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Cardio Catch-Up: Advisory Panel Gives Recor Momentum Toward US Launch Of RDN System

by Reed Miller

The majority of FDA's circulatory systems devices panel agreed that ReCor's Paradise ultrasound renal denervation system offers a safe and effective therapy for patients with hypertension. The panel's endorsement means ReCor will likely be the first company to reach the US market with an RDN system.

ReCor Medical, part of *Otsuka Holdings Co*, appears to have bypassed *Medtronic* in the race to launch the first renal denervation (RDN) system in the US.

RDN is a catheter-based nerve-ablation procedure to attenuate sympathetic nerve activity that contributes to arterial pressure throughout the body. (Also see "*News We're Watching: ReCor And Medtronic Head To RND Panel, Clearances For Anika And Sequel, ZimVie And Brainlab Partner*" - Medtech Insight, 18 Aug, 2023.)

On 22 August, the *US Food and Drug Administration's circulatory system devices panel* reviewed ReCor's premarket approval application (PMA) for its Paradise ultrasound RDN system to treat uncontrolled hypertension. On 23 August, the same panel reviewed Medtronic's PMA for its Symplicity Spyral radiofrequency RDN system. Both devices have a CE Mark and as well as FDA's *breakthrough designation*.

A clear majority of the panel agreed that the benefits of RDN with Paradise outweigh its risks. [See Box Below]

But, the next day, about half of the panelists concluded that the benefits of RDN with Medtronic's Symplicity Spyral are not clear and may not outweigh the procedure's risks. (Also see "*Cardio Catch-Up: Medtronic Still Has Work To Do On RDN After FDA Advisory Panel*" - Medtech

Insight, 30 Aug, 2023.)

For the past decade, most analysts predicted that Symplicity Spyral would be the first RDN system to earn FDA approval to treat uncontrolled hypertension. The outcome of this advisory panel review suggests ReCor is now the favorite to launch the first RDN system in the US.

"We will continue to work closely with the FDA in advance of our anticipated PMA approval and feel confident in the impact that Paradise Ultrasound RDN could have in addressing a significant unmet need," ReCor CEO Lara Barghout said.

Final Advisory Panel Votes

The panel voted 12-0 to agree that Paradise is safe for the intended application.

The panel voted 8 to 3, plus one abstention, to conclude that Paradise is effective at reducing blood pressure in patients with uncontrolled hypertension.

The panel then voted 10-2 in favor of concluding that the benefits of renal denervation with Paradise outweigh its risks.

RADIANCE Review

ReCor's *PMA for Paradise* is based on the results of three sham-controlled clinical trials – *RADIANCE SOLO*, *RADIANCE TRIO*, and *RADIANCE II*.

All three trials met their primary efficacy endpoints, showing that RDN reduces decreases blood pressure in patients with mild to moderate hypertension and hypertension. The trials also easily hit their safety endpoints; the major adverse event rate in all three RADIANCE trials combined was just 1.1%. (Also see "*News We're Watching: Renal Denervation Trial Highlights, TAP Pilot Update, Cardiohelp Safety Alert*" - Medtech Insight, 3 Mar, 2023.)

The *two-month results from 146 patients in RADIANCE-HTN SOLO* showed ultrasound RDN with Paradise reduced daytime ambulatory systolic blood pressure in patients who had stopped taking antihypertensive medications. The blood pressure in the treatment group improved by an average of 8.5mmHg while the improvement in the sham-control group averaged 2.2mmHg.

RADIANCE TRIO evaluated Paradise RDN in patients taking a once-daily, fixed-dose, single-pill combination of a calcium channel blocker, an angiotensin receptor blocker, and a thiazide diuretic. *The two-month results* from that trial showed RDN reduced daytime ambulatory systolic blood by an average of 8 mmHg, compared to 3 mmHG in the sham-control group.

On 22 August, the panel reviewed ReCor's PMA for Paradise ultrasound renal denervation system to reduce blood pressure in patients with hypertension.

RADIANCE II was designed to further study the efficacy and safety of ultrasound RDN in the absence of the potentially confounding influence of antihypertensive medications. (Also see "*Hypertension Experts Push For New Trial Of Renal Denervation To Show Efficacy*" - Medtech Insight, 24 Jul, 2014.)

The patients in RADIANCE II met two criteria to show their hypertension was treatment-resistant: a seated office blood pressure of at least 140/90 mmHG despite taking up to two antihypertensive medications; and, after a four-week "washout" of hypertensive medications, an ambulatory blood pressure between 135/85 mmHg and 170/105 mmHg.

Results from 224 patients in that trial, published in the *Journal of the American Medical Association*, also showed that RDN with Paradise significantly improved patients daytime ambulatory systolic blood pressure; the average improvement in the treatment group was 7.9mmHg and the average improvement in the sham-control group was 1.8 mmHg.

All the panelists agreed that RDN with Paradise is generally safe. Most of the panelists agreed that it is at least modestly effective and that the benefits of the therapy outweigh its risks. But they also suggested that the therapy should probably be reserved for patients who are intolerant of antihypertensive medication or are likely to be noncompliant with an antihypertensive drug regimen.

"[Paradise ultrasound RDN] was effective within the parameters of the study design," said Matthew Corriere, a cardiovascular surgeon at the University of Michigan in Ann Arbor. "But the effect was quite modest and there are very important contextual factors that require a clinical judgment about whether or not to use this device based on the severity of the presentation and what alternatives there are."

Several panelists predicted the benefits of RDN will not be durable past a few months for most patients.

Secondary-endpoint data from the RADIANCE trials included measurements of the patients' total medication burden, as well as their blood pressure, at six and twelve months. In its executive summary of the RADIANCE data, the FDA pointed out that the differences in both medication burden and blood pressure at 12 months were narrower compared to these differences at the two and six-month follow-up points.

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> *benefit for some people." – Robert Yeh*

Keith Allen, the director of surgical research at St Luke's Hospital in Kansas City, concluded that the "marginal" benefit of RDN it is not enough to justify the treatment if this benefit is not durable. "The risk is very low, but the benefit – if there is any – is acute and is not durable."

Although the average benefit of RDN in the RADIANCE trials was small, it was also highly variable. Robert Yeh, a cardiologist and outcomes researcher at Harvard University, suggested that postmarket studies could help define which patients derive the most benefit from RDN.

"We may be underestimating both the magnitude and durability of benefit for some people," he said. "Those are important considerations for postmarket evaluations."

What Is Next For RDN?

Before the panel, Medtronic projected that the FDA could approve Symplicity Spiral in the second half of fiscal 2024, which ends in April 2024.

ReCor did not say when it expects the FDA to approve Paradise. JP Morgan analyst Seiji Wakao predicted the FDA will approve it by the end of 2023, but that it may take the company a while to ramp up its US sales organization. "We think sales contribution and market penetration could take some time, as the company says insurance coverage will take time and this marks the company's first full-scale foray into medical device sales."

> *"Medtronic's ability to develop the RDN market through better-resourced physician education and sales teams could insulate market share in the long term if FDA eventually approves the devices." – Patrick Wood*

Following the advisory panel meeting, some analysts suggested that Medtronic may *never* win FDA approval for Symplicity Spyral, giving ReCor the whole US RDN market for the foreseeable future. However, that is not the consensus view on Wall Street.

“We still see a greater than 50% chance of approval [for Symplicity Spyral] given the strong safety and breakthrough status due to the high unmet clinical need,” Larry Biegelsen wrote following the panel meetings.

Even if Paradise reaches the US market before Symplicity Spyral, Medtronic may be able to catch up quickly, according to Morgan Stanley analyst Patrick Wood.

“ReCor has clearly closed the gap [with Medtronic],” he wrote in a 23 August note. “[But] Medtronic's ability to develop the RDN market through better-resourced physician education and sales teams could insulate market share in the long term if FDA eventually approves the devices.”

Jayson Bedford of Raymond James believes both companies will shift their efforts toward winning the broadest possible indication for their respective RDN systems and then work to convince third-party payers to cover it.

“We think, given the sizable unmet need, that both Medtronic and ReCor receive FDA approval, reflecting the clear safety profile, and mostly positive efficacy,” he wrote. “Labeling and payer reimbursement will be the next critical factors regarding the ultimate benefit/impact.”