24 Hour Summary of the Circulatory System Devices Panel Meeting
August 22, 2023

Introduction:

The Circulatory System Devices Panel of the Medical Device Advisory Committee met on August 22, 2023 to discuss, make recommendations, and vote on the benefit-risk profile of the ReCor Paradise Ultrasound Renal Denervation (uRDN) System, including whether the device demonstrates a reasonable assurance of safety and effectiveness in the treatment of hypertension (HTN) patients with the following indications for use.

The sponsor has proposed the following indications for use:

> The Paradise Ultrasound Renal Denervation System is indicated to reduce blood pressure in patients with uncontrolled hypertension, who may be inadequately responsive to, or who are intolerant to anti-hypertensive medications.

Panel Deliberations/FDA Questions:

QUESTION #1. Acute and midterm procedural and device safety profile.

The panel agreed that the risks are low for ultrasound renal denervation (uRDN) based on the data available from the clinical trials. Procedural risk was concentrated on vascular access complications, and the event rates seemed lower than typically observed for other transfemoral access procedures. The panel believed that the risk of hemodynamically significant renal artery stenosis through 12-months post-procedure was low. They noted that limited long-term safety data are available and that longer term follow-up data would be valuable to identify any safety issues that could emerge at later time points.

***QUESTION #2*. Blood pressure (BP) measurement method.**

The panel concluded that ambulatory blood pressure measurement (ABPM) was preferable to office blood pressure measurement (OBPM), although several panelists indicated that OBPM also provides value. The panel agreed that ABPM was considered the gold standard, has been shown to have greater prognostic value for cardiovascular events and is more accurate. No panelists thought that OBPM alone would be sufficient. Panelists highlighted the importance of collecting 24-hour, daytime and nighttime ABPM because patients with nocturnal HTN are at higher risk for some cardiovascular events, particularly just prior to and after waking. Office BP and home BP (where multiple measurements can be made) would be useful in future clinical studies and post-approval studies.

The panelists noted that results of ambulatory and office, and home BP reduction measurement showed a consistently greater BP reduction from baseline in the uRDN group compared to the Sham group.

QUESTION #3. Magnitude of BP reduction in the clinical trials and relative importance of absolute BP reduction vs between-group difference in BP reduction.

The panelists indicated that the device showed effectiveness in the three randomized trials. In the RADIANCE-II and SOLO trials, there was a statistically and clinically significant 6.3 mmHg mean BP reduction at 2 months in favor of the uRDN group vs. the Sham group. While TRIO showed a 4.5 mmHg between-group difference, the panelists agreed that this reduction was also clinically significant. Panelists noted that patients with less severe HTN may benefit most from uRDN.

The panel agreed that the difference between uRDN and sham groups at 2 months is more important than an absolute reduction from baseline due to placebo effects. Several panelists felt the point estimate limits the ability to see the heterogeneity of treatment and that the distribution of BP reduction (e.g., waterfall plot) and the percentage of subjects in each arm who reached thresholds of BP reductions (e.g., >5 mmHg, >10 mmHg) is also important to consider.

QUESTION #4. Durability of BP reduction.

While the panel agreed that uRDN lowers BP at 2 months, panelists were split on whether the effect persists beyond 2 months. Panelists noted that the studies were not designed to assess durability and the effect of uRDN at later timepoints was challenging to interpret because of the use and escalation of BP medications, unblinding of study subjects to their treatment assignment, and crossover of many Sham subjects to uRDN treatment. Longer-term trial data (i.e., beyond 2 months) showed generally similar BP control between the uRDN group and the Sham group. Panelists felt it was critical to ensure the labeling communicates realistic expectations in terms of blood pressure lowering and the potential need for fewer BP medications. One panelist expressed uncertainty of whether uRDN will be durable due to reinnervation.

The panel expressed some disagreement regarding the clinical significance of the observed benefit. It was noted that approximately 25-30% of patients had a substantial BP reduction at 2 months, which is meaningful, but the gap between the Sham and uRDN group decreased over time. Other panelists observed that the between-group differences at 6- and 12-months were small for both BP reduction and medication burden. While there may be benefit in some patients, it will be important to consider that the number of BP medications were reduced by only a very small margin.

QUESTION #5. Patient Preference Study.

Panelists appreciated the patient preference information for consideration. Panelists noted that some patients were willing to accept the risks of the interventional procedure for a potential reduction in BP. In general, panelists expressed that while patient preference (PP) is important, the PP study provided limited meaningful insight for this device due to the disconnect between the PP study and the clinical trial data.

QUESTION #6. Indications for use statement.

Panelists recommended substantial changes to the proposed indications statement. Panelists emphasized that the indications should reflect that uRDN should be viewed as an adjunct and not an alternative to antihypertensive medications. The indications should avoid the implication that uRDN is more effective than medications or that it is likely to succeed for patients in whom medications are ineffective. The panel

expressed concern that the terms 'uncontrolled' hypertension and 'intolerant' to medication were not defined in the indications and that these populations were not evaluated in the clinical studies. The panel agreed that the indication should reflect patient populations enrolled in the clinical trials,. It was recommended that the indications for use statement identifies the expected magnitude of benefit in some way (e.g., anticipated medication reduction and BP reduction).

QUESTION #7. Labeling and renal artery imaging follow-up.

The panel noted the low incidence of adverse outcomes observed in the imaging in the clinical studies, which limited the need for further imaging follow up. Panelist opinions were mixed on whether post-procedure ultrasound imaging should be specified in the labeling. Overall, the panel recommended against routine computerized tomography (CT) or magnetic resonance angiography (MRA) at 6- or 12-months.

The panel recommended further labeling information on patients excluded from the study and where limited data are available (e.g., for certain sub-populations poorly represented in the study, subjects with eGFR< 60mL/min).

QUESTION #8. Benefit/Risk.

The panel noted that based on available data, the risk profile of uRDN appeared to be low such that a relatively small benefit would support a favorable benefit-risk determination.

Panelists noted that the benefit of uRDN is real, but modest, and is comparable to an additional HTN drug in its impact on BP reduction. The panel emphasized that not all subjects appeared to respond to uRDN but that subgroups of responders were present and could derive meaningful benefit. The panel felt that benefit was clear at the 2-month timepoint, but that substantial uncertainty remained at later time points. Given the Breakthrough Device designation of the Paradise uRDN System and the unmet clinical need, the panel noted that a higher degree of uncertainty could be acceptable if a rigorous PAS is conducted, and if the clinical results and uncertainty are clearly communicated to the clinicians and patients.

QUESTION #9. Post-market study (a) size and endpoints, (b) patient population diversity, (c) design, and renal artery imaging.

a. The panel indicated that the proposed PAS sample size of 500 new subjects may not be adequate and suggested that the PAS sample size be based upon specific study objectives and hypotheses and to capture key subgroups (e.g., African Americans, Hispanic Americans, women, elderly, subjects with diabetes, chronic heart failure, kidney disease).

   The panel agreed that the PAS should evaluate safety in a real-world patient population. Effectiveness may be evaluated by absolute reduction of BP, reaching a pre-specified target (e.g., a 5-20 mmHg reduction or a particular BP goal) and changes in medications. The panel noted that long term outcomes would be important for additional safety and effectiveness, along with identifying particular groups which are responders or non-responders. Additional endpoints to consider were cardiovascular events and patient reported outcomes.

b. The panel noted the under-representation of African-American and Hispanic-American populations in the IDE studies and agreed that the PAS should be designed to target better enrollment of these

groups. Other key subgroups recommended for enrollment were women, the elderly, subjects with diabetes, chronic heart failure, or kidney disease, and those with an eGFR <60 mL/min.

c. The panel believed that a single arm study would be more feasible than a randomized controlled trial, but they were concerned that a single arm study would not be able to answer outstanding questions regarding long-term durability of BP reduction. The panel suggested alternative ways to incorporate a control.

d. The panel generally recommended against protocol-driven imaging and instead monitoring renal function and using it as a trigger for follow-up imaging. Because limited long-term data are available, some panelists recommended that 12-month ultrasound imaging may be appropriate.

Vote:

**Note that the summary below represents the official vote for this Advisory Committee meeting. Two advisory committee members (Drs. Lewis and Nachman) were unable to vote during the meeting, but their votes were recorded afterwards and are included in the official tally.*

Voting Question 1:
Is there reasonable assurance that the ReCor Paradise Ultrasound Renal Denervation System is safe for use in patients who meet the criteria specified in the proposed indication?
The panel voted as follows:

- Yes: 14
- No: 0
- Abstain: 0

Voting Question 2:
Is there reasonable assurance that the ReCor Paradise Ultrasound Renal Denervation System is effective for use in the patients who meet the criteria specified in the proposed indication?
The panel voted as follows:

- Yes: 8
- No: 5
- Abstain: 1

Voting Question 3:
Do the benefits of the ReCor Paradise Ultrasound Renal Denervation System outweigh the risk for use in the patients who meet the criteria specified in the proposed indication?
The panel voted as follows:

- Yes: 10
- No: 4
- Abstain: 0

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Transcripts may be downloaded from:
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