Panel Questions for the Advisory Committee Meeting for the ReCor Paradise uRDN System – August 22, 2023

DISCUSSION QUESTIONS

Safety

1. The primary safety endpoint was a composite of major adverse events (MAEs) through 30 days and new renal artery stenosis RAS through 6 months in uRDN-treated subjects in the RADIANCE-II study. The primary safety event rate was 0% (n = 150; 95% CI 0.0-1.63%), which met the 9.8% pre-specified safety performance goal. The safety event rate for pooled uRDN-treated subjects (initial and crossover) in SOLO, RADIANCE-II, and TRIO was 1.1% (n = 367 subjects; 95% CI 0.3-2.77%). There were 6 events in the pooled analysis, including 2 deaths, 2 major vascular complications (1 pseudoaneurysm, 1 DVT), 1 hypotensive crisis, and 1 hospitalization for major cardiovascular or hemodynamically related event (presyncope).

   There were no clinically significant changes in eGFR or serum creatinine.

   No cases of hemodynamically significant RAS (i.e., a >70% diameter stenosis, DS) were observed in 238 uRDN-treated subjects through the 12-months follow-up with evaluable CTA/MRA imaging. However, there was a 0.8% rate of 51-70% DS, a 2.1% rate of 31-50% DS, and a 1.3% rate of 1-30% DS. Although mild to moderate renal artery narrowing is not associated with a functional reduction in renal blood flow, long-term follow-up data are limited, and it is not clear if renal artery lesions will change over time.

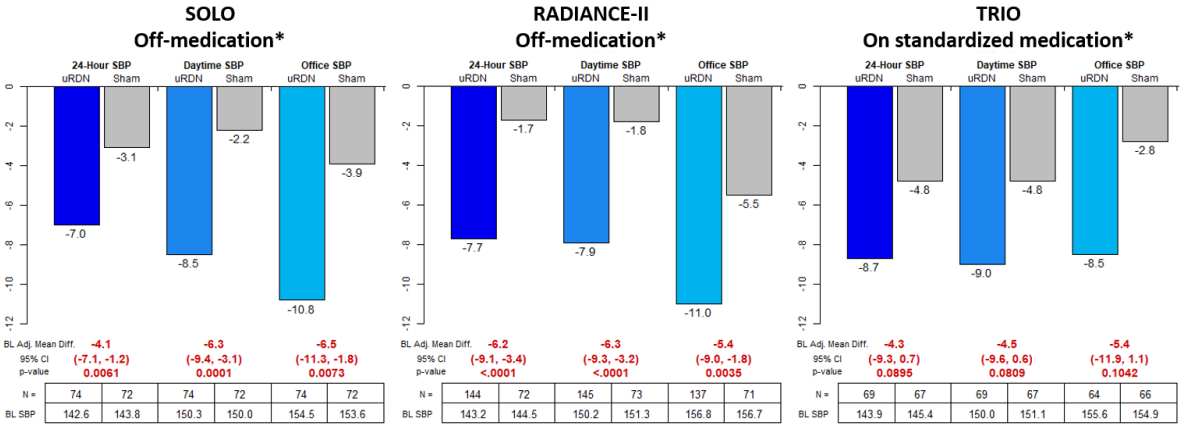
   Please discuss the 30-day procedural and device safety profile of uRDN and the clinical significance of renal arterial responses to uRDN treatment.

Effectiveness

2. *BP Measurement Method*. Data were presented using both ambulatory blood pressure measurement (ABPM) and office blood pressure measurement (OBPM). Most prior hypertension trials have used OBPM. However, ABPM has been shown to have greater prognostic value compared to OBPM and was identified as the preferable method at the 2018 Circulatory System Devices Advisory Panel meeting. This may be due to the large number of measurements made for ABPM that are free from potential confounders (e.g., the white coat effect).

   In SOLO, RADIANCE-II, and TRIO, the results for ambulatory systolic blood pressure (ASBP) and office systolic blood pressure (OSBP) reductions (vs. baseline) at 2 months followed similar trends, with results favoring uRDN over Sham. In SOLO and RADIANCE-II (Figure 1), OSBP reduction was greater than ASBP in both uRDN and Sham groups. In TRIO, the ASBP reduction was comparable to OSBP in the uRDN group. The OSBP reduction was smaller than ASBP in the Sham group.

Figure 1



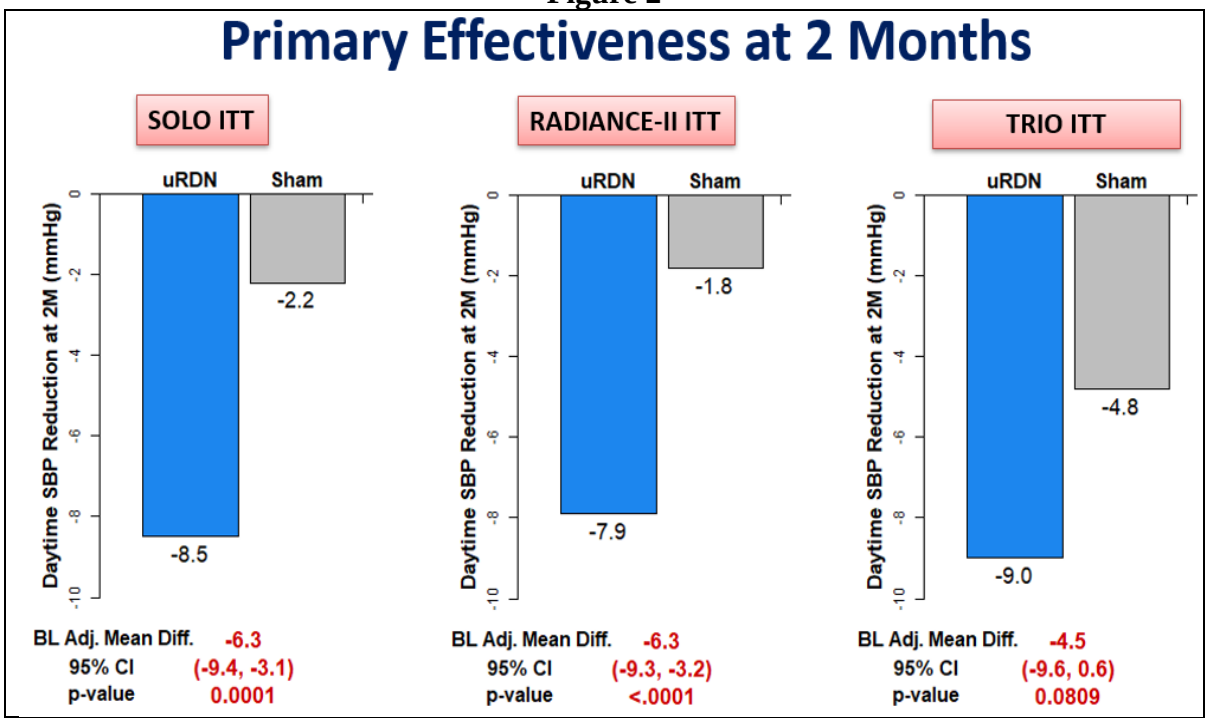
*At 2 months

Please discuss the relative value of ABPM and OBPM in assessing changes in blood pressure in evaluating the effectiveness of uRDN.

3. *Magnitude of BP Reduction*. FDA and the Sponsor reviewed the discussions during the 2018 Circulatory System Devices Advisory Panel, and there is debate regarding the Panel's opinion regarding the relative importance of absolute BP reduction from baseline (associated with a specific treatment) compared to the relative BP reduction between treatment groups. In FDA's interpretation of the Panel's discussions, they considered a 5 mmHg difference in systolic blood pressure reduction (measured by ABPM) between treatment groups to be clinically significant.

   The primary effectiveness endpoint in SOLO, RADIANCE-II, and TRIO was the difference in mean reduction in daytime ambulatory systolic BP (ASBP) at 2 months between uRDN and Sham. The ITT population results (Figure 2) showed a between-group difference of 6.3 mmHg in favor of uRDN for the off BP medication studies (SOLO and RADIANCE-II) and a 4.5 mmHg difference in favor of uRDN for the on standardized BP medication (triple pill) study (TRIO).

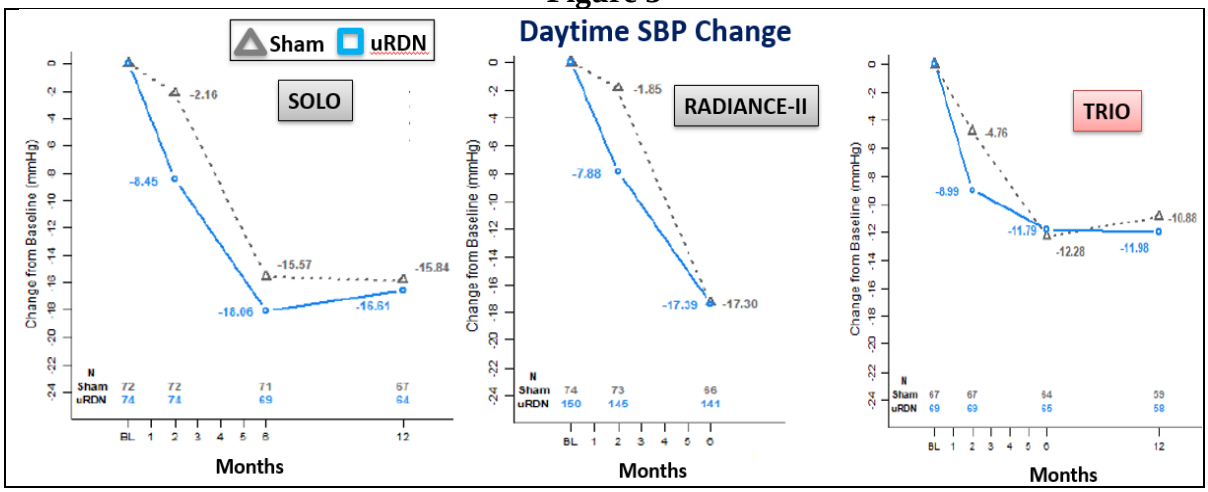
Figure 2



Please discuss the clinical significance of the absolute SBP reduction from baseline in uRDN subjects and the difference in BP reduction between the uRDN and Sham groups in evaluating the treatment effect in SOLO, TRIO, and RADIANCE-II.

4. *Durability of BP Reduction.* The difference in daytime ASBP reduction between the uRDN and Sham groups at 2-months was statistically significant for SOLO, TRIO, and RADIANCE-II (Figure 3). Further blood pressure lowering vs. baseline after 2 months was seen in both uRDN and Sham groups in all 3 studies, but the difference in mean daytime ASBP reduction between uRDN and Sham was not significant at 6-months and beyond.

Figure 3



Changes in medication may impact the blood pressure results. The medication burden in the uRDN and Sham groups at 2, 6 and 12 months is shown in Table 1. In general, at 6 and 12 months, the Sham group took more medications and had a higher medication load index compared to uRDN at 6 and 12 months, but the differences appear small.

Table 1

		SOLO		RADIANCE-II		TRIO	
		Average # of BP Meds	Med Load Index	Average # of BP Meds	Med Load Index	Average # of BP Meds	Med Load Index
2 months	uRDN	0.1 ± 0.3	0.0 ± 0.1	0.1 ± 0.3	0.1 ± 0.2	3.1 ± 0.5	2.1 ± 0.4
	Sham	0.2 ± 0.5	0.1 ± 0.3	0.1 ± 0.4	0.1 ± 0.2	3.1 ± 0.8	2.1 ± 0.5
6 months	uRDN	1.0 ± 0.9	0.5 ± 0.4	1.3 ± 1.0	0.7 ± 0.6	3.8 ± 1.0	2.3 ± 0.6
	Sham	1.3 ± 0.9	0.7 ± 0.5	1.5 ± 1.0	0.8 ± 0.6	4.1 ± 1.1	2.4 ± 0.6
12 months	uRDN	1.0 ± 0.9	0.5 ± 0.5	NA	NA	3.7 ± 1.5	2.3 ± 0.9
	Sham	1.3 ± 0.9	0.7 ±0.5	NA	NA	4.0 ± 1.2	2.5 ± 0.7

NA = Not available

Challenges in interpreting longer-term BP data include:

a. BP medication prescription followed a pre-specified escalation protocol to attain a target BP of ≤135/85 mmHg between 2 and 6-months for all studies.
b. Studies were unblinded at 6-months for SOLO and TRIO and 12 months for RADIANCE-II.
c. Crossover from sham to treatment group was allowed starting at 6-months for SOLO and TRIO and at 12-months for RADIANCE-II, which reduced the sample size of the Sham groups at later timepoints.
d. RADIANCE-II had limited data beyond 6-months. In SOLO, OBP was available for 56 uRDN and 43 Sham subjects at 24 months. In TRIO, OBP was available for 42 uRDN and 43 Sham subjects at 24-months.

Please discuss the strengths and limitations of longer-term BP data in patients treated with uRDN including:

- Whether uRDN provides a durable reduction in BP;
- The clinical significance of longer-term BP reduction in uRDN subjects vs. Sham subjects; and
- The clinical significance of BP medication differences between uRDN subjects and Sham subjects

Patient Preference Study

5. ReCor conducted a patient preference study using a discrete choice experiment with 258 patients to ascertain preferences for uRDN procedure compared to standard of care medication therapy. Overall, the study was conducted in alignment with the CDRH guidance "Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and

Inclusion in Decision Summaries and Device Labeling" recommendations for these types of studies. The results of the study evaluated the level of risk that patients were willing to tolerate in order to receive the uRDN procedure based on expected outcomes. However, a few attribute levels do not correspond to levels supported by the evidence which may have impacted the patient preference study results. Please discuss the degree of importance that the patient preference study results should be given when considering supplemental benefit-risk assessment information.

Labeling

6. *Indications for Use Statement.* The sponsor evaluated subjects with mild-to-moderate HTN in SOLO, resistant HTN in TRIO, and Stage 2 HTN in RADIANCE-II, as defined in the table below.

	SOLO	**TRIO**	**RADIANCE-II**
Sample size	146 (69 uRDN: 37 Sham)	136 (74 uRDN: 72 Sham)	224 (150 uRDN: 74 Sham)
OBP	• ≥140/90 & <180/110 mmHg on 0, 1 or 2 meds; *or* • ≤140/90 on 1 or 2 meds	≥140/90 on ≥3 meds, including a diuretic	• ≥140/90 & <180/120 mmHg on 0, 1, or 2 meds; *and* • Previous or currently prescribed antihypertensive therapy
Daytime ABP	≥135/85 & <170/105 mmHg after washout	≥135/85 mmHg after stabilization	≥135/85 & <170/105 mmHg after washout
Antihypertensive Medication	0, 1, or 2	At least 3	0, 1, or 2

Proposed indications for use statement:

The Paradise uRDN 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.

a. Please discuss whether the available clinical data support the proposed indications for use.
b. Please discuss if "inadequately responsive to or intolerance to anti-hypertensive medications" should be further defined in the labeling, and if so, please discuss definitions.

7. Please discuss whether labeling should contain recommendations for post-uRDN renal artery imaging, and if recommended, please discuss labeling language to be included. Please identify any other labeling recommendations.

Benefit/Risk

8. Given the totality of the evidence presented regarding the safety and effectiveness of the device, please comment on the benefit-risk profile of this device.

Post-market Study

9. ReCor proposed a postmarket registry study that will incorporate uRDN subjects from RADIANCE-II and the continued access study with enrollment of up to 500 new subjects that meet the indications for use (uncontrolled hypertension, who may be inadequately responsive to, or who are intolerant to anti-hypertensive medications). This proposed study will collect office and home measured BP (and not 24-hour ABP).
    a. Please comment on the sample size, proposed endpoints, and BP measurement methods.
    b. Please discuss whether the post-approval study enrollment should pre-specify a more diverse patient subgroups.
    c. Please discuss the strengths and limitations of a single arm study design for the PAS.
    d. No protocol-driven renal arterial imaging follow-up is planned. Please discuss the need for a pre-specified imaging follow-up protocol to confirm long-term uRDN safety.