

Final FDA Discussion Questions

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)
 - Serious groin complications necessitating repair or transfusions
- B. There were certain subgroups that were reported in the published studies as having a possible increased risk of a cardiac perforation during the implant procedure i.e. female patients and patients with a low BMI. Based on the adverse event rates associated with leadless pacemaker devices shown, is there any subgroup you would exclude from receiving this device or that you would specify in the labeling?
- 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

This question will ask the panels' opinion on the structure, size and content of the Post Approval Study (PAS). It is broken down into four sections to address acute 30 day performance, long term performance, device issues at end-of-life (EOL), and device issues when placed next to an abandoned transvenous pacemaker (TV PM) lead.

- 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 which includes both the pre-discharge/24 hours post implant data and the post-discharge to 30 days data. Based on current, publically available data, the adverse events most likely to occur within 24 hours include groin complications, hematoma, vascular issues, and perforations. The events most likely to occur between 24 hours and 30 days include dislodgements and threshold increases.
- Please indicate which acute performance issues you believe should be captured through collection of post approval data. If there are other acute (30 day) issues you believe should be captured 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. This rate usually includes adverse device effects, serious adverse device effects, and complications (which require invasive intervention or lead to death). 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.
 - v. When considering long term performance and potential complications that may occur, does this change the appropriate sample size determined from Part A above?

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- C. FDA is considering 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
 - an ICD (in the event the patient develops an indication for one)
- Turn OFF the existing LP and implant
 - an adjacent LP next to it
 - an adjacent transvenous pacemaker next to it.
 - an adjacent ICD (in the event the patient develops an indication for one)

FDA expects that physicians may prefer one or two approaches over the others. It should be noted that it is suspected that the LP may be fully encapsulated after several years, which differs from traditional pacemaker/lead systems. FDA expects data collection on the EOL device management as part of the PAS to be observational (not hypothesis driven). Please comment on the following questions:

- i. Please discuss the value of collecting data on what clinicians decide to do with devices after they reach EOL. If you believe such data should be collected, please discuss items ii-iv.
- ii. 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?
- iii. Regarding the scenarios outlined above, what is an appropriate follow-up time to observe for new device interactions with the previously implanted device?
- iv. Please recommend an approach to evaluate device removal/extraction i.e. how often it is attempted, success rates, and complications associated with removal/extraction?

D. A physician may choose to implant a leadless pacemaker to replace a transvenous VVIR pacemaker system when a patient has a faulty or non-functional lead. Currently, the FDA is not aware of published literature on mechanical or electrical interactions between a leadless pacemaker and transvenous pacemaker leads. Please discuss if the post-approval study design should incorporate data collection for patients who receive a LP as a replacement for a transvenous system and what type of data should be collected.

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

Given the lack of long term clinical experience with this technology, please discuss your views on the clinical role of this technology in patients currently indicated for conventional transvenous single chamber (VVI) pacemakers. This may include sedentary patients, or those with significant comorbidities or challenges related to vascular access. In your discussion, please specifically address the following clinical subgroups:

- Patients in sinus rhythm with symptomatic paroxysmal or permanent second or third degree AV block
- Patients with paroxysmal or transient sinus node dysfunction
- Patients with tachycardia-bradycardia syndrome
- Patients with pacemaker syndrome
- Patients in sinus rhythm and frequent pacing is not expected
- Patients with carotid sinus syndrome