EUROPEAN COMMISSION

Expert decision and opinion in the context of the Clinical Evaluation Consultation Procedure (CECP)

Expert panels on medical devices and in vitro diagnostic devices (Expamed)

Contents

Scope of this expert opinion

This scientific opinion reflects the views of independent experts (MDR Article 106) on the clinical evaluation assessment report (CEAR) of the notified body. The advice is provided in the context of the clinical evaluation consultation procedure (CECP), which is an additional element of conformity assessment by notified bodies for specific high-risk devices (MDR Article 54 and Annex IX, Section 5.1).

The notified body is obliged to give due consideration to views expressed in the scientific opinion of the expert panel and in particular in case experts find the level of clinical evidence not sufficient or have serious concerns about the benefit-risk determination, the consistency of the clinical evidence with the intended purpose including the medical indication(s) or with the post-market clinical follow-up (PMCF) plan.

Having considered the expert views, the notified body must, if necessary, advise the manufacturer on possible actions, such as specific restrictions of the intended purpose, limitations on the duration of the certificate validity, specific post-market follow-up (PMCF) studies, adaption of instructions for use or the summary of safety and clinical performance (SSCP) or may impose other restrictions in its conformity assessment report.

In accordance with MDR Annex IX, 5.1.g., the notify body shall provide a full justification where it has not followed the advice of the expert panel in its conformity assessment report.

1. ADMINISTRATIVE INFORMATION

Date of reception of the dossier	19/01/2024
Notified Body number	NB123
Internal CECP dossier #	EMA/EX/0000165655
Medical device type	Dual chamber leadless pacemaker
Intended purpose	To provide bradycardia pacing as a pulse generator with built-in battery and electrodes for implantation in the right ventricle and right atrium.
Risk class / type	☒ class III implantable ☐ class IIb active device intended to administer or remove medicinal products(s)
Screening step: medical field / competence area	Circulatory system

PART 1 - DECISION OF SCREENING EXPERTS: NOTIFICATION OF NB AND COMMISSION REGARDING THE INTENTION TO PROVIDE AN OPINION

1.1. Decision of the screening experts

Table covers all three criteria, intended to support their consistent and conscientious application

Date of decision	14/02/2024
Screening panel decision	
Is there intention to provide a scientific opinion?	☒ **Yes** ☐ **No** ☐ **Insufficient information to reach a conclusion**
In case the information was found insufficient to reach a conclusion: summary of reasons (see MDR Annex IX Section 5.1 point c)	
N/A	
Summary as to why there is intention to provide an opinion	
The device under evaluation is a multi-chamber leadless pacer system that is new to the European market. Parts of the system (i.e. atrial LP stimulation) are very innovative, and it is the first LP designed to be implanted for sensing and pacing in the RA, so there are no other similar comparable devices. Comparative literature and data from competitors also do not mention this indication and traditional pacemakers with electrodes are only partial comparators.	
Summary as to why there is *no* intention to provide an opinion	
N/A	
Any other comments	
N/A	

1.2 Assessment of the three screening criteria

Criterion 1: Novelty of device under assessment and possible clinical / health impact
1.1 Overall degree of novelty
☐ No novelty: Neither device nor clinical procedure is novel ☐ Low level of novelty ☐ Medium level of novelty ☒ High level of novelty
Short description of the novelty, including main dimension(s) of novelty

The device under evaluation is a multi-chamber leadless pacer system new to the European market. It includes the two very novel features mentioned before and in addition, there are other new features such as the use of temperature sensors as activity sensors and new communication methods between the leadless pacer modules and the Link module via skin electrodes and a newly developed telemetry.

Although the current development shows some similarities with the system previously sold by the company regarding screw fixation in the myocardium, this is overall a new development with modifications to the battery system, electrode collation and the insertion and retrieval catheter. The pacemaker's architecture is new in relation to the atrial parts and partially newly developed in relation to the ventricular parts. The RA LP is 32.2 mm long, and the RV LP is 38 mm long. Both have a diameter of 6.5 mm. With a volume of 1.0 cc (RA LP) and 1.1 cc (RV LP) and a weight of 2.1 g and 2.4 g for the RA LP and RV LP.

A part of the entire system is fixed and operated in the cardiac atrium. This positioning is completely new for leadless pacemakers. Atrial and ventricular devices communicate wirelessly. This is a new technology.

The other devices have a different fixation and pacing system and only include univentricular systems. Data is therefore not directly transferable and interpretable in relation to this highly new system. There are currently no comparison products or data for atrial leadless pacemakers. Conventional, electrode-based pacemakers should be used as a comparison cohort here. Due to the significantly different design and risk profile, direct transferability does not appear to exist.

Although other single and multi-chamber systems have been recently been places on the European market, the fixation and application mechanisms as well as the architecture of this device and the investigated risk profile differ.

1.2 Possible negative clinical / health impact resulting from novelty

Estimated* possible clinical and/or health impact related to the novel aspects of the device

* This can entail uncertainty. Not only *known* clinical / health impacts but also *possible* ones (conceivable uncertainties, hazards, risks) should be taken into account but need to be supported by a scientific, clinical or technical reasoning.

☐ No clinical or health impact
☐ Minor clinical or health impact
☒ Moderate clinical or health impact
☐ Major clinical or health impact

Possible major clinical or health impact related to the novel aspects of the device

Leadless pacers are associated with a higher rate of cardiac wall perforations. RV perforations rates of up to 1.6% and tamponades even up to 1% have been described. The screw mechanism used here offers advantages when recovering the system, but it is suspected of presenting a higher risk of injury. In the right atrial wall, which is anatomically much thinner, the potential for injury appears to be higher compared to the right ventricular wall, but on the other hand, the risk of spontaneous dislocations and embolization or those provoked by magnetic fields also appears to be higher. The use of the system, which was deemed 1.5 and 3.0 Tesla MRI-compatible, is subject to strict restrictions and programming recommendations when using magnetic fields and is certified according to ISO/TS 10974 for the assessment of the safety of magnetic resonance imaging for patients with an active implantable medical device.

Initial data from the Leadless II Phase 2 study with a ventricular pacemaker module show cardiac injury-related complications rates of up to 1.9% and vascular access complications of up to 1%. The competitor product shows access-related complications in 0.7-0.75%. In summary, the risk of cardiac tamponade has increased by 18.5% and the risk of access increased by 42.8% for a single RV device. However, this system may include 2 pacemakers (RA and RV) with increased risk of cardiac injury.

Corresponding risks add up to the number of changes necessary during EOS of the system, as these mean complete cardiac re-interventions with complete explantation and reimplantation. Nevertheless, previous concerns regarding the lifetime of the batteries as they existed in the former system provided by the company seem to be removed as the device batteries have been reworked.

Overall, these risk considerations are faced with a complication rate of pocket infections and electrode problems with conventional pacemakers that must be weighed up but are based on the novelty of the system itself and must therefore be assessed in terms of their importance.

Criterion 2: Scientifically valid health concerns leading to significantly adverse changes in the benefit-risk profile of a specific group / category of devices and relating to

a) Component(s)
b) Source material(s)
c) Impact on health in case of failure of the device

2.1 Information received from Secretariat:	☐ Yes ☒ No
2.2 Other information available to experts:	☐ Yes ☒ No

Criterion 3: Significant increase of serious incidents of a specific group / category of devices relevant for the device under assessment ***(if information is available, it will always be provided by the expert panel secretariat)***

3.1 Information received from secretariat?	☐ Yes ☒ No

1.3 Indication of appropriate thematic panel in case opinion is required

Indication of appropriate thematic panel and competence area		
	Expert panels	Medical and scientific/technical competence areas (these may correspond to sub-groups)
☐	**Orthopaedics, traumatology, rehabilitation, rheumatology**	☐ 1. Joint replacements (hip, knee, shoulder) ☐ 2. Spinal devices ☐ 3. Non-articulating devices, rehabilitation
☒	**Circulatory system**	☐ 1. Prosthetic heart valves and devices for heart valve repair ☐ 2. Cardiovascular stents (metallic and bio-resorbable) and vascular prostheses ☒ 3. Active implantable cardiac devices and electrophysiological devices ☐ 4. Structural interventions and new devices (e.g. LAA/PFO occluders, heart failure devices) ☐ 5. Cardiac surgery including extracorporeal membrane oxygenation, cardiopulmonary bypass devices, artificial hearts and left ventricular assist devices
☐	**Neurology**	☐ 1. Central and peripheral nervous system devices ☐ 2. Implants for hearing and vision (sensory recovery) ☐ 3. Neurosurgical devices
☐	**Respiratory, anaesthesiology, intensive care**	☐ Respiratory and anaesthetic devices
☐	**Endocrinology and diabetes**	☐ Endocrinology and diabetes devices
☐	**General and plastic surgery Dentistry**	☐ 1. Surgical implants and general surgery ☐ 2. Plastic surgery and wound care ☐ 3. Maxillofacial surgery & Devices for dentistry e.g. oral surgery, implantology, dental materials etc.
☐	**Obstetrics and gynaecology including reproductive medicine**	☐ Devices for obstetrics and gynaecology
☐	**Gastroenterology and hepatology**	☐ Devices for gastroenterology and hepatology
☐	**Nephrology and urology**	☐ Devices for nephrology and urology
☐	**Ophthalmology**	☐ Devices for ophthalmology

PART 2 – SCIENTIFIC OPINION OF THE THEMATIC EXPERT PANEL/SUB-GROUP

2.1. Information on panel and sub-group

Date of opinion	28/03/2024
Expert panel name	Circulatory System
Sub-group of expert panel (where relevant)	CECP- EMA/EX/0000165655 Group

2.2 Detailed aspects of the opinion as required by MDR Annex IX Section 5.1

Opinion of the expert panel on the specific aspects of the clinical evaluation assessment report of the notified body (CEAR)[1]
1. Overall opinion on the NB's assessment of the manufacturer's clinical evaluation report
This opinion was based on the documents presented to the consultation procedure, namely the Clinical Evaluation Assessment Report (CEAR) prepared by the Notified Body (NB) and the manufacturer's Clinical Evaluation Report (CER). The experts were able to understand how this device was assessed, including how it compares to the predecessor version, how it is to be implanted, for which patients it is intended and how the benefit-risk determination was carried out. Overall, the expert panel confirms a thorough and sufficiently detailed assessment.
2. Opinion on the NB's assessment of the adequacy of the manufacturer's benefit-risk determination
It is the opinion of the panel that the NB and the manufacturer adequately evaluated the qualitative and quantitative aspects of clinical safety. Regarding the safety of the device under evaluation, the rates of certain adverse events (overall complication-free rate (CFR) ≤1-year post-implant, freedom from chronic complications, lead complication-free rate, pocket complication-free rate, all-cause mortality rate) reported for the device under assessment are in line with the rates known from the state-of-the-art (SOTA). The complications of the predecessor device are also included in the analysis of the NB. Modifications to the design of the battery and the docking button resulted in no evidence of component separation or detachment within the LPs in the pivotal study. Besides this, the NB raises concerns regarding specific complication rates, particularly the reported 3.3% incidence of cardiac arrhythmia in the device under assessment compared to the rates reported for the Micra. Mechanically induced premature beats and resulting atrial fibrillation as well as

[1] According to Annex IX Section 5.1 of Regulation (EU) 2017/745 - Assessment procedure for certain class III and class IIb devices.

transient complete atrioventricular block are also known complications of conventional dual-chamber pacemaker implantation. A literature analysis comparing the rates of atrial fibrillation with the implantation of conventional dual-chamber pacemakers and the device under assessment would better categorise the risk. It should be emphasised here that, due to the novelty of the device under assessment, comparisons with other leadless dual-chamber pacemakers are not possible. A comparison is currently only possible with the Micra leadless pacemaker, which, however, does not consist of 2 implants with the potentially increased risk of cardiac arrhythmia events associated with them, but rather consists of only one implant and is intended for a different group of patients with a different indication for pacemaker implantation. The NB addresses this in the CEAR: "however, a direct comparison is challenged by the Micra being a single-chamber device without an atrial lead. Notably, within the Aveir DR system, atrial fibrillation emerged as the predominant periprocedural complication, constituting 3.3% of reported cardiac arrhythmia events.". It remains unclear whether the implantation of the RA LP could continue to be a trigger for arrhythmias in the medium to long term, which could increase the rate of atrial fibrillation and complications. Therefore, attention should be paid to this type of complication in the PMS.

Looking at the intra- and post-procedural device dislodgements, it is noticeable that the rates of patients with these complications in the Aveir DR i2i Study after 3 months were at 1.7% each and that 5 out of 6 and 5 out of 5 were caused by the atrial LPs. This may be related to the fact that the fixation of the RA LP was inadequate or new, the optimal implantation site in the RA has not yet been found or - according to the anatomy of the target site of implantation - the RA LP was fixed in the atrium against gravity and could therefore cause a higher rate of these complications. Even with conventional dual-chamber pacemakers, it is known that the rate of dislodgements is increased due to the anatomy of the atrium compared to the ventricle (there is a rate of 1.9% for atrial lead dislodgement within 2 months in real-world experience with transvenous pacemakers known). The manufacturer reports in the CER (p 357) an “increased post-procedural atrial dislodgment observed in the ongoing study as an unanticipated adverse device event (UADE) because the arterial dislodgement rate reached 2.5% in all atrial implanted patients (including patients with an already implanted Aveir RV LP, upgraded to leadless dual-chamber pacing), which was above the anticipated dislodgement rate of 1-2%. An investigation concluded that the initial dislodgement rate was most likely underestimated at the beginning of the phase and that additional training on the implantation site can reduce the rate of dislodgment incidences.“ Thus, despite the novelty of the device, special attention should be paid to further RA LP dislodgement during training and in the PMS.

In the Aveir DR i2i study, after 3 months it was found that the mean atrial pacing capture threshold (at 0.4 msec) was 0.82±0.70 V (during implantation 2.57 ± 1.56 V), and the mean P-wave amplitude was 3.58±1.88 mV (during implant 1.95 ± 1.17 mV). In addition, the CEAR of the NB stated that “with respect to threshold elevation, a serious adverse events (SADEs) rate of 0.7% at 6 months was reported in the Aveir DR i2i study, which is approximately twice the rate reported in single chamber studies, but within the expected range." The PMS should therefore also focus on the electrical measurements of the RA LP, in particular the capture threshold.

When comparing SADEs rates in the Micra pivotal study versus this device at 12 months, Micra had a rate of 4% and the latter a rate of 12%. In the CEAR, the NB also addresses possible differences between the studies, including the definition of SADE (as atrial fibrillation is not considered a SADE in all the studies) and the complication rates due to the presence of two implants instead of one. However, the complication rate of this device could still be compatible with the SOTA for leadless

pacemakers (as the SADEs rate for a mixed Nanostim/Micra population can be as high as 16%[2]). This Expert Panel understands this reasoning but recommends further consideration in the context of the PMS.

In addition to potential risks, the device under assessment also has potential benefits. These include the possible expansion of patient groups that could benefit from the additional RA LP of a leadless dual-chamber pacemaker compared to leadless single-chamber pacemaker, namely patients with sick sinus syndrome who require frequent atrial pacemaker stimulation. 63.3% of patients in the Aveir DR i2i Study had sinus node dysfunction as the primary pacemaker indication. A positive effect on AV synchrony outcome was also demonstrated for patients with AV nodal disease in the device under assessment due to the additional presence of an RA LP and communication with the RV LP using the newly developed i2i communication. A superiority of the AV synchrony compared to the Micra was demonstrated.

One of the feared SADEs is the occurrence of pericardial effusion. It is noteworthy that, apart from 2 implants, the incidence of pericardial effusion was lower for the device under assessment (0.7%) than for the Micra with only one implant in the Micra TPS Study (1.6%).

The retrieval of already implanted leadless pacemakers can also be important for patients during their disease. While the manufacturer of the Micra system does not offer its own retrieval tool and refers to commercially available partially off-label components for retrieval, a specially designed retrieval tool is now available for the device under assessment, which has successfully confirmed retrieval without harm to patients. This additional tool for the device under assessment can be seen as an advantage for patients.

3. Opinion on the NB's assessment of the consistency of the manufacturer's clinical evidence with the intended purpose, including medical indication(s)

This Expert Panel agrees with the NB that the clinical evidence submitted by the manufacturer matches the medical indications claimed for the device "to provide bradycardia pacing as a pulse generator with built-in battery and electrodes for implantation in the right ventricle and right atrium. The LP is intended to provide sensing of intrinsic cardiac signals and delivery of cardiac pacing therapy within the implanted chamber for the target treatment group. The LP is also intended to operate optionally with another co-implanted LP to provide dual-chamber pacing therapy".

The conclusions of the NB on the manufacturer's clinical evidence summarised in section H of the CEAR on the consistency of the data with the intended purpose and medical indications can be followed.

4. Opinion on the NB's assessment of the consistency of the manufacturer's clinical evidence with the PMCF plan

The clinical evidence presented is consistent with the PMCF plan. This Expert Panel agrees with the conclusions and recommendations of the NB. The clinical outcomes beyond 12 months of follow-up are still unknown and should be assessed with the long-term clinical data from the Aveir DR Real-World Evidence Study.

Specific topics of concern to be followed in the PMS were mentioned in previous sections.

[2] Vaidya *et al*. Real-world experience with leadless cardiac pacing. PACE. Mar 2019.

2.3 Summary of expert panel opinion

The system to be assessed is the first leadless dual-chamber pacemaker for which CE approval is being sought. In contrast, conventional dual-chamber pacemaker systems have existed for several decades. They consist of an impulse generator and two leads. In the past, the existence, length, size, and type of implantation of conventional dual-chamber pacemaker systems resulted in limitations and risks for patients that could potentially be partially overcome by a leadless dual-chamber pacemaker system. The leadless dual-chamber pacemaker system combines the functionality of the impulse generator and the leads of the conventional system by also monitoring the intrinsic cardiac rhythm and electrically stimulating the heart as required. In contrast to conventional pacemaker systems, the implantation of leadless dual-chamber pacemaker systems is carried out via a venous access in the groin. The leadless implants are inserted directly into the heart cavities, fixed in place and - with few exceptions - should remain there in the future. The type of implantation, repositioning and removal of the leadless pacemaker as well as the hardware and software of the implant for the right ventricle (RV), including insertion set, delivery catheter and fixation in the heart essentially correspond to the already CE-marked leadless single-chamber pacemaker from the same manufacturer. For this reason, the NB agrees with the equivalence claimed for the RV implant.

Compared to the leadless single-chamber pacemaker already CE-marked, the leadless dual-chamber pacemaker system to be assessed here consists of not one, but two small leadless implants, namely an implant for the RV and a slightly smaller implant for the right atrium (RA) and the required communication technology implemented with the LP in the RV when the system is used as a dual-chamber pacemaker.

The existence of two leadless implants results in extended target patients compared to the leadless single-chamber pacemaker. In these patients, in addition to the detection of intrinsic cardiac rhythm and the stimulation of electrical impulses in the RV, detection and stimulation can also take place in the RA as required, so that in addition to patients with significant bradycardia and normal sinus rhythm with only rare episodes of AV block or sinus arrest or chronic atrial fibrillation, patients with sick sinus syndrome can now also be treated.

Until now, these extended target patients could only be treated with conventional dual-chamber pacemaker systems. In addition, the leadless dual-chamber pacemaker system to be assessed here can avoid accompanying complications due to the different implantation technique compared to the conventional dual-chamber pacemaker system.

However, the risks of the leadless dual-chamber pacemaker system also need to be assessed. These relate to the design, the structure, the implantation technique and the communication technology of the two implants.

This Expert Panel confirms a thorough, adequate, and sufficiently detailed NB's assessment, including the qualitative and quantitative aspects of clinical safety and that the clinical evidence submitted by the manufacturer matches the intended purpose.

This Expert Panel agrees with the NB that the clinical evidence submitted by the manufacturer is consistent with the PMCF plan, provided that the safety and performance threshold values and acceptance criteria are constantly reviewed during the PMCF activities.

2.4 Recommendations

From the data presented, it can be concluded that the rate of SADEs with the occurrence of atrial fibrillation, dislodgement and threshold elevation of the RA LP of the device under assessment may be higher than the comparison group (albeit it could still be within the expected range). Therefore, this Expert Panel recommends special consideration in the context of the PMS.

2.5 Stakeholder information, where available

Relevant information provided by stakeholders, if applicable[3]
Has the Secretariat provided information from stakeholders?
☐ Yes ☒ No
Summary of the information that was taken into account and how it was taken into account.
Not applicable.

2.6 Divergent positions in case no consensus was reached

Please indicate how many of the experts of the panel or sub-group had divergent views
Zero experts.
Summary of divergent positions
Not applicable.

[3] According to Article 106.4 of Regulation (EU) 2017/745, expert panels shall take into account relevant information provided by stakeholders including patients' organisations and healthcare professionals when preparing their scientific opinions.