

**FDA EXECUTIVE SUMMARY MEMORANDUM**

***General Issues: Leadless Pacemaker Devices***

Prepared for the February 18, 2016 meeting of the  
Circulatory System Devices Advisory Panel  
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## ***I. Introduction***

This is an Executive Summary for the General Issues Panel Meeting on Leadless Pacemaker Devices. This panel is being held for the Committee to discuss and make recommendations on clinical trial, post-approval study (PAS) design, and physician training for leadless cardiac pacemaker device technology. Specifically, the Committee will be asked to make recommendations on generally acceptable acute and chronic profiles of key adverse event rates as well as indications for use for this device type (given availability of other technologies with different adverse event profiles), manufacturer-required training and acceptability of observed learning curves for the new device type, and necessary elements for post-approval study collection.

The Executive Summary provides a discussion of the general history of pacemaker technology, available public clinical data on leadless pacemaker devices, specific considerations made for the development of the pre/post market balance paradigm for this class of devices, and current thinking from the Food and Drug Administration (FDA or “the Agency”) on the known and unknown information. The Panel’s review and discussion of the information will inform the Agency’s recommendations in terms of appropriate post-approval study design and device labeling.

## ***II. General History***

The first pacemaker implant took place in Sweden in 1958. Soon after, the first pacemaker implant in the United States occurred in 1960<sup>1</sup>. Nearly one million people worldwide are implanted with implantable pacemakers each year<sup>2</sup>. Implantable pacemakers are life-sustaining, life-supporting Class III devices. They consist of a power supply and electronics that can provide periodic electrical pulses to stimulate the heart. Often referred to as pulse generators, pacemakers are intended to be used as a substitute for the heart’s intrinsic pacing system to correct cardiac rhythm disorders. They are implanted with leads, or wires, that interact directly with the heart to sense and pace as needed.

A premarket approval application (PMA) or PMA supplement is required to be submitted to FDA for any new or revised pacemaker system and/or lead<sup>3</sup>. The PMA is reviewed by FDA to determine whether there is reasonable assurance of safety and effectiveness of the device. Furthermore, PMAs contain valid scientific evidence, which is evaluated by FDA to determine if the probable benefits of the device outweigh the risks<sup>4</sup>. Historically, FDA has often required extensive pre-clinical and clinical data to be provided in a PMA in order to evaluate the safety and effectiveness of a pacemaker system. Depending on the nature of the new device and its similarities and differences to market-approved technology from the same manufacturer, various types of testing contribute to the overall understanding of device performance. Bench data are used to establish functional acceptability of hardware, software and feature design and manufacturing. Animal data are often necessary to support biocompatibility and durability of new materials. Clinical data are well suited to assess acute and chronic system-level performance including proper functioning at the biological interface (assessment of pacing capture threshold and sensing abilities). Pacemakers vary in system complexity and can have multiple functions as a result of the ability to sense and/or stimulate both the atria and ventricles.

The technology of leadless pacemakers mimics the inherent functionality of conventional, transvenous pacemaker systems, without the need for compatible leads. Leadless pacemakers, as reported in the literature, are currently being studied for VVIR pacing.

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<sup>1</sup> Kenny, T. *The Nuts and Bolts of Cardiac Pacing*. John Wiley & Sons 2008.

<sup>2</sup> Reddy VY, Exner DV, Cantillon DJ, et al. Percutaneous implantation of an entirely intracardiac leadless pacemaker. *N Engl J Med* 2015;373:1125-1135

<sup>3</sup> Section 515(a) of the Federal Food, Drug and Cosmetic Act (FD&C Act)

<sup>4</sup> Section 513(a) of the FD&C Act and 21 CFR 860.7.

### III. Device Description

There are two leadless VVIR pacemaker devices that have been studied and reported in the literature, the Medtronic Micra device and the St. Jude Medical Nanostim device. These devices share common characteristics, as they are both programmable, single-chamber ventricular pacemakers, self-contained in a hermetically sealed capsule<sup>5</sup>. The capsule houses a battery and electronics to operate the system. The tip of the capsule includes a fixation mechanism and monolithic controlled release device (MCRD). The MCRD elutes glucocorticosteroid to reduce acute inflammation at the implantation site. The devices have an estimated longevity of about 7-12 years, depending on the programmed parameters. Both devices have rate-responsive functionality. The absence of a need for a pacemaker pocket and right ventricular (RV) pacing lead are major potential advantages of these devices.

The Medtronic Micra transcatheter pacemaker has a volume of 0.8 cm<sup>3</sup>, a length of 25.9 mm, an outer diameter of 6.7 mm and a weight of 2.0 g. The device utilizes four electrically inactive nitinol tines to attach to the myocardium for fixation. The device is packaged with a steerable catheter delivery system and is implanted via a 23-French introducer through the femoral vein into the right ventricle. The rate-responsive feature is accelerometer-based. The Micra device is compatible with Medtronic's remote monitoring system. The Micra device received Conformité Européenne (CE) Mark on April 14, 2015 based on clinical results from sixty (60) patients implanted with the device for over three (3) months in the Medtronic Micra TPS Global Clinical Trial<sup>6</sup>.

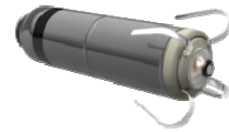


Figure 1: Micra Leadless Pacemaker<sup>7</sup>

The St. Jude Medical Nanostim Leadless Pacemaker measures 4 cm long, 6 mm wide, and 2 g in weight. The device is fixated to the right ventricle using a non-retractable helix; this differs from the tines of the Micra device, but is similar to conventional, transvenous, active-fixation leads. Like the Micra device, the Nanostim device is implanted via a catheter through the femoral vein to the right ventricle, albeit with an 18F introducer. Unlike the Micra device, the rate-responsive feature in the Nanostim device is temperature-based. Remote monitoring is not available for this device. The Nanostim device received CE Mark on August 5, 2013 based on clinical results from thirty-three (33) patients over three (3) months in the LEADLESS study<sup>8</sup>.



Figure 2: Nanostim Leadless Pacemaker<sup>9</sup>

Boston Scientific recently announced its plans to develop a leadless pacemaker to complement its Subcutaneous-Implantable Cardioverter Defibrillator (S-ICD). While details on the technology have not been made publically available, the device will use transcatheter delivery, similar to the Micra and Nanostim devices. In this case, because it is being developed with the S-ICD in mind, "patients who need defibrillators but who also need pacing, or also need anti-tachycardia pacing, [will have a] full, comprehensive option for anti-tachycardia pacing or back up VVI pacing"<sup>10</sup>.

### IV. Comparison of Transvenous and Leadless

Conventional, transvenous pacemaker systems include pulse generators and leads. This well-known technology has matured over the years with well-established, acceptable performance.

<sup>5</sup> Link, MS. Achilles' Lead: Will Pacemakers Break Free? N Engl J Med 2015; 1-2.

<sup>6</sup> Medtronic press release retrieved from <http://newsroom.medtronic.com/phoenix.zhtml?c=251324&p=irol-newsArticle&ID=2034837>

<sup>7</sup> Image retrieved from <http://www.dicardiology.com/content/medtronic-announces-preliminary-outcomes-micra-transcatheter-pacing-system>

<sup>8</sup> Nanostim press release retrieved from <http://www.businesswire.com/news/home/20130510005816/en/Nanostim-Announces-Preliminary-Results-LEADLESS-Study-Late-Breaking>

<sup>9</sup> Image retrieved from <http://www.medicalexpo.com/prod/st-jude-medical/product-70886-569901.html>

<sup>10</sup> Perriello, B. Boston Scientific readies leadless pacer program. MassDevice 2015. Retrieved from: <http://www.massdevice.com/boston-scientific-readies-leadless-pacer-program-0/>

Early performance of transvenous pacemaker systems from implant through 60-90 days has usually demonstrated acceptable pacing capture thresholds and sensing. Intermediate performance from 90 days through more than 5 years has usually demonstrated reliability of the pulse generator and lead technology. As expected, chronic performance from 5 to 10 years includes a predictable decline in battery life and mechanical reliability. However, a vast majority of pacemaker patients receive excellent pacing and sensing free of operative or mechanical reliability failures.

The FOLLOWPACE study was a prospective, multi-center cohort study conducted in Denmark that was intended to assess the “incidence and determinants of short- and long-term complications after first [transvenous] pacemaker implantation for bradycardia”<sup>11</sup>. It should be noted that this study incorporated both single-chamber and dual-chamber transvenous pacemaker implants. The study found that for a total of 1517 patients in 23 Dutch pacemaker centers, 12.4% patients developed any pacemaker complication within two months of implantation and 4.2% developed a complication that required reoperation<sup>12</sup>. This is comprised mostly of the following complications: pneumothorax (2.2%), pocket issues (4.75%), and lead issues (5.5%). The majority of pocket complications were hematomas which were self-limiting. The majority of lead-related issues were due to lead dislodgement which did require reoperation; slightly over half of these were atrial, not ventricular, dislodgements. The complications requiring reoperation included lead dislodgement (3.3%), significant bleeding (0.3%), pocket infection (0.3%), lead insulation problem (0.3%), and discomfort (0.1%).

A meta-analysis of randomized trials comparing dual-chamber to ventricular single-chamber pacemaker implants found a 3.2% rate of implant complications in ventricular single-chamber implants<sup>12</sup>. In Denmark, where all pacemaker implants are recorded in a national registry, two separate studies looking at this national database found a roughly 2.0% incidence of any lead-related complication and 1-2% non-lead complications such as perforation or hematoma (as defined by these studies)<sup>13,14</sup>. It should be noted that FDA considers perforations to be lead-related complications for transvenous devices.

Table 1 below shows the comparison of complication rates for transvenous and leadless pacemakers. As shown in Table 1, there are no pocket complications associated with leadless pacemakers, as a pocket is not required for implantation. Similarly, given that there is no pocket or lead required, there are no reported cases of device-related infections for leadless pacemakers. However, these devices do appear to have a greater rate of RV perforation and tamponade compared to transvenous systems. Furthermore, leadless pacemakers have femoral vascular access complications which are not present with transvenous systems since transvenous systems are not implanted from the femoral vein.

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<sup>11</sup> Udo, EO, Zuithoff, NP, van Hemel, NM, de Cock, CC, Hendriks, T, Doevendans, PA, Moons, KG. Incidence and predictors of short- and long-term complications in pacemaker therapy: the FOLLOWPACE Study. *Heart Rhythm Society* 2012; 9:728-735.

<sup>12</sup> Healey, JS, Toff, WD, Lamas, GA, Andersen, HR, Thorpe, KE, Ellenbogen, KA, Lee, KL, Skene, AM, Schron, EB, Skehan, JD, Goldman, L, Roberts, RS, Camm, AJ, Yusuf, S, Connolly, SJ. Cardiovascular Outcomes with Atrial-Based Pacing Compared with Ventricular Pacing. *Circulation* 2006;114:11-17.

<sup>13</sup> Kirkfeldt, RE, Johansen, JB, Nohr, EA, Moller, M, Arnsbo, P, Nielsen, JC. Risk Factors for lead Complications in Cardiac Pacing: A population based cohort Study of 28,860 Danish patients. *Heart Rhythm* 2011;8:1622-1628

<sup>14</sup> Kirkfeldt, RE, Johansen, JB, Nohr, EA, Jorgensen, OD, Nielsen, JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. *Eur Heart J* 2014;35:1186-1194.

**Table 1: Comparison of Transvenous and Leadless Pacemaker Complication Rates**

Complications	Transvenous Pacemaker Rate* (new implants) <sup>12,15,16</sup>	Leadless Pacemaker Rate <sup>17 18</sup>
<b>Traumatic Complications (all)</b> <ul style="list-style-type: none"> <li>• <b>RV perforation</b></li> <li>• <b>RV perforation with tamponade</b></li> <li>• <b>Pneumo(hemo)thorax</b></li> </ul>	<ul style="list-style-type: none"> <li>• 0.2-0.8%</li> <li>• 0.07-0.4%</li> <li>• 0.7-2.2%</li> </ul>	<ul style="list-style-type: none"> <li>• 1.6%</li> <li>• 1.0%</li> <li>• 0.2%**</li> </ul>
<b>Pocket Complications</b> <ul style="list-style-type: none"> <li>• <b>Including all hematomas, difficult to control bleeding, infection, discomfort, skin erosion</b></li> <li>• <b>Including only those requiring invasive correction or reoperation</b></li> </ul>	<ul style="list-style-type: none"> <li>• 4.75%</li> <li>• 0.66-1.0%</li> </ul>	Not applicable
<b>Lead-related Complications</b> <ul style="list-style-type: none"> <li>• <b>(Including lead fracture, dislodgement, insulation problem, infection, stimulation threshold problem, diaphragm or pocket stimulation, other)</b></li> <li>• <b>Migration with device embolization during implant***</b></li> </ul>	<ul style="list-style-type: none"> <li>• 1.6%-3.8%</li> <li>• Not applicable****</li> </ul>	<ul style="list-style-type: none"> <li>• 0-1.1% (dislodgements only)</li> <li>• 0-0.4%</li> </ul>
<b>All system related infections requiring reoperation or extraction</b>	<ul style="list-style-type: none"> <li>• 0.5-0.73%</li> </ul>	<ul style="list-style-type: none"> <li>• 0%</li> </ul>
<b>Femoral vascular access issues (requiring intervention)</b> <ul style="list-style-type: none"> <li>• <b>AV fistula or Pseudoaneurym</b></li> <li>• <b>Excessive Bleeding</b></li> </ul>	Not applicable	<ul style="list-style-type: none"> <li>• 0.6-0.7%</li> <li>• 0.4%</li> </ul>

\*Rates are for ventricular single chamber devices when data were available. Some rates listed in this column are for single and dual chamber devices when data were not separated in the publication.

\*\*This was caused by peri-procedural resuscitation and not directly device-related.

\*\*\*Acute migration occurs when the device becomes unattached from the RV and has migrated outside of the heart and needs to be retrieved

<sup>15</sup> Kirkfeldt, RE, Johansen, JB, Nohr, EA, Moller, M, Arnsbo, P, Nielsen, JC. Risk Factors for lead Complications in Cardiac Pacing: A population based cohort Study of 28,860 Danish patients. Heart Rhythm 2011;8:1622-1628

<sup>16</sup> Kirkfeldt, RE, Johansen, JB, Nohr, EA, Jorgensen, OD, Nielsen, JC. Complications after cardiac implantable electronic device implantations: an analysis of a complete, nationwide cohort in Denmark. Eur Heart J 2014;35:1186-1194.

<sup>17</sup> Reddy VY, Exner DV, Cantillon DJ, et al. Percutaneous implantation of an entirely intracardiac leadless pacemaker. N Engl J Med 2015;373:1125-1135

<sup>18</sup> Reynolds, D, Duray GZ, Omar R, Soejima K, Neuzil P, Zhang S, Narasimhan C, Steinwender C, Brugada J, Lloyd M, Roberts PR, Sagi V, Hummel J, Bongiorno MG, Knops RE, Ellis CR, Gornick CC, Bernabei MA, Laager V, Stromberg K, Williams ER, Hudnall JH, Ritter P. A Leadless Intracardiac Transcatheter Pacing System. N Engl J Med 2015.

\*\*\*\*In a transvenous system, leads can become dislodged but cannot migrate outside of the heart since they are tethered at the pocket

Regarding chronic complications, transvenous leads are often viewed as the “Achilles’ heel” of a conventional pacemaker system, as they tend to deteriorate over time and “necessitate ... risky removal and replacement”<sup>19</sup>. According to Gold, MR, “there are ~65,000 lead failures annually in the more than 4 million implanted systems worldwide”<sup>20</sup>.

Clinical data has not revealed similar chronic outcomes for leadless pacemaker devices, as the devices have not been studied to device end-of-life and little publically available information is available on explantation and co-implantation of additional devices.

## ***V. Pre/Post Market Balance Paradigm for Leadless Pacemakers***

As noted above, lead reliability is extensively analyzed for conventional pacemaker systems as it tends to be one of the key limiting factors for overall performance. Lead reliability is stress (time) dependent and therefore requires many years of study depending on the specific mode of failure. Failures can impact survival and are relatively rare, making it necessary to enroll a large sample of subjects to provide adequate results for a high resolution, single-cause failure study.

FDA’s Total Product Life Cycle (TPLC) device development paradigm evolved in the area of pacing and defibrillation based on a growing understanding that lead performance testing (particularly for complex defibrillator leads) needed to better characterize low rates of clinically important failures. The design requirements for the life-cycle testing of cardiac leads include a total clinical evaluation period of 5 years and a bench evaluation of 10 years (400 million cycles testing). Approval is based on the following:

1. Performance based on substantial overall enrollment, follow-up of an initial cohort through 6-24 months and some leads reaching 1-2 years dwell time.
2. Ability to detect single-cause failure rates as low as 0.4% with 1.0% upper confidence limit at study completion; sample size driven by resolution to detect single failure modes.

One of the Center for Device and Radiological Health’s (CDRH) 2014-2015 strategic priorities<sup>21</sup> challenged regulators and manufacturers to find more efficient ways to complete clinical trials while maintaining an appropriate pre- and post-market balance of data collection. The clinical trial strategy for leadless pacemakers was developed in this light. Common failure modes for pacemaker systems were known and could be applied as needed to the design of leadless pacemaker clinical trials. Therefore, Investigational Device Exemption (IDE) approval for these clinical trials was based on an initial cohort up to approximately 700 subjects, followed for one year. The results from the first 300 patients at six (6) months have been reported in the literature. The primary safety and effectiveness endpoints reflected a complication-free rate and electrical performance evaluation that was comparable to transvenous pacemakers. The overall purpose of this study design was to capture early safety events and effectiveness through a stable, uneventful period (post 30 days to one year), and deferring to post-approval studies for device end-of-life issues.

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<sup>19</sup> Link, MS. Achilles’ Lead: Will Pacemakers Break Free? N Engl J Med 2015.

<sup>20</sup> Gold, MR. Are Leadless Pacemakers a Niche or the Future of Device Therapy? JACC 2015;65:1505-1508. (<http://dx.doi.org/10.1016/j.jacc.2015.02.021>)

<sup>21</sup> CDRH Strategic Priorities retrieved from <http://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cdrh/cdrhvisionandmission/ucm384576.pdf>

## **VI. Leadless Pacemaker Knowledge Base – FDA’s Perspective**

### **A. Acute Performance**

Reddy et al note that from the initial 300-patient cohort for the Nanostim device, successful implantation was above 95%, 30% required repositioning, and two procedure-related deaths occurred<sup>22</sup>. Reynolds et al note that from the initial 300 Micra patients, successful implants are above 99%, 15% required repositioning, and one procedure-related death occurred<sup>23</sup>. Therefore, the acute implantation success rates for leadless pacemakers seem to be quite high. It should be noted that the patients enrolled in the clinical trials tend to be older and frailer with other comorbidities than historical control patients implanted with traditional pacemakers<sup>24</sup>.

Based on publically available clinical data for leadless pacemaker devices, it is known that the overwhelming majority of complications occur within 30 days, most within 14 days. Many of these complications with leadless pacemakers are related to the femoral access site and the implantation/release of the device. Of the femoral access related complications, the more common complications seem to be groin hematomas and access site bleeding. There have also been arteriovenous (AV) fistula and pseudoaneurysm groin complications reported<sup>25</sup>. Regarding the release of the device into the right ventricle, published information on clinical studies has shown that ventricular perforations are the most common problem. Acute perforation rates for the leadless pacemaker trials tend to hover around 1.6%. Table 1 above summarizes the complication rates for leadless pacemaker trials based on publically available data.

### **B. Known Intermediate and Long-term Performance**

After the 30-day post implant window, the adverse event rates become much lower and the interrogation data is quite stable over the subsequent sixth months. Again, Reddy et al note that 93% met the endpoint of R wave >5mV and threshold <2V at six months (first 300 Nanostim patients). Furthermore, Reynolds et al note that 98% met the endpoint of R wave >5mV and threshold <2V at 6 months (first 300 Micra patients).

Human and animal data on the long term histology of leadless pacemakers are currently limited. Kypta et al reported on a case of complete encapsulation of a leadless pacemaker. The patient died after one year of implantation due to respiratory failure caused by pulmonary fibrosis<sup>26</sup>. The autopsy revealed that the device was in place where it had been implanted initially. The device was completely covered by semitransparent tissue and adhered to adjacent papillary muscle. This is a single case study, and while illustrative, may not reflect the actual expected time to encapsulation in all patients.

In an accompanying commentary, Fisher, JD noted that encapsulation may help protect the implant from infection; however, it poses a challenge for device removal<sup>27</sup>. Patients experience different amounts of scar tissue in both traditional pocket implants and leadless devices. This variation among patients makes it difficult to assess its impact on extraction.

A pilot study was completed to assess extraction of leadless devices in 10 sheep<sup>28</sup>. An 18Fr introducer sheath was used to remove the device via the right femoral vein after five (5) months post-implant. Fluoroscopy was utilized to

<sup>22</sup> Reddy VY, Exner DV, Cantillon DJ, et al. Percutaneous implantation of an entirely intracardiac leadless pacemaker. *N Engl J Med* 2015;373:1125-1135

<sup>23</sup> Reynolds, D, Duray GZ, Omar R, Soejima K, Neuzil P, Zhang S, Narasimhan C, Steinwender C, Brugada J, Lloyd M, Roberts PR, Sagi V, Hummel J, Bongioni MG, Knops RE, Ellis CR, Gornick CC, Bernabei MA, Laager V, Stromberg K, Williams ER, Hudnall JH, Ritter P. A Leadless Intracardiac Transcatheter Pacing System. *N Engl J Med* 2015.

<sup>24</sup> Link, MS. Achilles' Lead: Will Pacemakers Break Free? *N Engl J Med* 2015.

<sup>25</sup> Reddy VY, Exner DV, Cantillon DJ, et al. Percutaneous implantation of an entirely intracardiac leadless pacemaker. *N Engl J Med* 2015;373:1125-1135

<sup>26</sup> Kypta A, Blessberger H, Lichtenauer M, Steinwender C. Complete Encapsulation of a leadless cardiac pacemaker. *Clin Res Cardiol* 2015.

<sup>27</sup> Fisher, JD. Leadless Pacemakers: Putting them in and Taking them out. *Pacing and Clinical Electrophysiology* 2015; 38: 1247.

<sup>28</sup> Bongioni MG, Segreti L, Di Cori A, Bonner M, Eggen M, Omdahl P. Retrieval of a Transcatheter Pacemaker in Sheep after a Mid Term Implantation Time. *Heart Rhythm Society* 2015.



guide the extraction and an average time of 2.35 minutes was observed for retrieval. Five of the sheep were implanted with a second leadless device and after six weeks, no embolisms or perforations were observed.

Bonner et al studied extraction of leadless devices in 4 sheep over 18 months<sup>29</sup>. Four different proximal end retrieval/extraction concepts were tested using prototype devices. Prototype extraction tools from Cook Medical were utilized and necroscopy results were analyzed as well. All devices were successfully extracted and encapsulation was observed on the distal portion of the devices.

### **C. Knowledge Gaps – Intermediate and Long-term Performance**

The long term (5 -10 years) safety profile of the leadless devices is currently unknown. FDA is not aware of late device failure rates or late (greater than 2 years) complications. Additionally, long term effectiveness and overall battery longevity in the real-world setting are unknown. FDA is only aware of battery projections based on bench testing which suggest that with projected use of 1.5 volts at a pulse width of 0.24 milliseconds, there should be reasonable battery longevity of 12.5 years<sup>30</sup>. Procedure/device related adverse events may increase once the leadless devices are market-approved and generally available to the public. It is also currently unclear how the leadless devices should be handled at their end-of-life (EOL). As noted above, substantial data on encapsulation, explanation and co-implantation are lacking and FDA is considering best approaches to collect data to determine how best to resolve these key EOL issues.

### ***VII. Post Approval Study (PAS)***

Currently, FDA has been implementing a pacing lead PAS paradigm, which involves studying 1000 patients over five (5) years to detect late failures. This paradigm was implemented since it is common for a patient to require a pulse generator change at the 5-year mark, giving investigators the ability to assess the status of implanted leads at this time point. The current paradigm does not capture data when the lead reaches its end-of-life (EOL), but is expected to capture intermediate and long-term failures that may occur around or after 5 years.

While this paradigm is applicable and beneficial to cardiac leads, FDA envisions the PAS for the leadless pacemaker devices to be used to gain understanding of EOL issues, extraction risks/success rates and risks of co-implantation. In this case, FDA anticipates collection of important safety and/or effectiveness information through completion of post approval studies, to maintain the appropriate pre/post market balance as described above. Examples include whether, how and under which circumstances some implanted devices can be removed.

It may not be possible at the time of approval to fully understand the safety of removing chronic leadless device implants or co-implantation of a second leadless pacemaker or transvenous system; however, it would not be in the best interest of the public health to delay approval and potentially prevent patient access to these devices for this reason. In such circumstances, a notation in the labeling can indicate the limits of current data collection and understanding of these issues, pending completion of post approval data collection. It is expected, therefore, that labeling will be modified over time as a result of a successfully completed PAS.

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<sup>29</sup> Bonner M, Neafus N, Byrd C, Schaerf R, Goode L. Extraction of the Micra Transcatheter Pacemaker System. Heart Rhythm Society 2014 Annual Conference. 2014 May 7-10; San Francisco, California

<sup>30</sup> Reynolds, D, Duray GZ, Omar R, Soejima K, Neuzil P, Zhang S, Narasimhan C, Steinwender C, Brugada J, Lloyd M, Roberts PR, Sagi V, Hummel J, Bongiorni MG, Knops RE, Ellis CR, Gornick CC, Bernabei MA, Laager V, Stromberg K, Williams ER, Hudnall JH, Ritter P. A Leadless Intracardiac Transcatheter Pacing System. N Engl J Med 2015.

## VIII. FDA Questions (draft)

### QUESTION #1

- A. Please discuss the clinical significance and any concerns you might have for the rate of occurrence of each of the following adverse events observed to occur at implant with leadless pacemaker devices as compared to traditional pacemakers.
- Cardiac Perforation
  - Pericardial Effusion
  - Dislodgement
  - Embolization (i.e. acute migration during implant necessitating retrieval)
  - Other events. (e.g. stroke, arrhythmia)
- B. Please identify any subgroups of patients (e.g., based on anatomical characteristics, demographics, etc.) as having an increased risk based on the adverse event rates associated with leadless pacemaker devices.
- C. Please discuss what measures you would recommend to ensure that implanting physicians are adequately trained/informed regarding adverse events and appropriate device and patient selection.

### QUESTION #2

- A. Please comment on how to best collect data for acute performance/ implant experience in the post- approval setting.
- i. Acute performance can be defined as 30 days from implant. Based on current, publically available data, the adverse events most likely to occur within these 30 days are dislodgements and threshold increases. Implant experience can be defined as pre-discharge/24 hours from implant. Based on current, publically available data, the events most likely to occur within these 24 hours include groin complications, hematoma, vascular issues, and perforations. Please indicate which issues you believe should be addressed through collection of post approval data. If there are other issues you believe should be addressed through the collection of postmarket data, please discuss those, as well.
  - ii. FDA would expect sample sizes large enough to provide estimates of adverse events to a specific resolution with confidence intervals (keep in mind the high occurrence of acute adverse events). Please indicate which sample size is appropriate based on the table below.

ODE assumed complication rate	Target CI Width	Minimum Sample Size Needed	Upper limit of the 95% CI
1%	+/- 0.5%	1741	1.6%
1%	+/- 1.0%	497	2.3%
1%	+/- 1.5%	251	3.2%

Please note that if a 5-year adverse event rate of 10% is assumed for a cohort of 1,000 patients, the CI width will be 0.038.

- B. FDA acknowledges that the long-term performance of leadless pacemakers is not well understood at this time. The estimated battery life for these devices is predicted to be anywhere from 6 to 12 years.
- i. Please comment on the types of late device failures you would expect to be important to capture, given the design of leadless pacemakers.

- ii. Based on the current paradigm for post-approval studies for leads, a complication-free rate is used as the endpoint for long-term performance. Please comment on the appropriateness of this endpoint for leadless pacemakers or suggest an alternative endpoint for long term performance of these devices.
  - iii. Please provide recommendations for ways to ensure the completion of a long-term post approval study considering the following:
    - a. the difficulty in implementing such a study;
    - b. patients lost to follow-up over the course of a long study;
    - c. the ability to characterize end of life device failures; and
    - d. the ability to accurately collect device disposition when a new device is placed.
  - iv. Please comment on the ideal duration of follow-up time to assess long term performance of leadless pacemakers.
- C. FDA is interested in collecting data on what clinicians decide to do with devices after they reach end of life (EOL).

FDA foresees four (4) likely scenarios for device EOL:

- Explant Leadless Pacemaker and implant
  - another LP
  - a transvenous pacemaker system
- Turn OFF the existing LP and implant
  - an adjacent LP next to it
  - an adjacent transvenous pacemaker next to it.

FDA expects that physicians may prefer one or two approaches over the others. It should be noted that the LP is expected to be fully encapsulated, which differs from traditional pacemaker/lead systems. FDA expects this aspect of the PAS to be observational. Please comment on the following questions:

- i. Given the observational nature of the Post Approval Study, what criteria should be used to determine the sample size i.e. acceptable rates of occurrence and precision of rates?
- ii. Regarding the scenarios outlined above, what is an appropriate follow-up time to observe for new device interactions with the previously implanted device?
- iii. Please recommend an approach to evaluate device removal/extraction i.e. how often it is attempted, success rates, and complications associated with removal/extraction?

### QUESTION #3

In the absence of data on long term performance and end-of-life options for leadless pacemakers, please comment on content and points to address for appropriate labeling regarding extractions, replacements, and best practices at this time.

### QUESTION #4

The Indications for Use (IFU) statement for single chamber, VVI transvenous pacemakers has historically been similar amongst manufacturers and to the ACC/AHA Pacing Guidelines and HRS/ACCF Expert Consensus Statement on Pacemakers. Currently, the IFU statements for leadless pacemaker devices have not been finalized.

There are some key differences that should be noted amongst the proposed IFU statements for the leadless pacemaker devices and the guidelines; these are outlined below:

- Language that has been proposed includes indicating the device for use in patients who have experienced symptomatic paroxysmal or permanent second- or third-degree AV block, symptomatic bilateral bundle branch block, symptomatic paroxysmal or transient sinus node dysfunction with or without associated AV conduction disorders, or bradycardia-tachycardia syndrome. Additionally, for one or more of the following permanent conditions: syncope, presyncope, fatigue, disorientation due to arrhythmia/bradycardia, or any combination of those symptoms. Ventricular Pacing is indicated for patients with significant bradycardia and normal sinus rhythm with only rare episodes of A-V block or sinus arrest, chronic atrial fibrillation, or severe physical disability.
- The ACC/AHA 2008 Guidelines specifically state that in the case of sinus node dysfunction, single chamber ventricular pacing can be used when maintenance of AV synchrony during pacing is not necessary. They also state that it is a Class I Recommendation (highest recommendation) to implement dual chamber pacing over single chamber ventricular pacing in adult patients with AV block who have documented pacemaker syndrome (symptoms +/- hypotension due to loss of AV synchrony) .
- The HRS/ACCF 2012 Expert Consensus Statement recommends VVI pacing as an alternative to DDD pacing in certain clinical situations such as sedentary patients, those with significant medical comorbidities, and those with technical issues such as vascular access limitations.

With this information in mind, if you were tasked with crafting an IFU statement for a single-chamber, rate responsive ventricular leadless pacemaker, what types of information/language would you consider? Please address the following:

- Should the Leadless Pacemakers be indicated for all patients with symptomatic paroxysmal or permanent second or third degree AV block?
- Should the Leadless Pacemakers be indicated for all patients with paroxysmal or transient sinus node dysfunction?
- Should the Leadless Pacemakers be indicated for all patients with bradycardia-tachycardia syndrome or should it be recommended only if infrequent pacing is expected in a patient with advanced age, sedentary lifestyle, anatomical limitations or based on comorbidities.
- Should the Leadless Pacemakers be contraindicated in patients with pacemaker syndrome?
- If Leadless Pacemakers are reasonable to implant in patients with rare episode of AV block, should "rare" be quantified in some way to minimize the possibility of implanting patients who will later develop pacemaker syndrome?