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Letters

RESEARCH CORRESPONDENCE

Primary Results on Safety and Efficacy From the LEADLESS II–Phase 2 Worldwide Clinical Trial

The first leadless cardiac pacemaker (LP; Nanostim, St. Jude Medical) was introduced in 2013 in international clinical trials (including LEADLESS II-Phase 1) (1), but it was removed from the market because of premature battery depletion. The redesigned LP (Aveir, Abbott) has key design improvements, including the use of standard transvenous pacemaker battery chemistry (lithium carbon-monofluoride) with a 12% longer battery life (1.1 years longer, to 10.4 years), an altered form factor (10% shorter, 1.5-F wider, to 19.5-F), a modified docking button (enabling retrievability), a modified delivery system with an ergonomic design, and a new application-specific integrated circuit (ASIC) chip designed to provide an expandable platform (to later support a dual-chamber pacing system once approved). Here we present the first-in-human experience with this novel, newly designed LP in the LEADLESS II-Phase 2 Investigational Device Exemption study (NCT04559945).

The LEADLESS II-Phase 2 trial is an international, multicenter clinical trial approved by the Food and Drug Administration. After Institutional Review Board approval, patients provided consented before enrollment. The study evaluated the safety and efficacy of the Aveir LP system in patients with standard VVI(R) pacing indications. The primary safety end point was freedom from serious adverse device effects (also referred to as complications) through 6 weeks of follow-up. The primary efficacy end point was a composite score of acceptable pacing thresholds (≤2.0 V at 0.4 ms) and R-wave amplitudes (≥5.0 mV or an equal or greater value at implantation) through 6 weeks of follow-up. An independent Clinical Events Committee adjudicated adverse events. The rates of safety and efficacy end points were compared with performance goals (on the basis of historical data) of 86% and 85%, respectively. All primary end points were analyzed with the use of Clopper-Pearson 2-sided 95% CIs and exact test for binomial proportions. The null hypothesis was to be rejected if the lower 95% CI was greater than the performance goals. The study evaluated a secondary end point of appropriate rate-response pacing during graded exercise testing by using the LP's temperature-based rate response feature. Statistical analyses were performed using SAS software version 9.4 (SAS Institute).

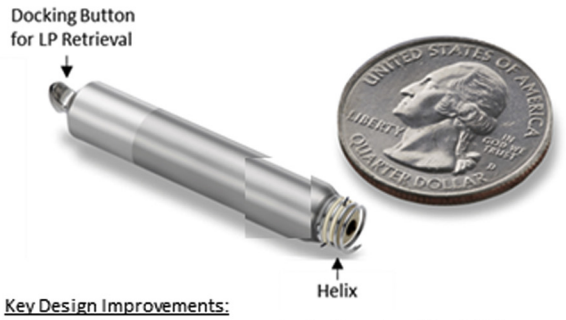
The study enrolled 200 patients across 43 sites in the United States, Canada, and Europe between November 2020 and June 2021, with a mean follow-up of 3.92 ± 1.87 subject-months. The mean age at enrollment was 75.6 ± 11.3 years, and 62.5% of the participants were male. The primary pacemaker indication was atrial fibrillation with atrioventricular block (52.5%). Procedures were typically performed without endotracheal intubation. Implant success was 98% (196 of 200) compared with 96.3% (289 of 300) in phase 1. Of the successful implants, 83.2% (163 of 196) did not require repositioning, compared with 70.2% (354 of 504) in phase 1.

The safety end point analysis was based on 200 enrolled participants with attempted implantation. The primary safety end point was met in 190 of 198 evaluable participants (96.0%; 95% CI: 92.2%-98.2%), of which the lower bound exceeded the performance goal of 86% ($P < 0.0001$). The most frequent complications were 3 cases of cardiac tamponade (1.5%, all during apical positioning, 2 requiring sternotomy) and 3 premature deployments (1.5%). The effectiveness end point analysis cohort included participants with successful implants. Among the 196 participants who underwent successful LP implantation, 188 (95.9%) met the effectiveness criteria (95% CI: 92.1%-98.2%), of which the lower bound exceeded the performance goal of 85% ($P < 0.0001$). Of the 8 participants who did not meet the effectiveness criteria, 4 failed the capture threshold criteria and 4 failed the R-wave amplitude criteria, but none failed both. These safety and effectiveness outcomes were improved over phase 1 results of 93.3% and 93.4%, respectively (**Figures 1A to 1D**).

The secondary end point of appropriate and proportional rate-response pacing during graded

FIGURE 1 Safety and Effectiveness Outcomes

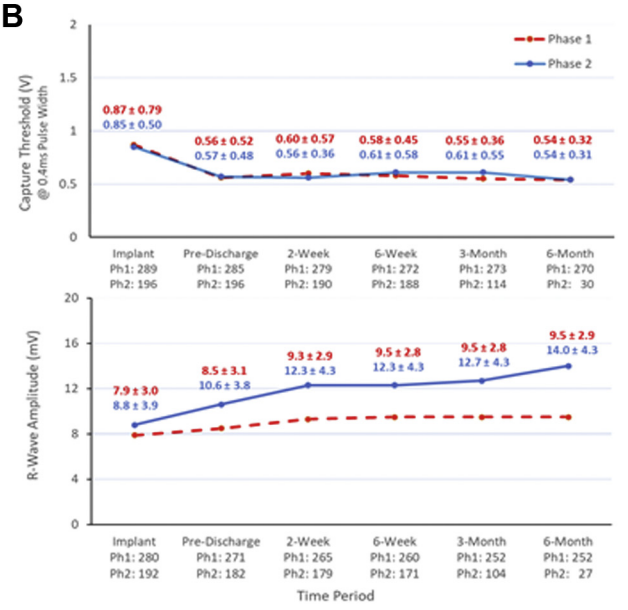
A



Key Design Improvements:

- Standard transvenous pacemaker battery chemistry (Lithium Carbon-Monofluoride, CFx) & 12% improved battery life (1.1 years longer to 10.4 years @ISO standard settings)
- Altered form factor (10% shorter, 1.5Fr wider to 19.5Fr)
- Modified docking button enabling retrievability
- Modified delivery system with an ergonomic design
- Extension length of the active fixation helix is 1.6 mm
- New ASIC chip designed to provide an expandable platform to later support a dual chamber pacing system once approved.

B



C

Procedural Characteristics	Phase 1 Primary Cohort (n = 289)	Phase 2 Primary Cohort (n = 196)
Implant Success - % (no. success/no. attempt)	96% (289/300)	98% (196/200)[1]
Duration of implantation – min		
Total: sheath insertion to removal	50.0 ± 27.3	39.9 ± 21.6
Procedure: insertion of delivery catheter to removal	30.4 ± 18.2	28.7 ± 19.6
Duration of fluoroscopy – min	14.9 ± 9.4	9.4 ± 8.5
Device repositioning – % (no.)		
None	68.9% (199)	83.2% (163)
1	18.3% (53)	13.3% (26)
2	8.3% (24)	2.6% (5)
>2	4.5% (13)	1.0% (2)
Final device position in right ventricle - % (no.)		
Apex	48.4% (140)	3.6% (7)
Apical septum	1.7% (5)	68.4% (134)
Mid septum	NA[2]	28.1% (55)
Outflow, septum, or other	49.8% (144)	0% (0)
Access site closure technique[3]		
Figure-of-8 stitch	NA	82% (160)
Manual pressure	NA	26% (51)
Mechanical compression device	NA	2% (3)
Other (tobacco-pouch suture, Z-stitch, Perclose™)	NA	18% (36)

[1] Of the 4 unsuccessful implants, 3 were due to complications during the procedure (2 cardiac perforations and 1 premature LP deployment), and 1 was due to an inability to access the right ventricle due to patient anatomy.
[2] Phase 1 data collection did not include an option to specify mid septum
[3] More than one closure technique was used in some cases. Data not collected during Phase 1.

D

Event	Phase 1 Primary Cohort (n = 300) No. of Events	No. of Patients	Event Rate, %	Phase 2 Primary Cohort (n = 200) No. of Events	No. of Patients	Event Rate, %
Total	22	20[1]	6.7%	9	8[1]	4.0%
Cardiac perforation/tamponade/pericardial effusion	4	4	1.3%	3	3	1.5%[2]
Premature deployment with device migration	0	0	0.0%	2	2	1.0%[3]
Premature deployment without device migration	0	0	0.0%	1	1	0.5%[4]
Access site bleeding event	2	2	0.7%	1	1	0.5%
Pulmonary embolism	1	1	0.3%	1	1	0.5%
Deep vein thrombosis	0	0	0.0%	1	1	0.5%
Device dislodgement	5	5	1.7%	0	0	0.0%
Threshold elevation resulting in LP retrieval	4	4	1.3%	0	0	0.0%
Arteriovenous fistula	1	1	0.3%	0	0	0.0%
Pseudoaneurysm	1	1	0.3%	0	0	0.0%
Asystole during implant procedure	1	1	0.3%	0	0	0.0%
Ventricular tachycardia or ventricular fibrillation during implant procedure	1	1	0.3%	0	0	0.0%
Pericarditis	1	1	0.3%	0	0	0.0%
Orthostatic hypotension with weakness	1	1	0.3%	0	0	0.0%

[1] Some patients had more than one event, and therefore the number of patients is less than the number of events
[2] All 3 cases resulted in cardiac tamponade of which 1 resolved with drainage and 2 resolved with subsequent sternotomy
[3] In both cases, the device migrated to the left pulmonary artery and was extracted without complication and successfully replaced with another Aveir LP in one case and a transvenous pacemaker in another case
[4] The device did not migrate, as it was fixated, and was electively replaced with another Aveir LP successfully

(A) Aveir leadless pacemaker
(B) Device electrical performance
(C) Implant procedure characteristics
(D) Serious Adverse Device Effects (SADEs)

exercise testing was met. The mean slope of the regression line between normalized workload and normalized sensor-indicated rate across 17 participants was 0.93 ± 0.29, for which the 95% CI (0.78-1.08) was within the required equivalence bounds of 0.65 and 1.35. These results also represent an improved overall rate response compared with phase 1 (0.51 ± 0.18; 95% CI: 0.44-0.58).

These results support the use of the novel LP for right ventricular pacing as an alternative to transvenous pacemakers. Unique aspects of this design include the following: 1) modifications to the delivery catheter, resulting in an improved implant success rate; and 2) contact mapping before LP fixation, resulting in low repositioning rates during implantation compared with phase 1. This single-chamber LP is designed to provide an expandable platform to later support a fully leadless dual-chamber pacing system once approved. Study limitations include an observational, nonrandomized trial design and limited follow-up. A limitation to the technology is the requirement for a 25-F venous introducer sheath; however, large sheaths are increasingly used in cardiovascular procedures. Furthermore, previous studies have established that complications of LP systems occur early and compare favorably with traditional systems in midterm follow-up (2).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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RESEARCH CORRESPONDENCE

Changes in Lead Parameters and Septal Morphology During Left Ventricular Septal Perforation

Preclinical Insights

Inadvertent perforation into the left ventricular (LV) cavity has been reported to occur between 2.1% to 4.9% during left bundle branch area pacing (LBBAP).[1-3] With the increasing adoption of LBBAP, our ability to avoid/detect septal perforation is particularly important because of potential concern for complications. We aimed to evaluate changes in lead parameters by purposefully perforating the pacing lead into the LV cavity during a simulated deep septal implantation procedure in swine. Experiments were approved by the institutional animal care and use committee at the Mount Sinai Medical Center, New York. Right internal jugular venous access was obtained in 3 swine (female, weight 40 to 45 kg), and simulated LBBAP was performed at the basal septum (hereafter referred to as deep septal pacing) using the 3830 pacing lead and sheath (Select Secure and C315HIS, Medtronic). Using described techniques, the pacing lead was advanced gradually until perforation into the LV cavity occurred under fluoroscopic and intracardiac echocardiographic (ICE) guidance. R-wave amplitudes, capture thresholds,