Primary Results on Safety and Efficacy from the *LEADLESS II-Phase 2* Worldwide Clinical Trial

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Condensed Abstract

A re-designed single chamber leadless pacemaker (LP; Aveir) was developed with the goal of improving safety and performance of its predecessor (Nanostim). Herein, we present the first-in-human experience with this novel newly-designed LP in the prospective, single-arm, pivotal LEADLESS II - Phase 2 IDE study. The primary safety and efficacy endpoints were met and improved over the Phase 1 results. These results support the use of the novel LP for right ventricular pacing as an alternative to transvenous pacemakers. This single-chamber ventricular pacer is designed to provide an expandable platform to later support a fully-leadless dual-chamber pacing system once approved.

The first leadless cardiac pacemaker (LP; Nanostim; by St. Jude Medical) was introduced in 2013 in international clinical trials (including *LEADLESS II – Phase 1*) [1], but was removed from the market because of premature battery depletion. The re-designed LP (Aveir; by Abbott) has key design improvements including use of standard transvenous pacemaker battery chemistry (Lithium Carbon-Monofluoride) with 12% longer battery life (1.1 years longer to 10.4 years), altered form factor (10% shorter, 1.5Fr wider to 19.5Fr), modified docking button (enabling retrievability), modified delivery system with an ergonomic design, and a new ASIC chip designed to provide an expandable platform (to later support a dual-chamber pacing system once approved). Herein, we present the first-in-human experience with this novel newly-designed LP in the *LEADLESS II – Phase 2* IDE study.

The LEADLESS II (Phase 2) trial is an international, FDA-approved multicenter clinical trial. After institutional review board approval, patients were consented prior to enrollment. The study evaluated safety and efficacy of the Aveir LP system in patients with standard VVI(R) pacing indications. The primary safety endpoint was freedom from serious adverse device effects (SADEs, also referred to as complications) through 6-weeks of follow-up. The primary efficacy endpoint was a composite score of acceptable pacing thresholds ($\leq$ 2.0 V at 0.4ms) and R-wave amplitudes ($\geq$ 5.0 mV or $\geq$ value at implant) through 6-weeks of follow-up. An independent Clinical Events Committee adjudicated adverse events. The rates of safety and efficacy endpoints were compared with performance goals (based on historical data) of 86% and 85%, respectively. All primary endpoints were analyzed with the use of Clopper-Pearson two-sided 95% confidence intervals and exact test for binomial proportions. The null hypothesis was to be rejected if the lower 95% confidence interval was greater than the performance goals. The study evaluated a secondary endpoint of appropriate rate-response pacing during graded exercise

testing using the LP's temperature-based rate response feature. Statistical analyses were performed using SAS-9.4.

The study enrolled 200 patients across 43 sites in the United States, Canada, and Europe between November 2020 and June 2021, with mean follow-up of 3.92 ± 1.87 subject-months. The mean age at enrollment was 75.6 ± 11.3 years, and 62.5% 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% (196/200) compared to 96.3% (289/300) in Phase 1. Of the successful implants, 83.2% (163/196) did not require repositioning – compared to 70.2% (354/504) in Phase 1.

The safety endpoint analysis was based on 200 enrolled participants with attempted implantation. The primary safety endpoint was met in 190 of 198 evaluable participants (96.0%; 95% confidence interval [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 cardiac tamponades (1.5%, all during apical positioning, 2 requiring sternotomy) and 3 premature deployments (1.5%). The effectiveness endpoint analysis cohort included participants with successful implants. Among the 196 successfully implanted participants, 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, with none failing both. These safety and effectiveness outcomes were improved over Phase 1 results of 93.3% and 93.4%, respectively (Figure 1).

The secondary endpoint of appropriate and proportional rate-response pacing during graded 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 improved overall rate-response compared to Phase 1 (0.51 ± 0.18; 95% CI 0.44 – 0.58).

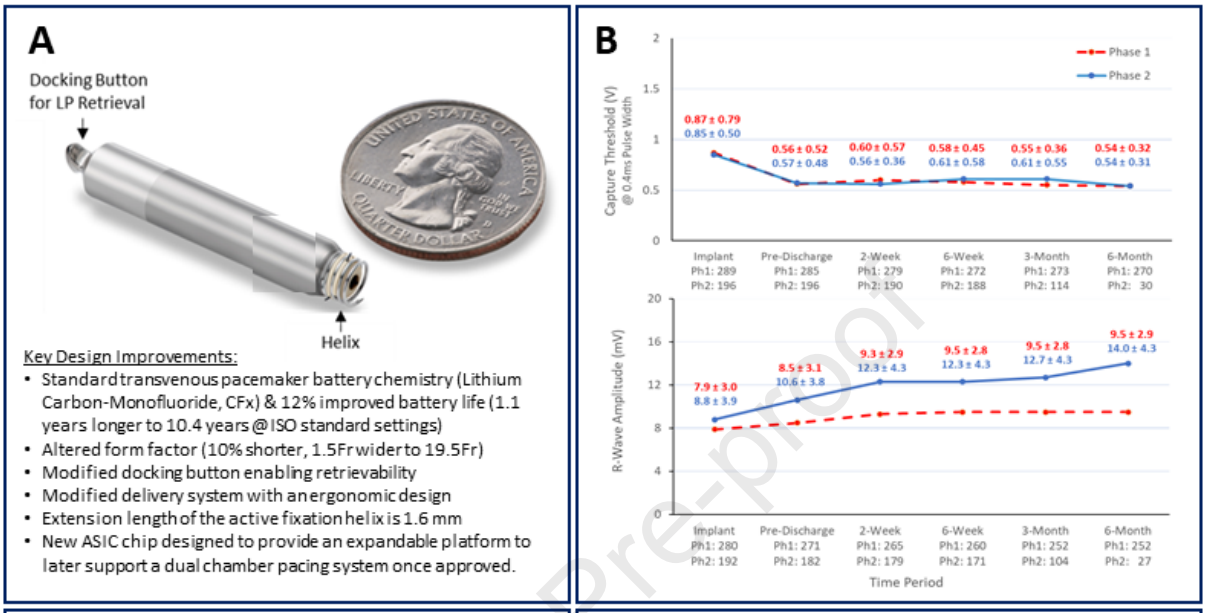
These results support the use of the novel LP for right ventricular pacing as an alternative to transvenous pacemakers. Unique aspects of this design include i) modifications to the delivery catheter—resulting in an improved implant success rate and ii) contact mapping prior to LP fixation—resulting in low repositioning rates during implantation compared to Phase I. 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, non-randomized trial design and limited follow-up. A limitation to the technology is the requirement for a 25-French venous introducer sheath; however, large sheaths are increasingly being used in cardiovascular procedures. Furthermore, prior studies have established that complications with LP systems occur early and compare favorably to traditional systems in mid-term follow-up [2].

References

1. Reddy VY et al. Percutaneous Implantation of an Entirely Intracardiac Leadless Pacemaker. N Engl J Med 2015;373:1125-35.

2. Cantillon DJ et al. Comparative study of acute and mid-term complications with leadless and transvenous cardiac pacemakers. *Heart Rhythm*. 2018;15(7):1023-1030.

Figure 1. Safety and Effectiveness Outcomes



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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.

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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)