applicant is reasonable for the following reasons:

- On the basis of the results of the i2i study, the proposed sample size is large enough to detect myocardial injury, which can be caused by the Aveir Ventricular LP as warned by the related academic society multiple times, in at least 1 patient newly enrolled in the dual chamber population (194 patients) with a power of 94%.
- The proposed follow-up period of 3 years is the same as that of the use-results survey of Micra. In addition, the i2i study showed a low incidence of SADEs after 3 months post-implantation. In the i2i study, the mean expected battery life of the Aveir Atrial LP used in the dual chamber mode was 4.7 years at 12 months post-implantation (Table 18, 5.7 years including the implantation period of 12 months) in the overseas pivotal cohort and 4.8 years at 12 months post-implantation (Table 18, 5.8 years including the implantation period of 12 months) in the Japanese cohort. The estimated duration of the follow-up period up to the time of application for the user-results survey is 3 to 4 years and 3 months for newly enrolled patients, and 6 years and 10 months to 7 years and 2 months for patients from the Japanese cohort of the i2i study. On the basis of these findings and estimations, the proposed duration of the follow-up period is long enough to assess the long-term results, including signals of early battery depletion to a certain extent.
- The proposed key survey item is SADEs, which were the primary safety endpoint of the i2i study. Therefore, a tendency in clinical practice can be shown in comparison with the results of the i2i study.
- The other proposed survey items are appropriate to investigate mutual interference with other devices, addition of the Aveir LP or other systems, infection, efficacy (parameters for pacing function), and safety (e.g., malfunctions, adverse events, and battery life) for evaluation of the long-term results of the Aveir Atrial LP from various aspects. In addition, the i2i communication-related malfunctions described earlier in Section 6.B.(5).6) and i2i communication conditions can be assessed in the post-marketing setting. The effect of the measures taken for those problems can also be investigated.

8. Documents Relating to Information on Precautions, etc. Specified in Paragraph 1 of Article 63-2 of the Act on Securing Quality, Efficacy and Safety of Products Including

Pharmaceuticals and Medical Devices, in Relation to Notification Pursuant to the Same Paragraph of the Act

8.A Summary of the data submitted

The applicant submitted the instructions for use (draft) as an attachment in accordance with the Notification titled "Application for Marketing Approval of Medical Devices" (PFSB Notification No. 1120-5, dated November 20, 2014).

8.B Outline of the review conducted by PMDA

On the basis of the conclusion of the Expert Discussion, PMDA concluded that there were no particular problems with the proposed instructions for use, provided that the applicant advises necessary caution.

III. Results of Compliance Assessment Concerning the New Medical Device Application Data and Conclusion Reached by PMDA

PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The medical device application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

IV. Overall Evaluation

The review of the Aveir LP focused primarily on (1) the efficacy and safety of the Aveir LP and (2) careful determination of patient eligibility and the post-marketing safety measures. PMDA has reached the following conclusions, taking account of discussion at the Expert Discussion.

(1) Efficacy and safety of the Aveir LP

PMDA's conclusion:

The i2i study evaluated the efficacy and safety of the Aveir LP in the treatment of bradycardia in patients with DDD mode. The primary efficacy endpoints of "composite success rate based on atrial pacing thresholds and P wave amplitudes at 3 months post-implantation" and "sitting/resting AV synchrony success rate at 3 months post-implantation," as well as the primary safety endpoint of "freedom rate from SADEs at 3 months post-implantation" exceeded the respective predefined performance goals of the overseas pivotal cohort. The Japanese cohort met the predefined performance goal for each primary endpoint, showing the extrapolability of overseas data to Japan. Therefore, it is of clinical significance to provide the Aveir LP as a new treatment option that will benefit patients needing dual chamber or atrial pacing who have been confirmed eligible for the treatment based on full understanding of the device characteristics.

(2) Careful assessment of patient eligibility and post-marketing safety measures

The clinical usefulness of the Aveir LP has been proven in patients who are unsuitable for transvenous PM but eligible for the dual chamber PM or require atrial pacing. Even so, to ensure the use of the Aveir LP in patients in whom a risk-benefit balance will be maintained, patient eligibility for the Aveir LP

must be assessed carefully and comprehensively, taking account of the risk of dislodgement, atrium-specific risks of LP implantation, the number of devices implantable, battery life, limited retrieval experience, as well as the age, characteristics, and life-style of patients, etc. To this end, it is important to comply with the statement that will be released by the related academic society, and this will be mentioned in the approval conditions.

Due to the limited experience with the Aveir LP in Japan and necessary verification of the post-marketing safety measures with the risks specific to the Aveir Atrial LP and the characteristics of i2i communication taken into account, a use-results survey should be conducted to evaluate the outcome of the Aveir LP in clinical use in Japan. Additional risk reduction measures should be taken as necessary. The use-results survey period should be 5 years and 6 months (preparation, 9 months; registration, 1 year and 3 months; follow-up, 3 years; analysis, 6 months).

As a result of the above review, PMDA has concluded that the Aveir LP may be approved for the intended use modified as below, with the following approval conditions.

Intended Use

The Aveir LP is an implantable cardiac pacemaker system with built-in electrodes to be placed in the right ventricle or/and right atrium percutaneously using a catheter. The leadless pacemakers are MRI-conditional, thus MRI scanning is allowed only under specific conditions.

Approval Conditions

1. The applicant is required to work with the related academic society to set qualification criteria for medical institutions and healthcare professionals so as to ensure that the Aveir LP treatment and MRI scanning be performed at medical institutions with assured safety and by healthcare professionals with adequate product knowledge. To this end, appropriate measures including training provision should be taken.
2. The applicant is required to give patients thorough education on the conditions for MRI scanning and establish a sufficient support system to assure safety.

The product is not classified as a biological product or a specified biological product. The product is designated as a medical device subject to a use-results survey. The use-results survey period should be 5 years and 6 months.

PMDA has concluded that the application should be subjected to deliberation by the Committee on Medical Devices and *In-vitro* Diagnostics.

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