PARADISE™ ULTRASOUND RENAL DENERVATION SYSTEM (uRDN)

CIRCULATORY SYSTEM DEVICES PANEL

MEETING DATE: 22 AUGUST 2023

SPONSOR EXECUTIVE SUMMARY AVAILABLE FOR PUBLIC RELEASE

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List of Abbreviations

Abbreviation	Full Definition
ABP	Ambulatory blood pressure
ACC	American College of Cardiology
ADE	Adverse device event
AE	Adverse event
AHA	American Heart Association
ANCOVA	Analysis of covariance
ARB	Angiotensin II receptor blocker
BMI	Body mass index
BP	Blood pressure
CABG	Coronary artery bypass graft
CCB	Calcium channel blocker
CEC	Clinical endpoint committee
CNS	Central nervous system
CTA	Computed tomography angiography
DBP	Diastolic blood pressure
DDD	Defined daily dose
eGFR	Estimated glomerular filtration rate
FDA	Food and Drug Administration
HCTZ	Hydrochlorothiazide diuretic
IDE	Investigational device exemption
ITT	Intention-to-Treat
MACE	Major adverse cardiac event
MAE	Major adverse event
mITT	Modified Intention-to-Treat
MRA	Magnetic resonance angiography
NYHA	New York Heart Association
PMA	Premarket approval
PP	Per Protocol
RF	Radiofrequency
SADE	Serious adverse device event
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
UPCR	Urine protein creatinine ratio
uRDN	Ultrasound renal denervation
US	United States
US-GPS	US-based Global Paradise System Registry

List of Definitions

Term	Definition
Adverse device effect (ADE)	Adverse event related to the investigational medical device, or the procedure.
Defined daily dose (DDD)	Calculated as the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO 2018).
Medication burden	Includes assessments of types of medications and total dose
Medication load index	The percentage of the maximum labeled daily dose for each agent for each medication a patient was taking added together (Wan et al 2009)
Serious adverse device effect (SADE)	Adverse device, or procedure related, effect that has resulted in any of the consequences characteristic of a serious adverse event.
Time-weighted average	Average calculated based on the relative proportion of time associated with each data point.

1 SYNOPSIS

1.1 Introduction

ReCor Medical is seeking approval of the Paradise™ Ultrasound Renal Denervation System (referred to as the Paradise System hereafter) to reduce blood pressure (BP) in patients with uncontrolled hypertension, who may be inadequately responsive to, or who are intolerant to antihypertensive medications. The Paradise System is a safe, minimally invasive, catheter-based procedure that delivers circumferential ultrasound energy to thermally ablate and disrupt overactive sympathetic nerves along the renal arteries, while simultaneously providing arterial wall protection. Results from 3 multicenter, randomized, double-blind, sham-controlled studies in 2 distinct patient populations consistently demonstrated that the Paradise System significantly lowers BP in patients with uncontrolled hypertension.

Hypertension is a major public health burden in the United States (US). For patients with uncontrolled hypertension, BP reductions are associated with a lower risk of cardiovascular morbidity and mortality (Blood Pressure Lowering Treatment Trialists 2021; Ettehad et al 2016; Weber et al 2004). Antihypertensive medications are standard of care for the treatment of patients who are unable to achieve optimal BP targets with lifestyle modifications alone. These medications effectively lower BP and some have been shown to reduce cardiovascular risk. However, there remains an unmet need for patients who are inadequately responsive or intolerant to antihypertensive medications, or unable to comply with prescribed treatment regimens and remain at increased risk of cardiovascular events including myocardial infarction, stroke, and death.

Overactivity of sympathetic renal nerves is a major contributor to hypertension and has been shown to enhance sodium retention and renin secretion in the kidneys, thereby increasing systemic sympathetic activity in the central nervous system (CNS) (Sata et al 2018). Disruption of this overactivity has been shown to prevent, delay, or reduce the magnitude of hypertension in animal models and human clinical trials (Azizi et al 2020; Azizi et al 2021; Azizi et al 2018; Azizi et al 2019; Campese and Kogosov 1995; DiBona et al 1997; Gosse et al 2021; Mahfoud et al 2021; Saxena et al 2022). Accordingly, renal denervation has emerged as an intervention to disrupt renal sympathetic nerve activity to reduce BP. Currently, no renal denervation device is approved in the US.

The Paradise System uses a novel catheter-based procedure to deliver ultrasound energy circumferentially to thermally ablate and disrupt overactive sympathetic nerves surrounding the renal arteries. At a target depth of 1–6mm, the system is designed to ablate ~80% of the renal sympathetic nerves. The unique thermal profile and first-of-a-kind cooling system protect the arterial wall and non-target organs from thermal injury. Additionally, the Paradise System does not require any treatment along the distal renal arteries and does not treat within the renal parenchyma. The Paradise System delivers ultrasound renal denervation (uRDN) therapy during a single, minimally invasive

procedure. Once the procedure is complete, the system is removed, and no device remains in the body.

The clinical development program for the Paradise System includes 3 multicenter, randomized, double-blind, sham-controlled studies that evaluated the safety and efficacy of uRDN in 2 distinct patient populations:

- Patients with mild-to-moderate hypertension taking ≤ 2 antihypertensive medications
- Patients with uncontrolled, treatment-resistant hypertension taking ≥ 3 antihypertensive medications

The prespecified primary effectiveness endpoint was met in all 3 studies, demonstrating that the Paradise System provides statistically significant and clinically meaningful reductions in average daytime ambulatory systolic BP (SBP). Reductions in BP were also seen across secondary endpoints, demonstrating a benefit of uRDN throughout the 24-hour circadian cycle, and were sustained through long-term follow-up. Moreover, the Paradise System has demonstrated a favorable safety profile.

The Paradise System would provide an important treatment option for patients who are unable to achieve BP control with standard of care antihypertensive medications and remain at increased risk of BP-related cardiovascular morbidity and mortality.

1.2 Background and Unmet Need

Hypertension is the leading cause of disease burden worldwide, causing an estimated 10 million deaths/year (Chobanian et al 2003). In the US, approximately 72 million adults > 20 years of age are reported to have Stage 2 hypertension (Muntner et al 2018). Hypertension and its risks affect both men and women, and rates increase with age.

Lowering BP significantly reduces the risk of major cardiovascular events. A meta-analysis of large-scale blood pressure lowering studies demonstrated that a reduction of office SBP of 10 mmHg was associated with a 20% reduction in major cardiovascular events, coronary heart disease, stroke, and heart failure (Ettehad et al 2016). Reductions of 5 mmHg in office SBP are associated with a 10% reduced risk of cardiovascular disease among a broad population of patients with hypertension, regardless of underlying risk factors (Blood Pressure Lowering Treatment Trialists 2021).

Current standard of care treatment for patients with hypertension includes lifestyle modifications, including dietary modifications and exercise, followed by antihypertensive medications. The 2017 American Heart Association (AHA)/American College of Cardiology (ACC) guidelines define Stage 1 hypertension as BP ≥ 130/80 mmHg and Stage 2 hypertension as BP of ≥ 140/90 mmHg. Pharmacological treatment is recommended for patients with ≥ 130/80 mmHg who are at high risk but should also be considered for all patients who are consistently above this threshold.

Typically, first-treatment regimens include the use of 1 or 2 drugs from different classes, with daily administration required. If hypertension progresses, the treatment regimen may intensify to a point where 3–6 daily medications can be prescribed. Antihypertensive medications can be effective in many patients; however, medication adherence presents a substantial challenge in the treatment of patients with hypertension. In fact, studies have shown that approximately 50% of patients with hypertension fail to fully adhere to their prescribed treatment regimens, and more than 80% of patients with uncontrolled hypertension are nonadherent to medications (Azizi et al 2016). Low adherence is recognized as a major contributor to poor outcomes. A large proportion of patients with hypertension fail to achieve targets of 130/80 mmHg, and 26% still fail to achieve 140/90 mmHg, with this rate increasing over the past 4 years (Muntner et al 2020). Additionally, among patients with Stage 2 hypertension, there is a subset (estimated 12%–15%) who are considered to be resistant to antihypertensive medications (Carey et al 2018).

In the SPRINT trial, patients randomized to more intensive BP lowering to a target BP of 120 mmHg had a large reduction in cardiovascular outcomes including cardiovascular mortality and all-cause mortality *during* the study compared with patients given standard treatment targeting < 140 mmHg (mean achieved SBP was 121 mmHg vs 136 mmHg, respectively). However, once patients returned to community care, the BP in the intensive treatment group rose to the same level as the standard treatment group, and all benefits in cardiovascular outcomes were equalized (Ambrosius et al 2014; Jaeger et al 2022). These findings reiterate that frequently prescribed antihypertensive medications do not present a long-standing solution for all patients with hypertension. Patients need a safe and effective treatment option that can reduce their BP and ultimately improve outcomes with less reliance on daily antihypertensive medications.

1.3 Overview of Paradise System

1.3.1 Description of Paradise System

The Paradise System is a novel, minimally invasive, catheter-based procedure that delivers ultrasound energy circumferentially to thermally ablate and disrupt overactive sympathetic nerves surrounding the renal arteries while simultaneously providing arterial wall protection. The system includes several key characteristics that contribute to its efficacy and safety profile:

- Delivers complete 360° energy (ultrasound) waves, requiring few (2–3) treatment sites to achieve renal nerve ablation, thereby minimizing energy delivery and improving ease of use.
- Provides deep penetration at a target depth of between 1 and 6 mm, effectively ablating up to 80% of the renal sympathetic nerves.

- Contains a unique thermal profile and first of its kind enclosed, circulating cooling system to protect the arterial wall and non-target organs from thermal injury during the procedure.
- Does not require direct tissue contact, thereby minimizing the risk of overheating the arterial wall with consequent tissue damage.
- Treats the main renal artery, accessories, and proximal branches (does not need to go distal or into the renal parenchyma).

The Paradise System consists of 2 main components:

1. The Paradise Generator controls the electronics and fluids for the System; energy delivery; circulation of the cooling fluid; and inflation and deflation of the balloon. A touch screen user interface is designed for ease of use and guides the user through each step of the procedure to ensure safe use. Ultrasound energy is delivered via an automated process to provide acoustic power based on catheter size to achieve a consistent ablation depth across a range of artery sizes.
2. A single use 6-French delivery catheter (transducer centered within the balloon), which delivers ultrasound energy and cools the surface of the artery wall to protect the artery from thermal injury during the energy delivery process.

1.3.2 Ultrasound Renal Denervation Procedure with Paradise System

The Paradise Catheter is introduced via femoral access under fluoroscopic guidance and advanced into the distal end of the main renal artery through a standard 6-French introducer sheath.

Once the Paradise Catheter is in position, the Paradise Generator controls the ultrasound energy delivery parameters through an automated process and actively adjusts the energy based on catheter size to achieve a consistent target depth. Through a proprietary algorithm, the Generator regulates balloon inflation with a coolant (sterile water), automatically centering the ultrasound transducer in the artery. Throughout the procedure, the Generator continuously manages balloon pressure to ensure consistently low pressure is applied to the vessel wall.

The procedure consists of 2–3 seven-second emissions per main renal artery, and up to 1 sonication in an accessory or proximal side branch. Once delivery at the target site is complete, the balloon automatically deflates, and the Paradise Catheter can be moved to additional positions. The Paradise Catheter is removed from the body, and the procedure completed according to standard interventional techniques.

The Paradise System is a novel device-based therapy that safely ablates renal sympathetic nerves during a simple, one-time procedure to reduce BP in patients with uncontrolled hypertension.

1.4 RADIANCE Studies

The Paradise System clinical development program includes 3 randomized, double-blind, sham-controlled studies: RADIANCE II, RADIANCE-HTN SOLO (referred to as SOLO hereafter), and RADIANCE-HTN TRIO (referred to as TRIO hereafter). The RADIANCE-HTN study, which included 2 cohorts of patients – those with mild to moderate hypertension (SOLO) and those with resistant hypertension (TRIO), was initiated in 2016. The SOLO study completed randomization and met its primary endpoint in early 2018. In 2018, the RADIANCE II study was initiated in the same patient population studied in SOLO to obtain data on a larger number of patients primarily to attain more safety data, given the low event rate observed with the Paradise System. RADIANCE II completed randomization and met its primary endpoint in 2022. The TRIO study, a more difficult patient population to enroll (those with true resistant hypertension), completed randomization and met its primary endpoint in 2020.

For ease of review, data in this document are presented based on the treated population. First, the results in patients with mild-to-moderate hypertension enrolled in SOLO and RADIANCE II are presented, followed by results in patients with resistant hypertension enrolled in TRIO. Notably, the safety and effectiveness outcomes across the patient populations are similar.

1.4.1 Study Designs

RADIANCE II and SOLO enrolled patients with mild-to-moderate Stage 2 hypertension who were taking 0–2 antihypertensive medications at the time of consent. After consenting, patients first completed a 4-week wash-out of all antihypertensive medications because the primary endpoint in these studies was the efficacy of uRDN in the absence of medications to minimize the confounding effect of concomitant medication. After wash-out, patients were assessed for eligibility based on protocol-defined BP thresholds (≥ 135/85 and < 170/105 mmHg daytime ambulatory BP [ABP]).

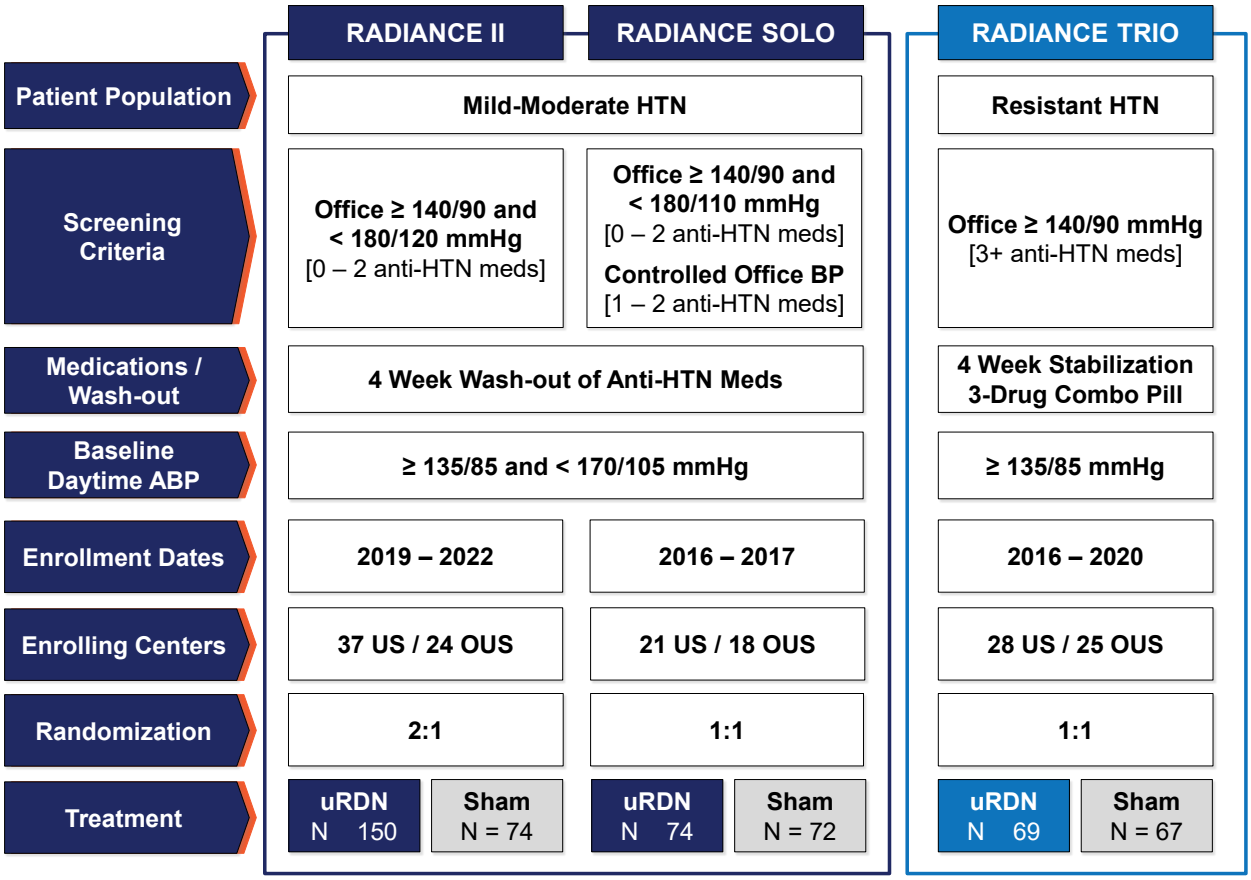
TRIO enrolled patients with uncontrolled hypertension despite the use of ≥ 3 antihypertensive medications. At screening, patients had their antihypertensive medications replaced with a standardized single tablet that included a combination of 3, fixed-dose antihypertensive medications. Use of this standard single pill minimized the confounding effect of treatment regimens requiring multiple tablets. After 4 weeks, patients meeting the baseline ABP threshold (≥ 135/85 mmHg) were randomized.

Prior to randomization, all patients had imaging performed via computed tomography angiography (CTA) or magnetic resonance angiography (MRA), plus renal angiography to confirm that their anatomy was suitable for treatment with the Paradise System. Eligible patients were randomized to receive uRDN treatment with the Paradise System or sham control. Standardized patient management was required to maintain blinding of the patients to treatment randomization. Patient sedation occurred prior to randomization, and all patients were provided headphones, music, and eye covers.

Procedure scripts were provided to sites for patients randomized to control in an attempt to standardize the procedure time and conduct. No study personnel responsible for any follow-up BP measurements were present at the point of randomization.

Key features of the RADIANCE studies are shown in Figure 1. More than 500 patients were randomized in the RADIANCE studies, with 293 randomized to receive uRDN with the Paradise System. The majority of patients across the 3 studies were enrolled in US sites, and time of enrollment overlapped across studies.

Figure 1: Key Design Features of RADIANCE Studies



ABP=ambulatory BP; BP=blood pressure; HTN=hypertension; OUS=outside US; US=United States; uRDN=ultrasound renal denervation.

The clinical development program was specifically designed to demonstrate the safety and effectiveness of uRDN on lowering BP in a range of patients with hypertension. Figure 2 shows the timeline of the 3 studies, highlighting the following:

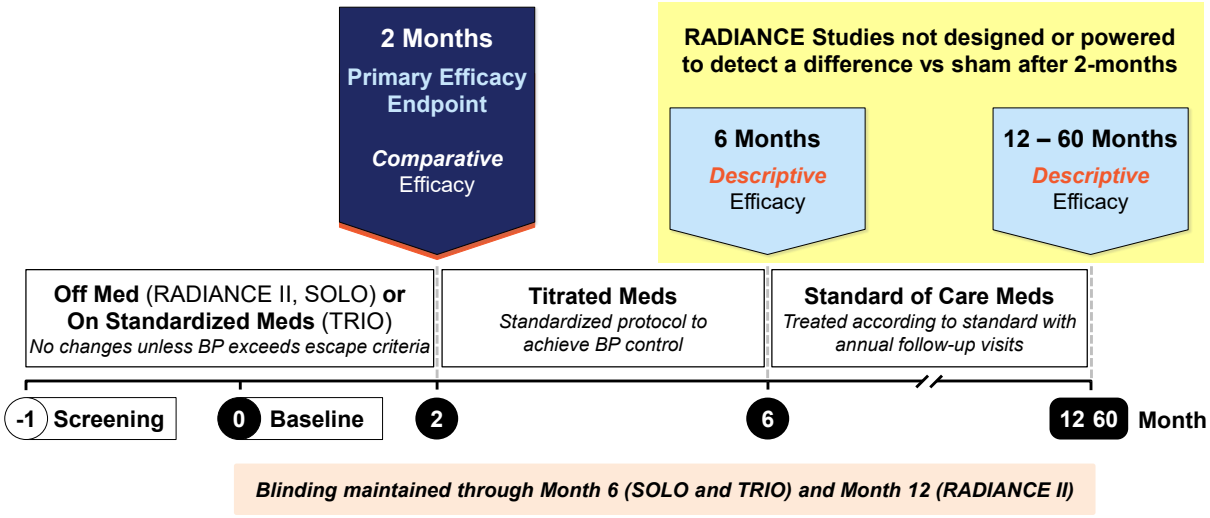
- The primary efficacy endpoint in all 3 studies was the difference in the reduction in average daytime ambulatory SBP between treatment (uRDN) and sham control (renal angiogram) from baseline to 2 months post-procedure. During the 2 months post-procedure, patients in RADIANCE II and SOLO were maintained off medication, and patients in TRIO were maintained on a standardized single-pill,

triple combination therapy (Amlodipine [10 mg], Valsartan [160 mg] or Olmesartan (40 mg), and Hydrochlorothiazide [25 mg]).

- Following the 2-month visit, all patients were treated according to a standardized medication titration protocol, monthly through 6 months (refer to Table 6 in Section 5.1.1 and Table 7 in Section 5.2.1.2) with a goal of achieving BP control. (note: TRIO patients had medications added to the single pill triple combination therapy, as needed). Therefore, the 6-month analysis provides an assessment of the impact of uRDN on medication burden (defined in List of Definitions) compared with sham when driving patients towards control.

After the 6-month visit, patients in SOLO and TRIO were unblinded and treated according to standard of care (note: after 6 months, the single pill triple combination therapy was no longer required for TRIO patients). Patients in RADIANCE II were also treated according to standard of care, but blinding was maintained through 12 months. Long-term assessments of office BP are conducted annually beyond 12 months up to 60 months to evaluate durability of treatment. At the time of the submission, all patients in RADIANCE II had completed the 6-month follow-up, and SOLO and TRIO have completed follow-up 36 and 24 months, respectively.

Figure 2: Timeline of RADIANCE Clinical Studies



BP=blood pressure.

1.4.2 Patient Populations

Baseline demographics were similar between randomized groups in each of the RADIANCE studies (Table 8 in Section 6.1). The majority of patients were male, with a mean age of 52–55 years. Across studies, 14%–20% of patients self-identified as Black or African American, and the mean BMI was approximately 30 kg/m^2. In general, patients in TRIO had more comorbidities than patients in RADIANCE II and SOLO (Table 9 in Section 6.1.3).

Baseline BP following the 4-week wash-out/medication stabilization period was elevated and similar between treatment groups across the studies; mean daytime ambulatory SBP was 150–151 mmHg, and mean daytime ambulatory DBP was 93–95 mmHg (Table 10 in Section 6.1.3.1).

At screening in RADIANCE II and SOLO, the proportion of patients taking 0, 1, or 2 anti-hypertensive medications was well balanced (Table 11 in Section 6.1.3.2). In TRIO, all patients were on ≥ 3 antihypertensive medications at Screening (mean of 4 medications).

Across the 3 studies, uRDN treatment was successfully delivered in > 95% of patients. The average procedure time (from sheath insertion to sheath removal) was 72–83 minutes, and the average device time (from catheter in to catheter out) was 33–40 minutes (Table 12 in Section 6.1.3.3).

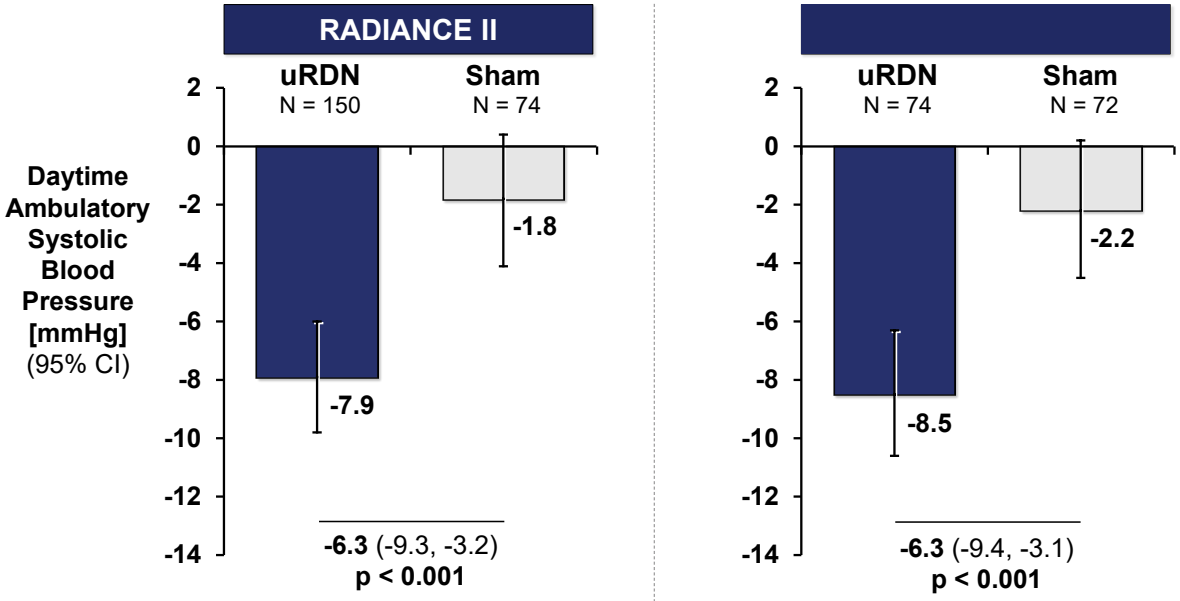
1.5 Effectiveness Findings

1.5.1 Primary and Secondary Efficacy Endpoint Results

1.5.1.1 Primary and Secondary Efficacy Endpoint Results at 2 Months in RADIANCE II and SOLO - Patients with Mild-to-Moderate Hypertension

Figure 3 shows the results of the primary efficacy outcome in RADIANCE II and SOLO, which included patients with mild-to-moderate hypertension. Both studies met the prespecified primary endpoint, demonstrating statistically significant and clinically meaningful reductions in daytime ambulatory SBP in patients receiving uRDN compared with sham at 2 months post-procedure. In both studies, the between-group difference in daytime ABP was 6.3 mmHg; for reference, a difference of approximately 7 mmHg in ABP approximates an office BP reduction of 10 mmHg (Mancia and Parati 2004). Importantly, the consensus of experts in the 2018 Circulatory System Devices Panel of the Medical Devices Advisory Committee in December 2018 agreed that a minimum of a 5-mmHg difference in ambulatory SBP between RDN and sham should be considered clinically meaningful (Circulatory System Devices Panel of the Medical Devices Advisory Committee December 2018).

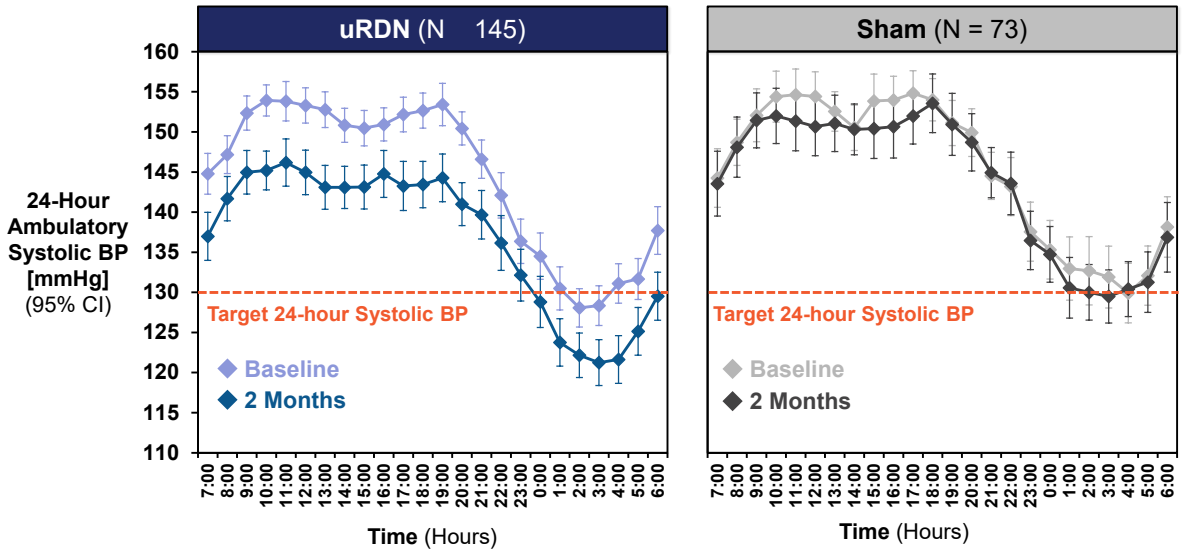
Figure 3: RADIANCE II and SOLO: Primary Effectiveness Results - Change in Ambulatory Systolic Blood Pressure from Baseline (ITT Population)



CI=confidence interval; uRDN=ultrasound renal denervation.
Note: In RADIANCE II, individual group changes are based on observed values uRDN N=145 and Sham N=73.

In both studies, uRDN delivered via the Paradise System was also shown to provide consistent BP reductions throughout the 24-hour circadian cycle. Figure 4 shows the statistically significant and clinically meaningful sham-adjusted reduction in systolic BP in patients receiving uRDN at all timepoints over 24 hours in RADIANCE II, and similar results were seen in SOLO. This “always-on” effect is an important feature of uRDN therapy.

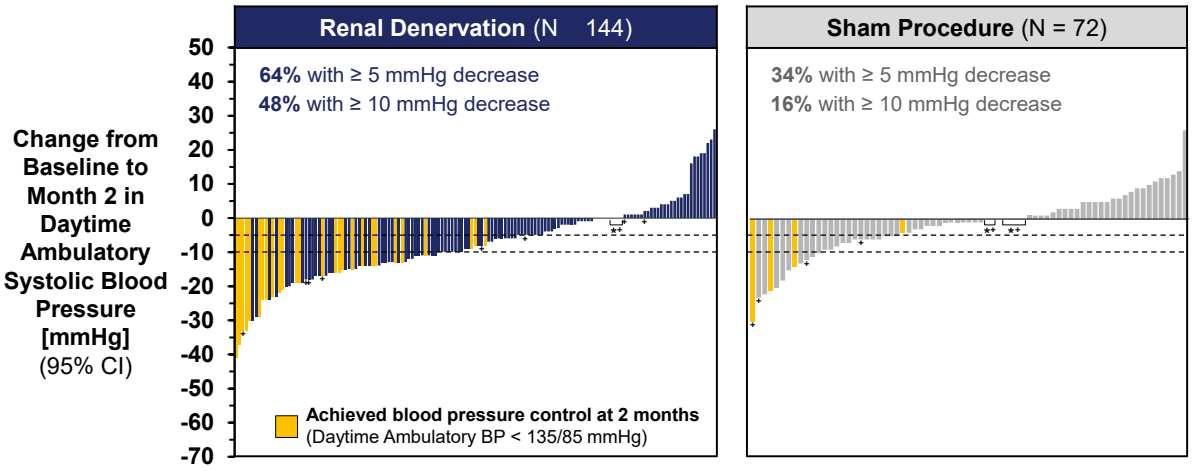
Figure 4: RADIANCE II: 24-Hour Ambulatory Systolic Blood Pressure at Baseline and 2 Months (ITT Population)



BP=blood pressure; CI=confidence interval; uRDN=ultrasound renal denervation.

Figure 5 shows that more patients who received uRDN had a reduction in daytime ambulatory SBP and more of these patients achieved BP control at 2 months compared with those who received the sham procedure.

Figure 5: RADIANCE II: Change from Baseline in Daytime Ambulatory Systolic Blood Pressure at 2 Months by Individual Response

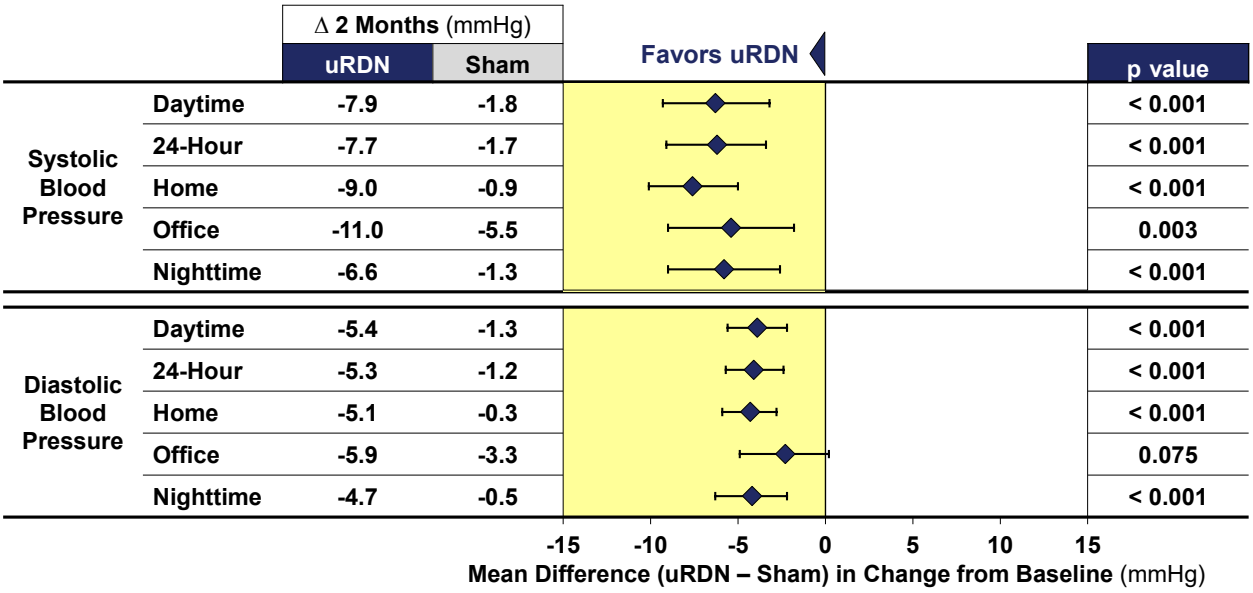


* Met escape criteria
\+ Received antihypertensive medications prior to 2-month ABP measurement

Treatment benefits were also consistent irrespective of baseline characteristics and disease severity (Figure 33 in Section 6.2.1.3 and Figure 38 in Section 6.3.1.2).

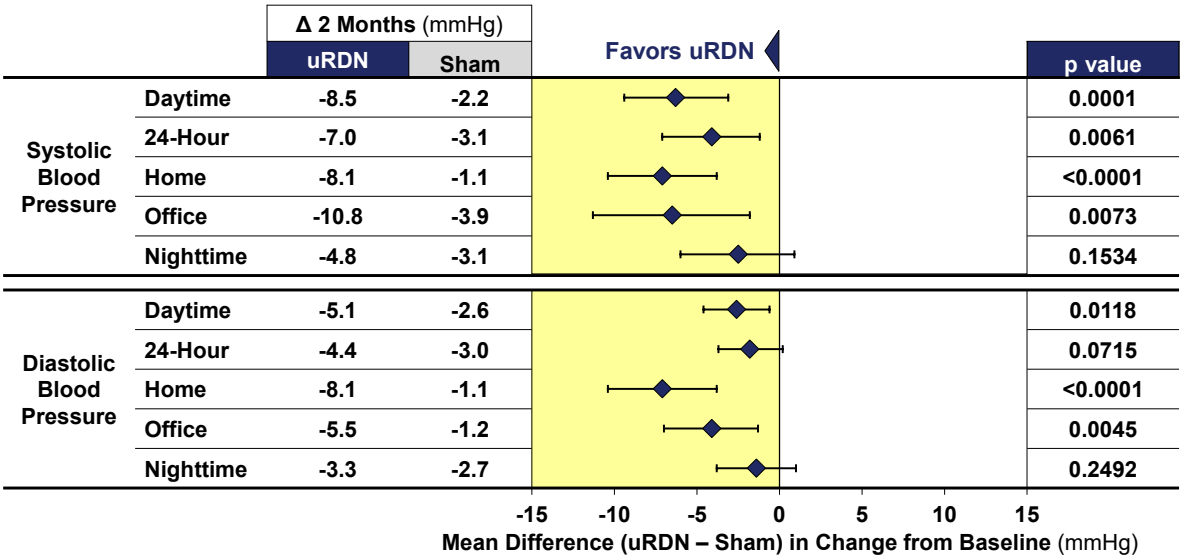
Results were consistent for secondary endpoints of 24-hour, home, office, and nighttime BP at 2 months in RADIANCE II and SOLO studies (Figure 6 and Figure 7, respectively). The reduction in office SBP was approximately 11.0 mmHg in both studies; literature supports that SBP reductions of 5 to 10 mmHg are associated with a lower risk of major cardiovascular events ranging between 10%–20% (Ettehad et al 2016; Rahimi et al 2021).

Figure 6: RADIANCE II: Secondary Endpoint Results at 2 Months (ITT Population)



ITT=intention-to-treat; uRDN=ultrasound renal denervation.

Figure 7: SOLO: Secondary Endpoint Results at 2 Months (ITT Population)



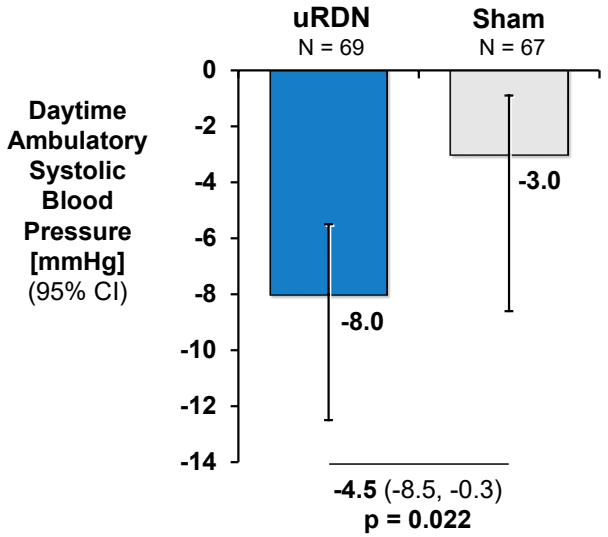
ITT=intention-to-treat; uRDN=ultrasound renal denervation.

1.5.1.2 Primary and Secondary Efficacy Results at 2 Months in TRIO – Patients with Treatment Resistant Hypertension

Figure 8 shows the results of the primary efficacy outcome in TRIO, which included patients with treatment-resistant hypertension despite the use of ≥ 3 antihypertensive medications who were treated with a standardized triple pill (Amlodipine [10 mg], Valsartan [160 mg] or Olmesartan (40 mg), and Hydrochlorothiazide [25 mg]) during the

study. The statistical analysis plan (SAP) for the RADIANCE studies prescribed prespecified analyses based on applying the ANCOVA model to ranked data to address issues with the normality assumption of the primary endpoint model. The Shapiro-Wilk test showed that normality was violated in TRIO, and therefore medians were to be used as a measure of central tendency as is customary for data that are not normally distributed (Hollander et al 1999). Importantly, the estimated treatment effect comparing the randomized groups using either means or medians are similar and not different from a clinical perspective. The uRDN group improved by a mean/median of 9.0/8.0 mmHg while the sham group improved by a mean/median of 4.8/3.0 mmHg, and the difference between groups was -4.5 using either means or medians in unadjusted and adjusted analyses in the ITT Population.

Figure 8: TRIO: Primary Effectiveness Results — Median Change in Ambulatory Systolic Blood Pressure from Baseline (ITT Population)



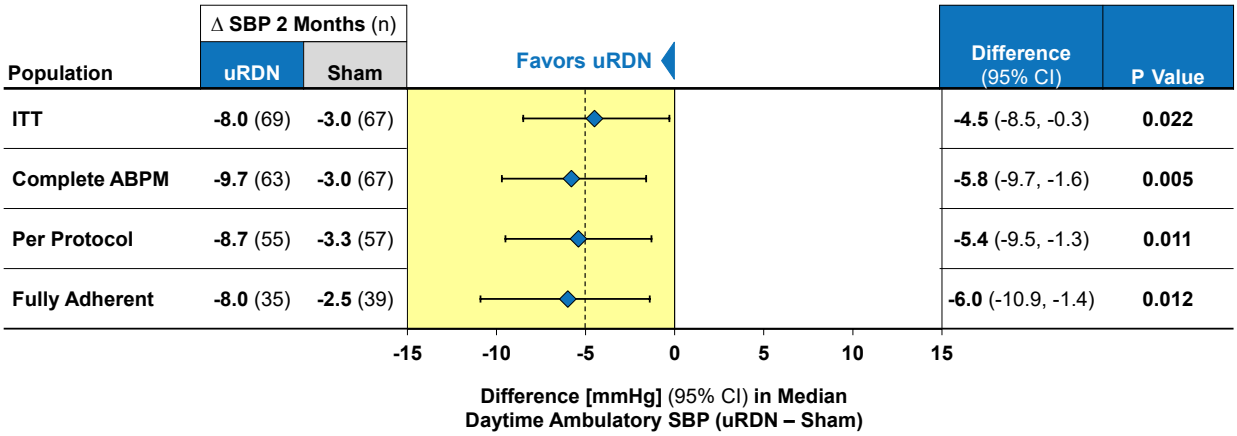
Note: Data presented as medians, and p-value is from baseline-adjusted ANCOVA on the ranks, as change from baseline is non-normal.

ReCor acknowledges that at 2 months, the between-group difference was slightly smaller in TRIO (4.5 mmHg) in the ITT population compared to the 6.3 mmHg difference in daytime ambulatory SBP in RADIANCE II and SOLO. Upon further exploration of the data, imbalances in missing values and adherence were identified. Per the SAP, if an ABP measurement was missing at 2 months, a clinically based, conservative approach was utilized to account for these missing values, and zero was imputed corresponding to no improvement from baseline. In TRIO, 6 patients assigned to uRDN and no patients assigned to sham had missing ABP values at 2 months; thus, more patients in the uRDN group had their ABP values imputed at 2 months due to missing data. Importantly, there were no safety events in the patients assigned to uRDN. Moreover, if a patient added medications prior to 2 months and met escape criteria (with demonstrated increased BP), their 2-month results were also imputed to baseline

values. Additional analyses of the primary endpoint were performed to account for these imbalances.

Analyses of the complete ABP (ie, ITT with complete 2-month ABP measurements) and fully adherent (ie, fully adherent to medications at both baseline and 2 months based on urine testing) populations showed a median between group difference of -5.4 mmHg and -5.5 mmHg, respectively (Figure 9), which exceeds the 5mmHg threshold deemed to be clinically important (Circulatory System Devices Panel of the Medical Devices Advisory Committee December 2018).

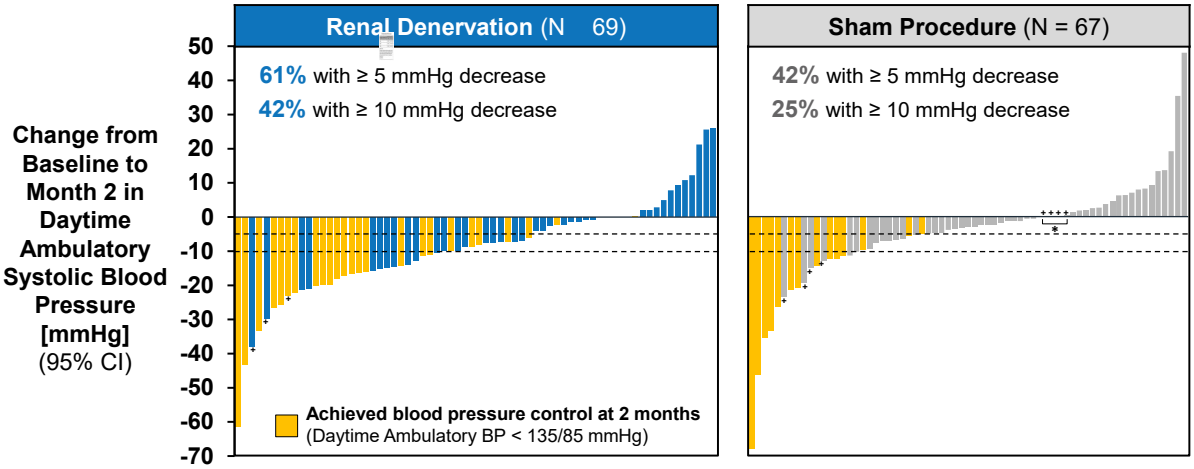
Figure 9: TRIO: Primary Effectiveness Endpoint Results by Analysis Methods with Imputation for Missing Data



Note: Data presented as medians as change from baseline is non-normal.

Figure 10 shows that a higher population of patients who received uRDN had a reduction of ≥ 5 mmHg and ≥ 10 mmHg in daytime ambulatory SBP compared with those who received the sham procedure.

Figure 10: TRIO: Change from Baseline in Daytime Ambulatory Systolic Blood Pressure at 2 Months by Individual Response

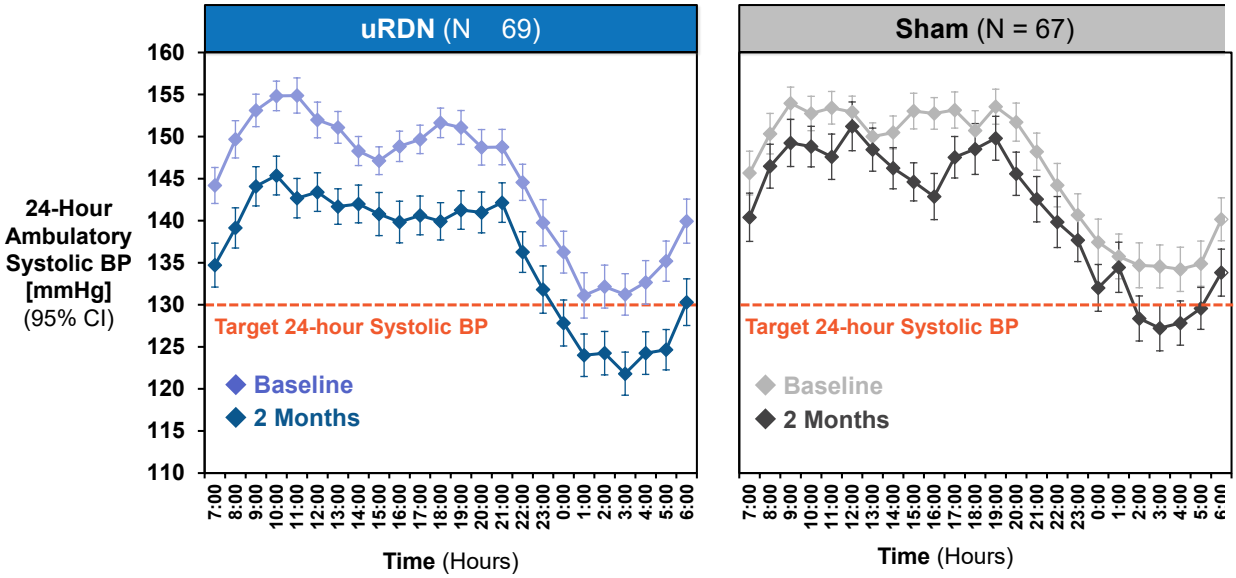


* Met escape criteria

+ Received antihypertensive medications prior to 2-month ABP measurement

Similar to RADIANCE II and SOLO, BP reductions with uRDN were achieved throughout the 24-hour Circadian cycle in TRIO (Figure 11).

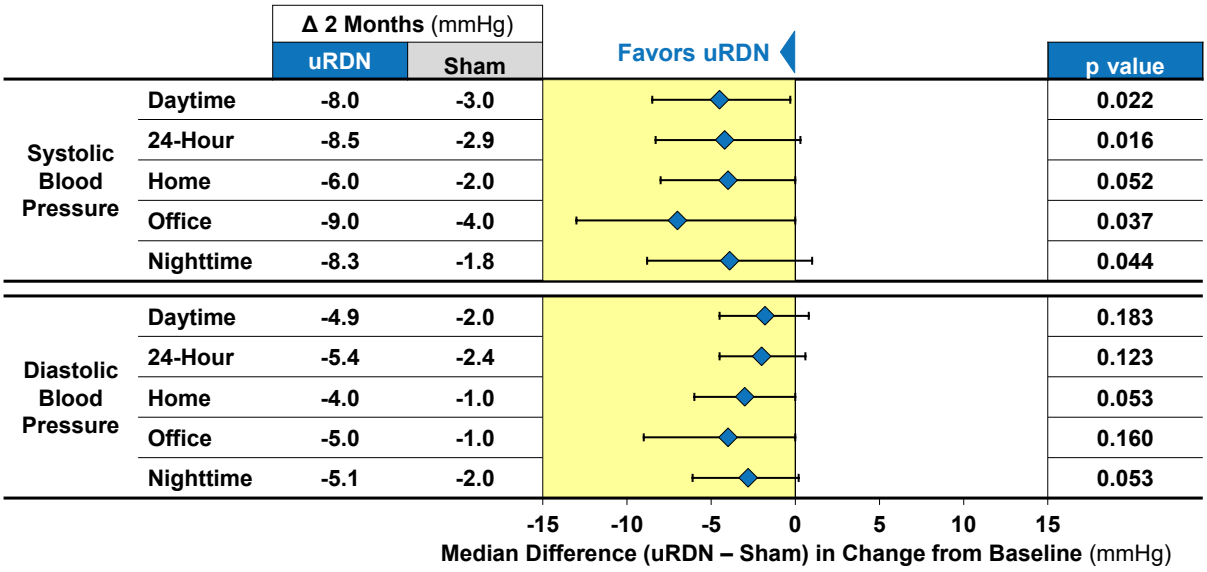
Figure 11: TRIO: 24-Hour Ambulatory Systolic Blood Pressure at Baseline and 2 Months



BP=blood pressure; CI=confidence interval; uRDN=ultrasound renal denervation

Results were consistent for secondary endpoints of 24-hour, home, office, and nighttime BP at 2 months (Figure 12). The reduction in office SBP was 9 mmHg, which exceeds the 5-mmHg threshold of reduction that is associated with a lower risk of major cardiovascular events (Circulatory System Devices Panel of the Medical Devices Advisory Committee December 2018).

Figure 12: TRIO: Secondary Endpoint Results at 2 Months (ITT Population)

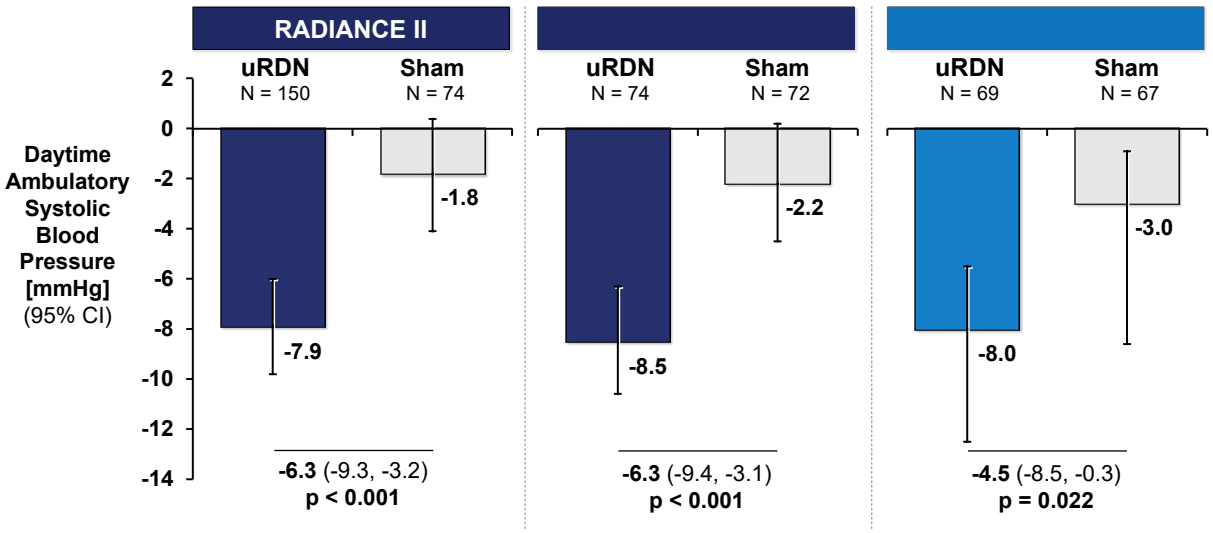


Δ=change; uRDN=ultrasound renal denervation

1.5.1.3 Primary Efficacy Endpoint Conclusions

All 3 studies met their prespecified primary effectiveness endpoint, showing statistically significant and clinically meaningful reductions in daytime ABP in patients who received uRDN compared with those who received sham procedure. The sham-adjusted difference in BP reductions ranged from 6.3–4.5 mmHg, with an overall reduction from baseline in the uRDN groups of approximately 8 mmHg (Figure 13).

Figure 13: RADIANCE-HTN Studies: Change from Baseline in Daytime Ambulatory Systolic Blood Pressure

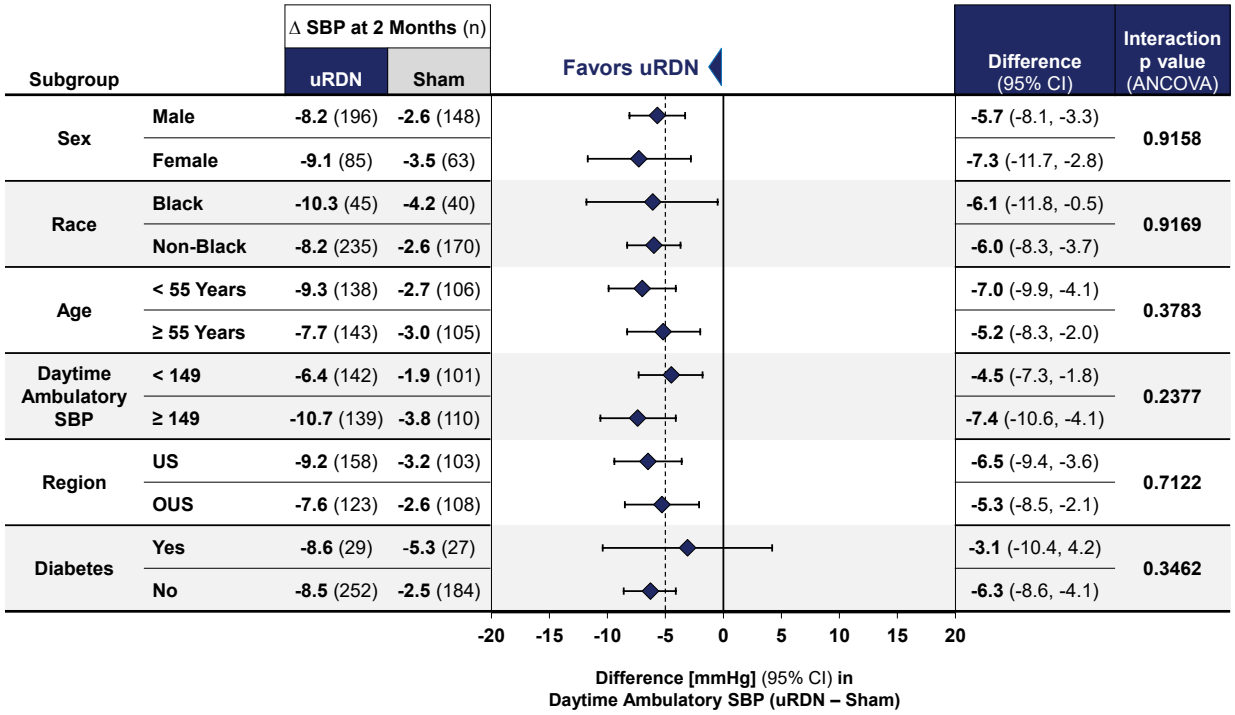


CI=confidence interval; uRDN=ultrasound renal denervation

Note: RADIANCE II individual group changes based on observed values uRDN N=145 and sham N=73.
TRIO data are presented as medians, and the p-value is from baseline-adjusted ANCOVA on the ranks as the change from baseline is non-normal.

Additionally, a patient-level pooled analysis examining 2-month BP outcomes across SOLO, TRIO, and RADIANCE II was performed and was recently published in JAMA Cardiology (Kirtane et al 2023). This analysis as shown in Figure 14 supports the benefits of uRDN on BP lowering across baseline demographics and disease characteristics.

Figure 14: Pooled RADIANCE-HTN Studies: Change from Baseline in Daytime Ambulatory Systolic Blood Pressure by Subgroup



1.5.2 Long-Term Efficacy Results

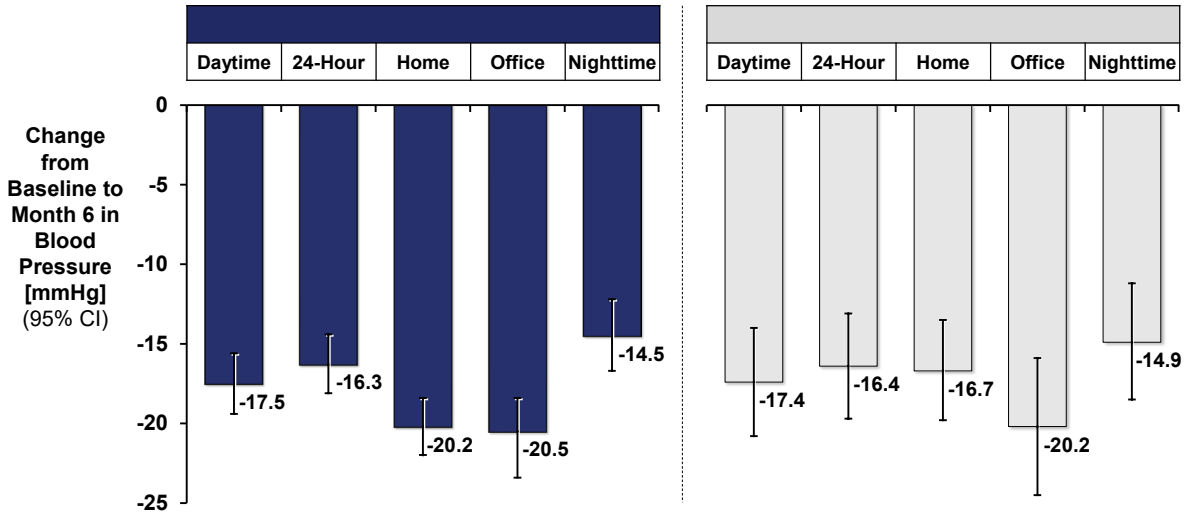
1.5.2.1 6-Month Efficacy Results

The RADIANCE studies were specifically designed and powered to demonstrate the effects of uRDN on BP lowering at 2 months compared with sham. Patients remained blinded through the 6-month follow-up visit, during which home BP measurements were recorded monthly. If patients experienced BP elevations > 135/85 mmHg, a standardized antihypertensive medication stepwise protocol was implemented to target BP control. As a result, it was expected that the BP reductions at 6 months would be similar in uRDN and sham.

The 6-month data reflect a mix of factors including asymmetric addition of medications across groups, physician inertia to control BP, and medication adherence during a clinical trial. While the 6-month and longer-term timepoints allow for evaluation of the potential effect of uRDN on medication burden and long-term benefits, these endpoints are descriptive only. Despite this, difference in BP and medication burden favoring uRDN were observed in all studies.

In RADIANCE II (Figure 15), as well as SOLO and TRIO (Figure 16 and Figure 19, respectively), larger reductions in BP were observed at 6 months compared to 2 months in both groups, as was expected given the medication protocol described above.

Figure 15: RADIANCE II: Change from Baseline to Month 6 in Systolic Blood Pressure Measures



HTN=hypertensive; uRDN=ultrasound renal denervation

The number of prescribed antihypertensive medications and medication burden were assessed at 6 months. In RADIANCE II, the total number of prescribed antihypertensive medications at 6 months was lower in uRDN-treated patients compared with sham (Table 2). Notably, 24% of uRDN-treated patients required zero antihypertensive medications compared with 16% of sham-treated patients. Despite the fact that uRDN-treated patients taking fewer antihypertensive medications, BP reductions favoring uRDN were seen across all endpoints, with baseline-adjusted differences between groups consistently favoring uRDN over sham.

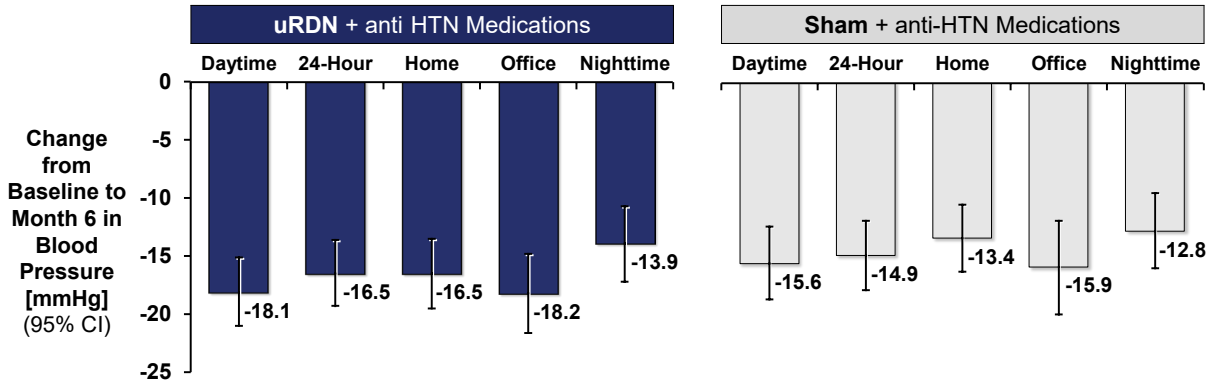
Table 1: RADIANCE II: Number of Antihypertensive Medications and Medication Burden at 6 Months

Measure (6-Months)	uRDN + Anti-HTN Meds N=143	Sham + Anti-HTN Meds N=67
	1.3 (1.0)	1.5 (1.0)
		16%
		2.2 (1.7)
		0.8 (0.6)

HTN=hypertensive; SD=standard deviation; uRDN= ultrasound renal denervation

The results in SOLO were similar to RADIANCE II. Larger reductions in BP were observed at 6 months compared to 2 months in both groups, and the total number of prescribed antihypertensive medications at 6 months was lower in uRDN-treated patients compared with sham (Table 2).

Figure 16: SOLO: Change from Baseline to Month 6 in Systolic Blood Pressure Measures



HTN=hypertensive; uRDN=ultrasound renal denervation

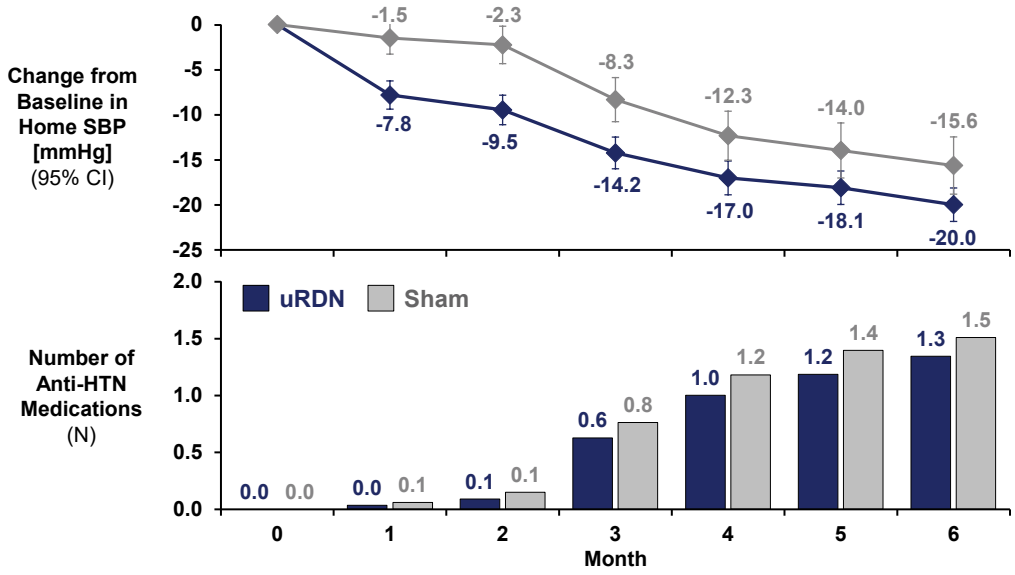
Table 2: SOLO: Number of Antihypertensive Medications and Medication Burden at 6 Months

Measure (6-Months)	RADIANCE-SOLO	
	uRDN + Anti-HTN Meds N=69	Sham + Anti-HTN Meds N=71
Anti-HTN Meds, mean (SD)	1.0 (0.9)	1.3 (0.9)
No Anti-HTN Meds	36%	17%
Medication Burden, mean (SD)		
Defined Daily Dose	1.1 (1.2)	1.8 (1.4)
Anti-HTN Med Load Index	0.5 (0.4)	0.7 (0.5)

HTN=hypertensive; SD=standard deviation; uRDN= ultrasound renal denervation

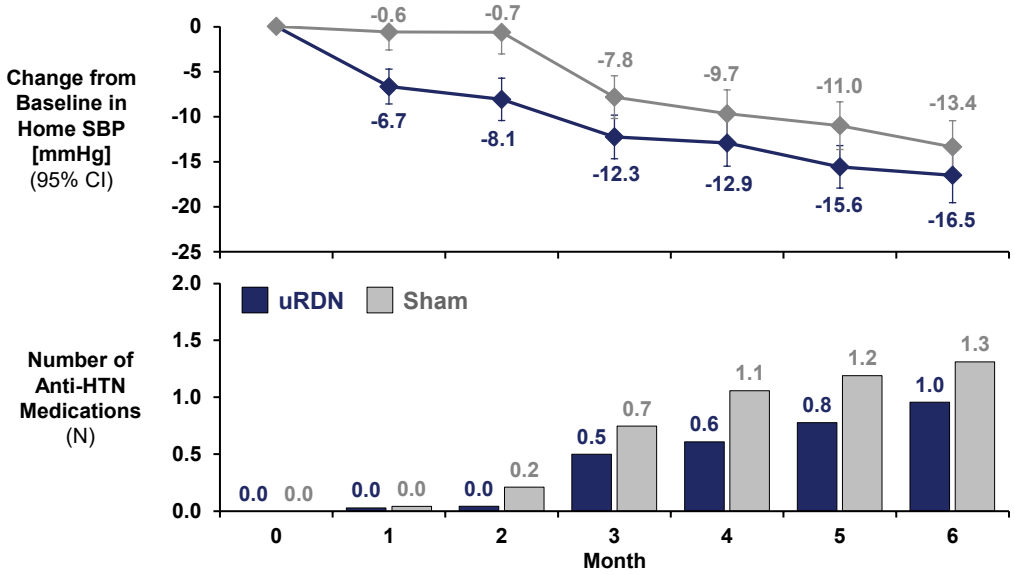
Patients recorded home BP measurements on a monthly basis, so these data can also be examined over time. Figure 17 and Figure 18 show home SBP and number of antihypertensive medications through 6 months in RADIANCE II and SOLO, respectively.

Figure 17: RADIANCE II: Change from Baseline in Home SBP and Number of Antihypertensive Medications Over 6 Months



HTN=hypertensive; SBP=systolic blood pressure; uRDN=ultrasound renal denervation

Figure 18: SOLO: Change from Baseline in Home SBP and Number of Antihypertensive Medications Over 6 Months



HTN=hypertensive; SBP=systolic blood pressure; uRDN=ultrasound renal denervation

In TRIO, at 6 months, patients in the uRDN group required fewer antihypertensive medications to be added to their daily regimen compared with the sham group (Table 30 in Section 6.4.3). Additionally, the use of aldosterone antagonists (the first step in the standardized treatment escalation protocol) was significantly less frequent in the uRDN group. Both groups had consistent reductions in BP at 6 months (Figure 19), but patients in the uRDN group required fewer antihypertensive medications, including aldosterone antagonists which were the first step in the drug escalation protocol, to achieve these results (Table 3).

Figure 19: TRIO: Systolic Blood Pressure Measurements at 6 Months

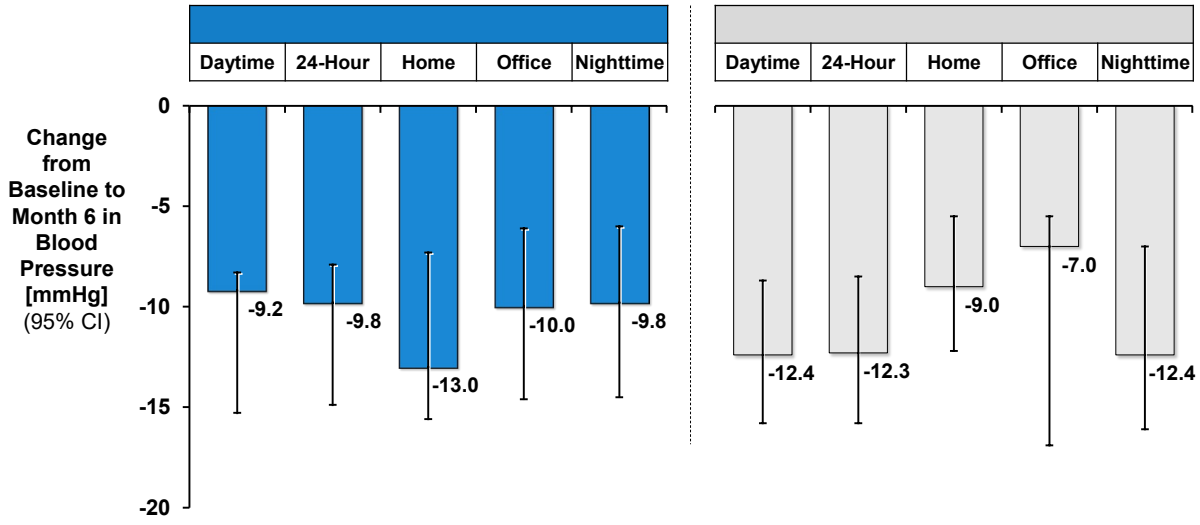


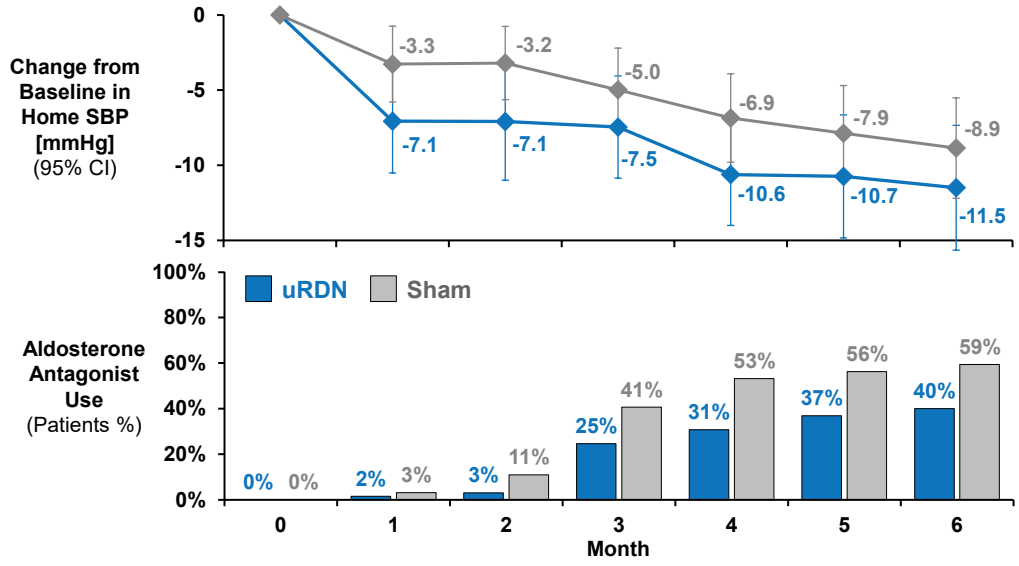
Table 3: TRIO: Antihypertensive Medications Taken at 6 Months after Procedure (ABP Population)

Measure (6 Months)	TRIO	
	uRDN (N=65)	Sham (N=64)
Anti-HTN meds, mean (SD)	3.8±1.0	4.1±1.1
Aldosterone antagonist use, % of patients	40%	59%
Medication dose burden		
Defined daily dose ± SD	5.2±1.3	5.7±1.5
Antihypertensive medication load index ± SD	2.3±0.6	2.4±0.6

ABP=ambulatory blood pressure; HTN=hypertensive; SD=standard deviation; uRDN=ultrasound renal denervation.
Note: P-value from students t-test or Wilcoxon rank sum test for continuous variables and Chi-square or Fishers exact test for categorical variables as appropriate comparing treatment arm to sham arm.

Figure 20 shows home SBP and aldosterone antagonist usage over 6 months.

Figure 20: TRIO: Change from Baseline in Home SBP and Aldosterone Antagonist Use Over 6 Months

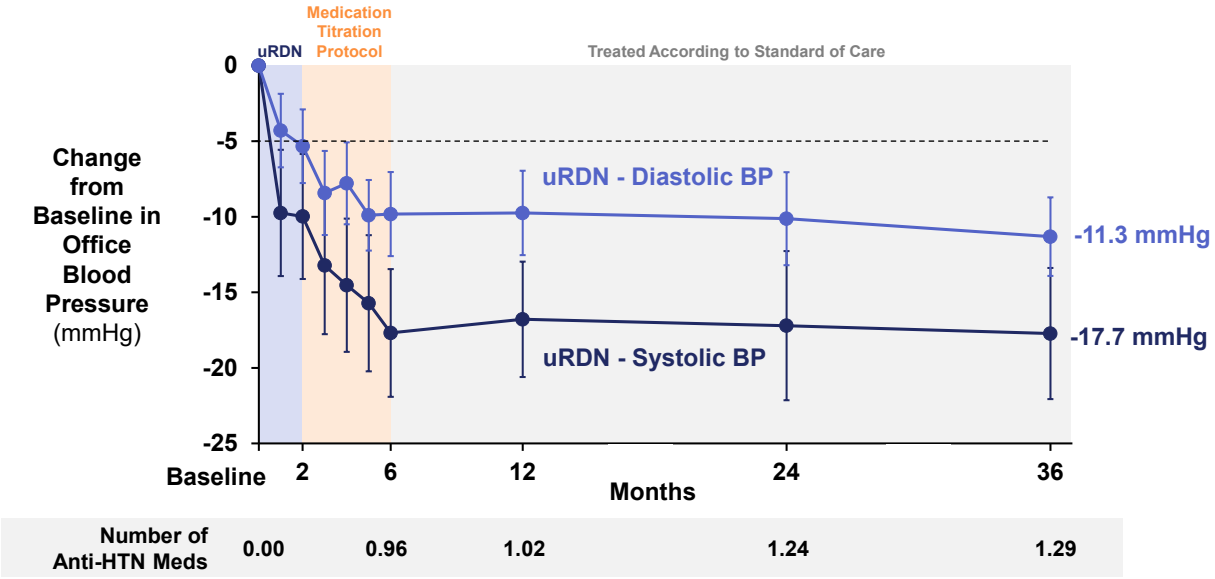


1.5.2.2 Long-Term Durability

At the time of submission, RADIANCE II only had data available through Month 6; therefore, long-term durability data are derived from SOLO and TRIO. After the 6-month visit, patients in SOLO and TRIO were unblinded and treated according to standard of care and were seen annually thereafter up to 60 months. Long term durability was assessed by 1) comparing to baseline (after the 4-week wash out of medications) and 2) by comparing to screening (the time of consent, prior to the protocol mandated 4-week wash out of medications).

SOLO: Of the 73 uRDN-treated patients with complete 2-month ABP in SOLO, 51 completed the study through 36-month follow-up and had an office BP measurement at Month 36. Between 2 months and 36 months, 5 patients withdrew consent, 5 patients were lost to follow-up, 1 patient was not treated due to a generator issue and then was subsequently treated, 1 patient was lost for “other reason," and the remaining patients completed clinical follow-up but did not have office BP measurements at Month 36. In the 51 remaining patients, there was a mean reduction in SBP of 17.7 mmHg and a mean reduction in DBP of 11.3 mmHg from baseline through Month 36 (Figure 21). Patients who received uRDN achieved clinically meaningful reductions in office SBP and DBP at 6 months in the presence of 1 medication, which was maintained through 36 months of follow-up.

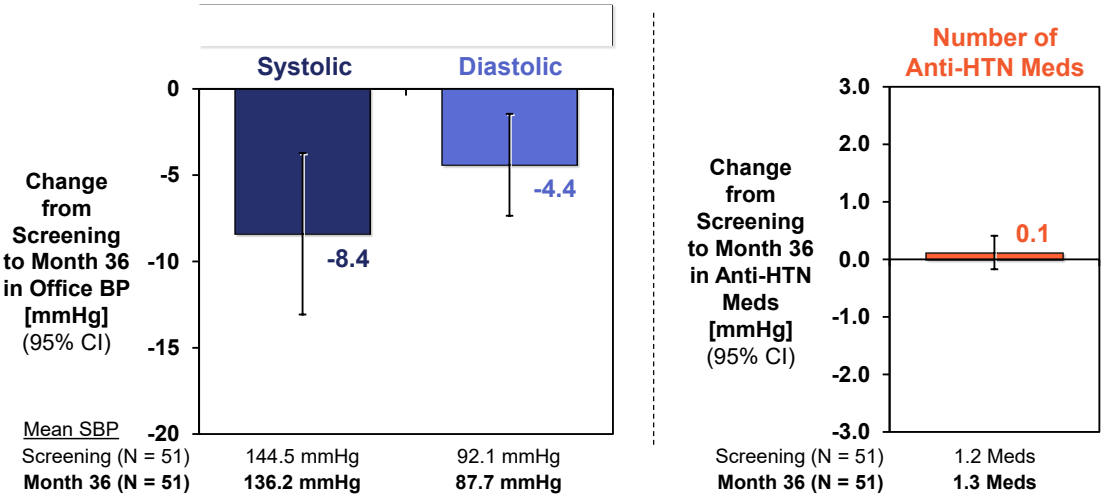
Figure 21: SOLO: Change from Baseline in Systolic and Diastolic Office Blood Pressure Through Month 36 in uRDN-Treated Patients



BP=blood pressure; HTN=hypertensive; uRDN= ultrasound renal denervation

Figure 22 shows the BP results and change in number of prescribed anti-HTN medications over time compared to screening. The average reduction in office SBP and DBP from screening to Month 36 was 8.4 mmHg and 4.4 mmHg, respectively, with no meaningful change in antihypertensive medications (mean of 1.2/1.3 medications) during the same time period. This analysis illustrates the change in BP at 36 months compared to screening BP in the presence of constant medications, which may provide some insight towards real-world outcomes.

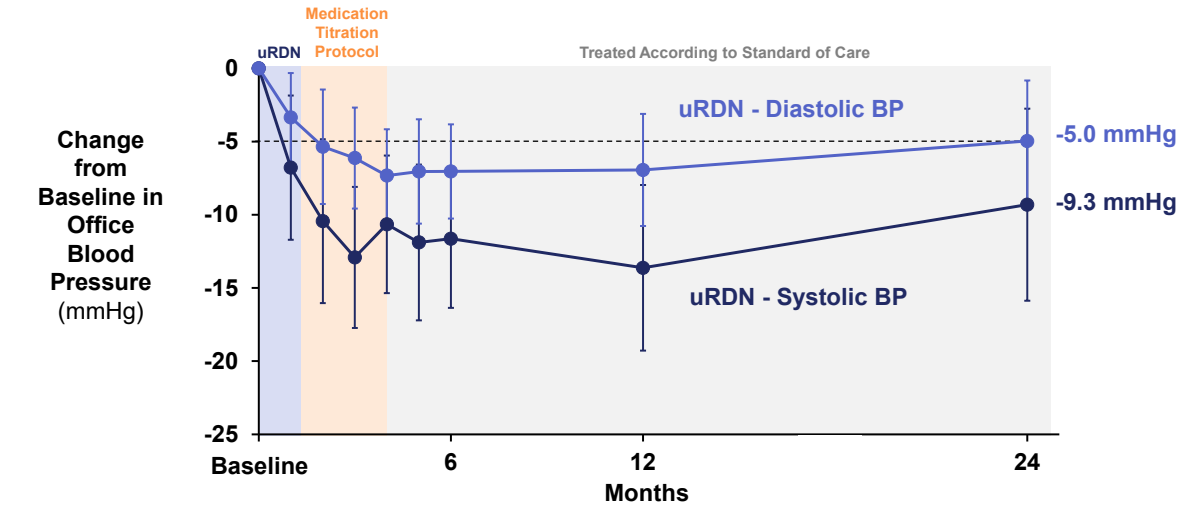
Figure 22: SOLO: Change from Screening in Office Blood Pressure and Number of Antihypertensive Medications at Month 36



BP=blood pressure; CI=confidence interval; HTN=hypertensive; SBP=systolic blood pressure

TRIO: Of the 63 uRDN-treated patients with complete 2-month ABP in TRIO, 51 completed the 24-month follow-up visit and had an office BP measurement at Month 24. Six patients were lost to follow-up, 1 patient withdrew consent, and the remaining patients completed clinical follow-up but did not have office BP measurements at Month 24. Figure 23 shows the change from baseline in systolic and diastolic office BP through Month 24 in those 51 patients. There was a mean reduction in SBP of 9.3 mmHg and a mean reduction in DBP of 5.0 mmHg at Month 24, compared to baseline.

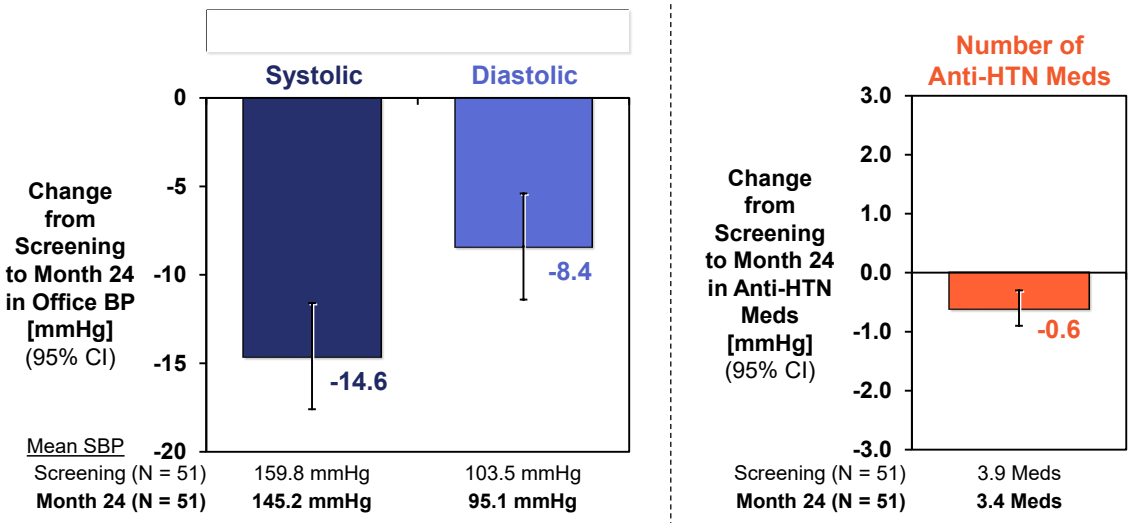
Figure 23: TRIO: Change from Baseline in Systolic and Diastolic Office Blood Pressure Through Month 24 in uRDN-Treated Patients



BP=blood pressure; HTN=hypertensive; uRDN= ultrasound renal denervation

The benefits in SBP and DBP seen at 6 months were sustained through long-term follow-up despite a slight decrease in the overall number of antihypertensive medications. From Screening, prior to the 4-week stabilization on a single triple pill (Amlodipine [10 mg], Valsartan [160 mg] or Olmesartan (40 mg), and Hydrochlorothiazide [25 mg]), to Month 24, office systolic and diastolic BP was reduced by 14.6 mmHg and 8.4 mmHg, respectively, and antihypertensive medications were reduced from 3.9 to 3.4 in patients receiving uRDN (Figure 24).

Figure 24: TRIO: Change from Screening in Office Blood Pressure and Number of Antihypertensive Medications at Month 24



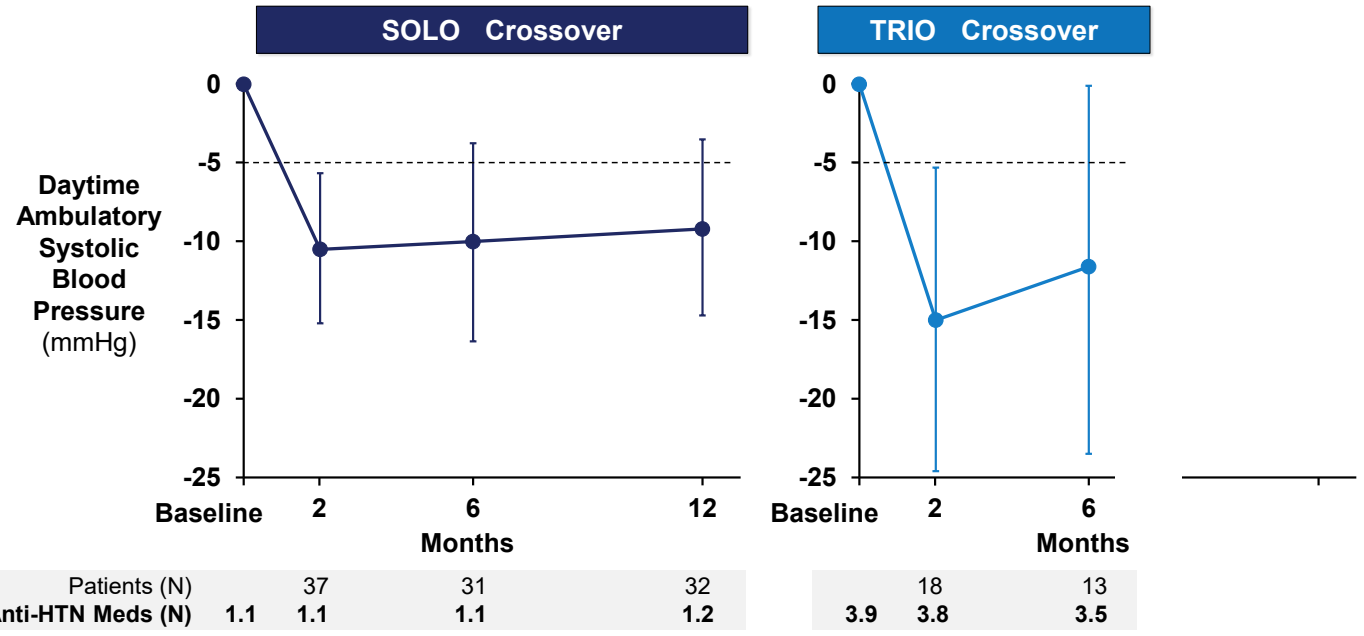
CI=confidence interval; HTN=hypertension

1.5.2.3 Cross-over Data

Patients randomized to the sham group in SOLO and TRIO with BP that remained elevated could cross-over and receive uRDN after ≥ 6 months if the primary efficacy endpoint was met.

Figure 25 shows that following cross-over, the BP decreased and was maintained through 12 months in SOLO while these patients were on consistent medications. Similarly in TRIO, a decrease in BP was observed at 6 months following the cross-over procedure, compared to the cross-over baseline visit BP, while patients were on fewer medications.

Figure 25: SOLO and TRIO: Change from Baseline Cross-Over Visit in Daytime Ambulatory Systolic Blood Pressure in Sham Patients who Crossed Over to Receive uRDN with Paradise System



HTN=hypertensive; uRDN= ultrasound renal denervation

1.6 Safety Findings

This briefing document includes all available safety data on patients enrolled in SOLO, TRIO, and RADIANCE II. Overall, findings from the three RADIANCE studies demonstrate that the Paradise System has a favorable safety profile, and no significant safety risks have been identified acutely or through long-term follow-up.

1.6.1 Primary Safety Endpoint Results

RADIANCE II included a prespecified primary safety endpoint, which was a composite of major adverse events (MAEs) occurring within 30 days and new onset renal artery stenosis > 70% within 6-months post-procedure. The within 30-day MAEs included:

- All-cause mortality
- New onset end-stage renal disease
- Significant embolic event
- Renal artery perforation
- Renal artery dissection
- Major vascular complications
- Hospitalization hyper/hypotensive crisis

- Hospitalization major CV events
- New onset stroke
- New onset myocardial infarction

All potential primary safety events were adjudicated by an independent clinical endpoint committee (CEC). The composite event rate was to be compared to a prespecified performance goal of 9.8%. No events in RADIANCE II met the definition of MAE in either treatment group.

1.6.2 Adverse Events and Adverse Device Events

Table 4 shows an overview of adverse events (AEs) reported in RADIANCE II, SOLO, and TRIO at any time during the study. All AEs as per ISO:14155:2011 were collected. The rate of AEs and serious adverse events (SAEs) was generally similar between groups across studies. The adverse device events (ADE) and serious adverse device event (SADE) rates are marginally higher in the treatment groups than in sham groups, as would be expected given that the treatment patients undergo a procedure that is lengthier than a renal angiogram (sham) and the uRDN procedure incorporates energy delivery to ablate nerves. As such, certain events are specific to the delivery of energy to ablate the nerves such as transient vasospasm, brief bouts of bradycardia, and the occasional vaso-vagal response. All of these events were attributed to the procedure and resolved quickly during the procedure, with either no intervention or intra-procedural medication such as nitroglycerin or atropine. It is important to note the majority of ADE/SADE were procedure-related and not device-related, the events resolved within a short period of time, and that the event rate for serious events was low.

There were no unexpected ADEs reported in any study. The pattern of events was similar when assessing only peri-procedural events that occurred ≤ 30 days post-procedure (Table 35 in Section 7.2.2).

Table 4: RADIANCE-HTN Studies: Summary of Adverse Events

	RADIANCE II		SOLO		TRIO	
Patients with, n (%)	**uRDN (N=150)**	**Sham (N=74)**	**uRDN (N=74)**	**Sham (N=72)**	**uRDN (N=69)**	**Sham (N=67)**
Any AE	83%	74%	72%	76%	86%	81%
ADE	61%	47%	55%	32%	54%	31%
Unexpected ADE	0	0	0	0	0	0
Serious AE	10%	9%	11%	11%	26%	24%
Serious ADE	7%	1%	7%	0	4%	3%
Unexpected serious ADE	0	0	0	0	0	0

AE=adverse event; ADE=adverse device event; uRDN=ultrasound renal denervation.

In RADIANCE II and SOLO, the only SAEs that occurred ≥ 2 times were hypertensive crisis and cholelithiasis (Table 38 in Section 7.2.5). In TRIO, ventricular tachycardia was reported in ≥ 2 patients, in addition to hypertensive crisis and cholelithiasis.

Importantly, the types and rates of ADEs seen in the clinical studies are consistent with what has been seen in other catheter-based procedures (Doyle et al 2008). Vascular access pain and vascular access site hematoma were the most frequently reported ADEs across studies (Table 39 in Section 7.2.7). Transient vasospasm was reported as an ADE in approximately 20% of patients treated with uRDN in SOLO and TRIO. The most commonly reported serious ADEs were vascular access site hematoma, syncope, and bradycardia related to drug therapy (Table 40 in Section 7.2.7). Overall, the majority (80%) of ADEs were transient (resolving within 30 days) and not unexpected given the use of ultrasound energy.

Seven deaths were reported in the RADIANCE studies: 2 among patients treated with uRDN and 5 in sham. No deaths were considered by the investigator as related to the procedure or device. One additional death due to pancreatic cancer occurred during the screening phase, prior to randomization. Details are provided in Section 7.2.8.

1.6.3 Safety Topics of Interest

Post-procedural pain; new onset orthostatic hypotension; renal function based on urine protein creatinine ratio (UPCR), estimated glomerular filtration rate (eGFR), and creatinine; and new onset renal artery stenosis (based on imaging of renal arteries) were safety topics of interest in the RADIANCE studies.

Patients were asked to evaluate their pre- and post-procedure pain using a visual analog scale (0=no pain to 10=worst pain) in all 3 studies. Overall, pain scores were low (1.2–2.1) post-procedure and similar between groups. Patients who received uRDN were more likely to report procedure-related pain lasting for > 2 days (Table 41 in Section 7.2.9). Of note, the reported post-procedure pain in both uRDN and sham patients was most often associated with the vascular access site (RADIANCE II 26/53 [49%], SOLO 12/16 [75%], TRIO 15/22 [68%]), and the pain resolved without sequelae.

Few patients experienced events of new onset orthostatic hypotension. Specifically, 1 patient in the RADIANCE II study and 2 patients in SOLO experienced new onset orthostatic hypotension, all in the uRDN group. One event occurred 221 days post-procedure; the patient reported feeling lightheaded when standing, did not experience fainting or falling, and the event resolved without treatment or sequelae. The other 2 events occurred < 1-day post-procedure, and both resolved the same day.

Given the importance of proteinuria as a proxy of kidney damage, proteinuria (estimated by UPCR) and serum creatinine and corresponding eGFR were assessed at baseline and Months 2, 6, and 12. There was no significant change from baseline in UPCR, eGFR, or serum creatinine in any group in any study. No patient experienced decreases in eGFR > 57% or a doubling of serum creatinine, and both parameters remained within normal ranges in all patients (details provided in Section 7.3.3).

As prespecified in the protocol, extensive imaging was performed in each study. All patients were required to undergo CTA or MRA to assess anatomic eligibility. All treated patients in SOLO, TRIO, and RADIANCE II were required to undergo CTA or MRA at 12 months post-procedure. Additionally, all randomized (treatment and sham) patients in RADIANCE II were required to undergo CTA or MRA at 6 months post-procedure. Follow-up imaging was reviewed by independent diagnostic radiologists (SOLO/TRIO) or by an Imaging Core Lab (RADIANCE II).

Six- and 12-month imaging data are available for 92% and 94%, respectively, of patients from RADIANCE II. Imaging evaluations with core lab adjudication showed no evidence of renal injury, nor of new onset renal artery stenosis > 70% in uRDN-treated patients. The vast majority (97% at 6 months and 94% at 12 months) of uRDN-treated patients had no measurable stenosis of any degree, and the proportion of patients with any renal artery stenosis was balanced between treatment groups, with no patients experiencing clinically significant, flow limiting- narrowing of > 70% (additional details in Section 7.5).

1.6.4 Pooled Safety Results

A pooled analysis of MAEs from all 3 studies was conducted to further characterize the safety profile of uRDN. Data from these studies were able to be pooled because of the similarities between the studies in terms of the procedure, treatment strategy, renal anatomy treated, and device. The pooled analysis used the primary safety composite endpoint from RADIANCE II and the performance goal of 9.8%. In this analysis of 367 patients, 6 met the definition for MAEs, for an overall composite rate of 1.1%. The events included 2 deaths, 2 major vascular complications, 1 hospitalization for hypotension, and 1 hospitalization for major cardiovascular event. All events were adjudicated by the CEC as unlikely to be related or not related to the procedure. There was no new onset of renal artery stenosis > 70% at 6 months.

Additionally, a pooled analysis was done whereby all available 12-month CTA/MRA from treated patients in SOLO, TRIO, and RADIANCE II (n=238 combined) were assessed by the Imaging Core Lab. The pooled 12-month imaging data from the 3 studies showed no evidence of renal injury in uRDN-treated patients. Based on core lab adjudication, no patients had new onset renal artery stenosis > 70%.

1.7 Patient Preference Study

ReCor conducted a patient preference study to better understand if patients would prefer a renal denervation therapy as opposed to current standard of care for the management of uncontrolled hypertension. The choice between medication and renal denervation to treat hypertension involves trading-off pill burden, minimally invasive procedures, cardiovascular outcomes, and treatment risks. This study quantified how patients make those trade-offs and consequently estimate the likelihood that patients would prefer the Paradise System over standard antihypertensive medications.

An online discrete choice experiment (DCE) was completed by US adults with uncontrolled hypertension despite being prescribed ≥1 medication. In 10 DCE tasks, participants chose between two hypothetical treatments defined by the 10-year cardiovascular risk, current treatments (procedure/number of pills per day), durability/need for future treatments (additional procedure or pills), and risks of mild-to-moderate and serious AEs. The attributes were developed through a targeted literature review, 10 qualitative interviews, and FDA feedback, and were refined through 5 cognitive pilot interviews. DCE data were analyzed using mixed logit models which were used to simulate treatment uptake in different scenarios.

The study sought to enroll patients with a similar background to those enrolled in the RADIANCE studies. Two hundred fifty-eight (258) patients were enrolled, of which 62% were female, 40% non-white, 63% from the South US, with a mean age of 53 years and mean BMI of 33 kg/m^2. The most frequent currently used antihypertensive was amlodipine (35%). Most participants reported that they had their hypertension diagnosis within 6 years (46.5%) and almost all reported a family history of hypertension (93.8%). While most of the participants did not have a history of a procedure (77.1%), some had received angioplasty (9.3%), stent replacement (8.9%), or intravascular ultrasound (7.4%).

Numeracy, literacy, and internal validity tests suggest the preference data was good quality. Most participants had high health literacy (n=248, 96%) and numeracy (n=244, 95%) and passed the stability test (n=233, 90%) and dominance test (n=246, 95%). The mean survey completion time was 11.9 min. While 61% of participants did not make choices based on a single attribute, one third of the participants made choices predominantly based on 10-year cardiovascular risk.

Participants put the most weight on cardiovascular risk when deciding between treatment options. Given the same number of pills, 42% would choose an interventional treatment if it reduced their 10-year cardiovascular risk by 5% more than medication alone. In addition, 42% of patients would prefer a one-time invasive procedure versus taking an additional pill if the procedure had the same effect on cardiovascular risk as medication alone.

A substantial number of patients taking medication for hypertension would be willing to undergo renal denervation to reduce their cardiovascular risk or to avoid an increase in their pill burden.

1.8 Benefit-Risk Summary

Hypertension is a major risk factor for cardiovascular diseases, including stroke, myocardial infarction, heart failure, arrhythmia (including sudden death), and kidney failure. It is well-established that a reduction in BP improves cardiovascular morbidity and mortality and provides substantial clinical benefit. Despite effective measures of BP management – lifestyle modifications and antihypertensive medications – uncontrolled hypertension is a persistent problem in the US and globally. Patients who are

inadequately responsive or intolerant to standard of care antihypertensive medications remain at increased risk and need a safe and effective treatment option that can reduce BP and ultimately improve outcomes with less reliance on daily antihypertensive medications.

A device-based therapy, such as the Paradise System, that requires a short standard interventional catheter procedure, may be an alternative option for physicians and patients to effectively manage BP and ultimately improve outcomes. The clinical data on the Paradise System indicates that this may be a therapeutic alternative for those patients that do not consistently take medications (intolerant or poorly adherent) or may be considered adjunctive to medications for those who are adherent with a medication regimen but would prefer to reduce their daily medication intake or do not adequately respond to standard antihypertensive medications.

The Paradise System has been studied in 3 randomized, blinded, sham-controlled clinical studies in patients with varying degrees of hypertension including mild-to-moderate and resistant hypertension, in the presence or absence of antihypertensive medications. Findings from these studies demonstrate that the Paradise System provides statistically significant and clinically meaningful continuous BP reductions in these patient groups, with an average sham-adjusted decrease in daytime ambulatory systolic BP of 8 mmHg at 2 months in each study. The magnitude of the effect is considered clinically meaningful and likely to translate into an overall relative risk reduction in cardiovascular events. Translation of a reduction in BP to clinical outcomes is well accepted and is based on published meta-analyses correlating risk reductions with reductions in BP (Ettehad et al 2016; Rahimi et al 2021).

Importantly, BP was lowered over a 24-hour period. This effect of renal denervation on BP is considered to be ‘always on’ in that there are no diurnal fluctuations, in contrast to medications which have peaks and troughs in their effect. Clinically meaningful reductions in BP were sustained through long-term follow-up.

The Paradise System has a favorable safety profile. No significant safety risks have been identified acutely or through long-term follow-up. Consistent with any catheter-based procedure requiring femoral access, access site pain/swelling was the most commonly reported AE in the RADIANCE studies. There have been few serious adverse device/procedure-related events (≤ 3%), of which all have been transient and resolved with no long-term sequelae. Injury to the renal artery and/or the kidneys is rare, and there have been no reports of new onset clinically significant renal artery stenosis requiring intervention.

In summary, the Paradise System would provide an important treatment option for patients who are unable to achieve BP control with standard of care antihypertensive medications and remain at increased risk of BP-related cardiovascular morbidity and mortality. The Paradise System has been shown to be safe and to significantly reduce BP, filling a critical treatment gap for patients with mild-to-moderate or resistant hypertension.

2 BACKGROUND ON UNCONTROLLED HYPERTENSION

Summary

- Patients with hypertension who are inadequately responsive to or intolerant to standard of care antihypertensive medications remain at increased risk of significant cardiovascular events including stroke, heart failure, heart attack, and death.
- In the US, hypertension is the leading risk factor for cardiovascular-related deaths.
- Approximately half of all patients with hypertension do not adhere consistently to prescribed antihypertensive medications.
- More than 80% of patients with uncontrolled hypertension are nonadherent to prescribed medications, which is directly linked to worse outcomes.
- Approximately 12%–15% of patients treated with antihypertensives have resistance to ≥ 3 medications and accordingly have limited treatment options.
- The afferent and efferent sympathetic nerves encircling the renal arteries and enervating the kidneys play an important role in BP regulation and the pathophysiology of hypertension.
- Decreases in activity among these nerves can lead to corresponding decreases in BP.
- Treatments targeting renal nerves have the potential to offer new treatment options for patients with hypertension.
- Patients with uncontrolled hypertension need a safe and effective treatment option that can reduce their BP and improve outcomes with less reliance on adherence to daily antihypertensive medications.

2.1 Overview of Uncontrolled Hypertension

Hypertension is a major public health burden, with a prevalence of more than 116 million patients and causing an estimated 670,000 deaths annually in the US (Bovet and Chiolero 2018; Mills et al 2016). Hypertension increases the risk of heart disease and stroke, which are the world's leading causes of death. From 2005 to 2015, the mortality rate associated with elevated BP rose by 10.5%, and the number of deaths attributed to hypertension increased by 37% (Benjamin et al 2018).

Nearly half (49.6%) of all US adults ages > 20 years are reported to have hypertension, and nearly 80% of US adults > 65 years of age have hypertension (Centers for Disease Control and Prevention 2023). Only 26% of US adults with hypertension have BP under

control. In the US, hypertension accounts for more cardiovascular-related deaths than any other risk factor and is projected to remain the most significant risk factor leading to years of life lost through 2040 (Foreman et al 2018; Forouzanfar et al 2017; Lim et al 2012).

A meta-analysis of 123 studies in more than 600,000 patients showed that BP-lowering treatment significantly reduced the risk of cardiovascular disease and death (Ettehad et al 2016). This analysis showed that a 10-mmHg reduction in office SBP reduces the risk of major cardiovascular events by 20%, with even greater reductions in individual risks of stroke and heart failure. Another recent meta-analysis of nearly 350,000 individuals with or without pre-existing cardiovascular disease showed that even a 5-mmHg reduction in office SBP can reduce risk of cardiovascular events by 10%, regardless of underlying risk (Rahimi et al 2021). As such, effective means of controlling hypertension are needed to reduce the global risk of cardiovascular disease and resultant mortality.

Additional studies support the benefit of BP control. Results from the VALUE study showed that patients reaching a SBP of < 140 mmHg by 6 months of treatment with different antihypertensive medications achieved significant benefits across major cardiovascular outcomes (Weber et al 2004). The SPRINT study showed further benefits on both cardiovascular mortality and all-cause mortality from additional BP reductions to < 120 mmHg achieved with intensive treatment; however, patients could not sustain this BP control, and the benefit was lost during long-term follow-up (Ambrosius et al 2014; Jaeger et al 2022).

2.2 Current Treatment Options

2.2.1 ACC/AHA Treatment Guidelines

Treatment guidelines from the American College of Cardiology (ACC) and the American Heart Association (AHA) define the threshold for initiating antihypertensive therapies as ≥ 130/80 mmHg (Stage I hypertension; Table 5). This threshold was updated in 2017 from the previous threshold of ≥ 140/90 mmHg (Stage II hypertension) (Whelton et al 2018).

Table 5: Categories of Hypertension, Associated Blood Pressure Readings, and Prevalence

	Blood Pressure Reading (mmHg)	
Blood Pressure Category	**Systolic BP**	**Diastolic BP**
Normal	< 120	< 80
Elevated	120 – 129	< 80
Stage I hypertension	130 – 139	80 – 99
Stage II hypertension	≥ 140	≥ 90
Hypertensive crisis	> 180	> 120
Rates Among US Residents	**Men**	**Women**
US prevalence of Stage I hypertension	48%	43%
US prevalence of Stage II hypertension	31%	32%
Rates of uncontrolled hypertension in US	50.7%	44.8%

BP=blood pressure; US=United States.
Source: Whelton 2017

First-line treatment for patients with hypertension focuses on lifestyle changes, including reduced consumption of salt, caffeine, and alcohol; increased exercise; and smoking cessation. Second-line treatments include the use of antihypertensive medications, such as calcium-channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and thiazide diuretics. Guidelines typically recommend initial use of 1 or 2 drugs from different classes.

2.2.2 Persistence of Uncontrolled Hypertension

Despite numerous treatment options, many patients struggle to control BP and might benefit from additional therapeutic options. The persistence of uncontrolled hypertension is in part due to medication non-adherence and/or variable medication adherence. Specifically, approximately half of patients with hypertension fail to adhere to prescribed medication, and more than 80% of patients with uncontrolled hypertension are nonadherent to medication (Abegaz et al 2017). Additionally, an estimated 12%–15% of patients with hypertension have treatment-resistant hypertension, which persists despite simultaneous use of ≥ 3 antihypertensive medications (Carey et al 2018).

2.2.3 Role of Overactive Sympathetic Renal Nerves

The underlying pathology of hypertension is complex and multifactorial. The majority (90%–95%) of cases are likely caused by a combination of lifestyle and genetics, although some cases may be idiopathic. However, an estimated 5%–10% of hypertension cases can be linked to overactivity of the sympathetic nervous system in the renal, vascular, and metabolic systems. Specifically, the afferent and efferent sympathetic nerves encircling renal arteries and innervating kidneys play an important role in BP regulation and the pathophysiology of hypertension (Guyenet 2006; Joyner et

al 2010). Renal nerves contribute to hypertension through effects on the kidney that enhance sodium retention, vasoconstriction, and renin secretion and by effects on the CNS that increase systemic sympathetic activity (Sata et al 2018).

Disruption of activity in renal sympathetic nerves has been shown to prevent, delay, or reduce the magnitude of hypertension in animal models and human clinical trials (Azizi et al 2020; Azizi et al 2021; Azizi et al 2018; Azizi et al 2019; Campese and Kogosov 1995; DiBona et al 1997; Gosse et al 2021; Mahfoud et al 2021; Saxena et al 2022). Proof of concept has been demonstrated in humans via surgical sympathectomy (splanchnicectomy), but this is a major invasive procedure that reduces BP at the cost of significant operative mortality (Smithwick and Thompson 1953) and has since been abandoned with the advent of effective pharmacotherapy and minimally invasive renal denervation therapies.

2.2.3.1 Percutaneous Renal Denervation Therapy

Disruption of the afferent and efferent sympathetic nerve bundles was originally investigated as a treatment for resistant hypertension using radiofrequency (RF) energy based on a surgical procedure from the 1930s. The goal of renal denervation therapy is to achieve a reduction in sympathetic overactivity with the resultant effect of reducing systemic arterial BP and mitigating future organ damage. uRDN represents a potential treatment option for patients who are inadequately responsive or intolerant to antihypertensive medications. These therapies directly target overactive renal nerves, a key characteristic of hypertension.

2.3 Patient Unmet Medical Need

The unmet medical need for novel hypertension treatments is currently high and expected to grow even higher over the coming decades. Despite the availability of several classes of antihypertensive medications, half of patients with hypertension fail to adhere consistently to prescriptions, while approximately 12%–15% of patients have hypertension that is resistant to treatment with multiple classes of antihypertensive medications. Patients who continue to experience hypertension or are inadequately responsive or intolerant to standard of care antihypertensive medications remain at increased risk of significant cardiovascular events including stroke, myocardial infarction, heart failure, and death. These patients need a safe and effective treatment option that can reduce their BP and improve outcomes with less reliance on daily antihypertensive medications.

3 PRODUCT DESCRIPTION

Summary

- The Paradise System is a catheter-based system that delivers ultrasound energy circumferentially to thermally ablate and disrupt the renal sympathetic nerves with the goal of achieving a reduction in systemic arterial BP.
- While delivering ultrasound energy into the tissue surrounding the renal arteries, the Paradise System simultaneously cools the artery wall to prevent thermal injury to the artery.
- The Paradise System consists of a portable Paradise Generator, which powers the transducer, and a single-use 6 French Paradise Catheter that delivers ultrasound energy to thermally ablate the renal sympathetic nerves.
- There is no direct tissue contact with the ultrasound energy source, minimizing the risk of overheating the arterial wall with consequent tissue damage.
- The Paradise Catheter is advanced over a standard guidewire into the renal artery where there is a high concentration of sympathetic nerve activity.
- 7 seconds of energy delivery enables fast procedure times with the Paradise System.
- Preclinical studies have confirmed histologically the presence of significant nerve injury within the tissue target ablation region of 1–6 mm from the renal artery wall with no evidence of thermal or mechanical injury to the renal artery.
- The recommended treatment strategy consists of 2–3 emissions along the main renal arteries and 1 emission in accessory and/or proximal side branches (note: it is not necessary to treat distal branches or treat within the renal parenchyma).
- Once the renal arteries have been treated, the Paradise Catheter is removed from the body, and the procedure is finished according to standard interventional techniques.

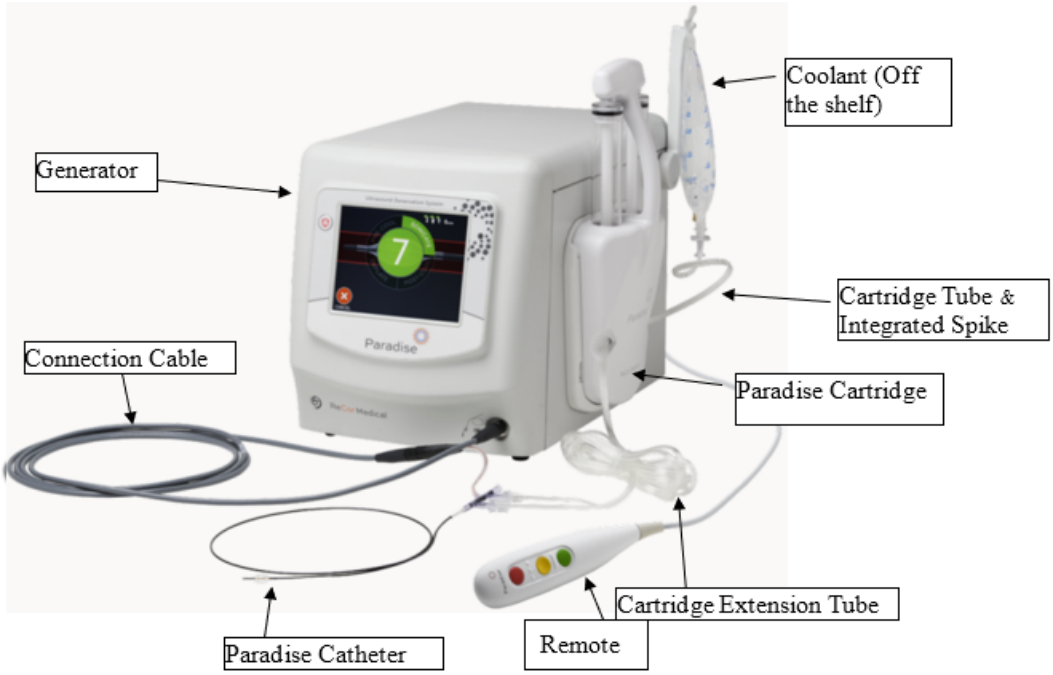
3.1 Proposed Indication

The Paradise System is indicated to reduce BP in patients with uncontrolled hypertension, who may be inadequately responsive to, or who are intolerant to antihypertensive medications.

3.2 Device and Procedure Overview

The Paradise System is a catheter-based system that delivers ultrasound energy circumferentially to thermally ablate and disrupt the renal sympathetic nerves with the goal of achieving a reduction in systemic arterial BP. The Paradise System comprises a catheter, generator, cartridge, and connection cable (Figure 26).

Figure 26: Schematic of Paradise System



The Paradise Generator is used in conjunction with the Paradise Cartridge and Paradise Connection Cable to circulate cooling fluid (ie, sterile water) and deliver electrical energy to the Paradise Catheter to ensure proper therapy. The Paradise Catheter, Cable, and Cartridge are single-use only components. The Generator uses a series of sensors and control software for management of fluid flow and ultrasound energy delivery to the Paradise Catheter. Fluid flow through the system allows for the transmission of ultrasound energy from the Paradise Catheter and removes unwanted heat during treatment.

The Paradise Catheter (with ultrasound transducer) is a 6-French renal artery catheter with a cylindrical piezoelectric ceramic ultrasound transducer located inside an inflatable balloon at the distal end of the Catheter. The Catheter has a memory chip that stores power delivery parameters used by the Generator to control the ultrasound energy power delivered by each catheter size, and thus provides for automatic setting of acoustic power for the corresponding artery size to produce the desired target ablation region. The catheter is available in 6 different balloon sizes: 3.5 mm, 4.2 mm, 5 mm, 6 mm, 7 mm and 8 mm in diameter. Each balloon size treats a range of artery diameters, thus allowing the catheter family to treat arteries ranging in size from 3–8 mm in diameter. The treating physician selects a balloon size based on the measured renal artery diameter under fluoroscopy.

The Paradise Catheter is delivered percutaneously via femoral access, under fluoroscopic guidance using commercially available compatible introducer sheaths and guiding catheters over a standard guidewire, into the renal artery. The Paradise Catheter is first advanced to the distal end of the main renal artery where there is a high

concentration of sympathetic nerve activity due to the branching of the nerves just behind the arterial wall. The Paradise Catheter's source of ablative energy is its ultrasound transducer that is mounted centrally inside the balloon of the catheter. Through a proprietary algorithm, the Paradise Generator regulates the inflation of the balloon with sterile water, automatically centering the ultrasound transducer in the artery. The Generator also continuously manages balloon pressure to ensure a constant, low pressure is being applied to allow gentle vessel wall contact. The Generator controls the fluid flow rate through the balloon, duration of acoustic energy delivery, and total acoustic power delivered; these parameters are fixed and non-alterable by the treating physician.

The Paradise Generator manages the uniform delivery of ultrasound energy circumferentially around the artery wall. The Paradise Cartridge is controlled by the Generator and drives the flow of coolant in and out of the Catheter in a closed-loop fluid circuit. The Paradise Connection Cable provides the electrical connectivity between the Generator and the Catheter, and it provides an electronic connection for accessing catheter information stored in the Catheter's memory chip. The circulation of fluid in the balloon during the heating cycle has a cooling effect at the surface of the artery, while the nerves are being heated and damaged at depth.

The balloon is automatically deflated after energy delivery has ended. The Paradise Catheter can then be moved to additional positions within the artery to provide additional therapy as needed. The procedure is repeated on the contralateral renal artery to achieve bilateral denervation. Once the renal arteries have been treated, the Paradise Catheter is removed from the body and the procedure is finished according to standard interventional technique.

3.2.1 Non-Clinical Studies to Determine the Ablation Settings for Use in the Paradise System

The target tissue ablation region is achieved by delivering an energy dose profile that combines thermal energy generation (from tissue ultrasound absorption) in the target tissue region, and thermal energy removal (from convective cooling) at the wall of the renal artery. The goal of the energy profile is to cool and thus preserve the renal arterial wall while ablating in the target region. The Catheter provides a balance of heating and cooling to deliver the appropriate energy dose while the Generator controls the input parameters to the Catheter (transducer frequency, power, duration, and fluid flow rate) to ensure proper and safe ablation.

The Paradise System delivers ultrasound energy in the form of heat, circumferentially. Energy is delivered along the length of the transducer resulting in a circumferential ablation band / toroid (~5 mm in length), extending to a mean depth of 6mm. The system has been optimized to deliver energy to a target ablation region (mean 1-6mm from the renal arterial wall) in the peri-adventitial tissue surrounding the renal artery to achieve significant nerve injury. The target ablation region has been chosen to ensure

minimal-to-no damage to the renal arterial wall and to non-target tissues (eg, iliopsoas muscle, large or small intestines, ureters) at depth, while maximizing renal sympathetic nerve injury to achieve a reduction in sympathetic nerve activity.

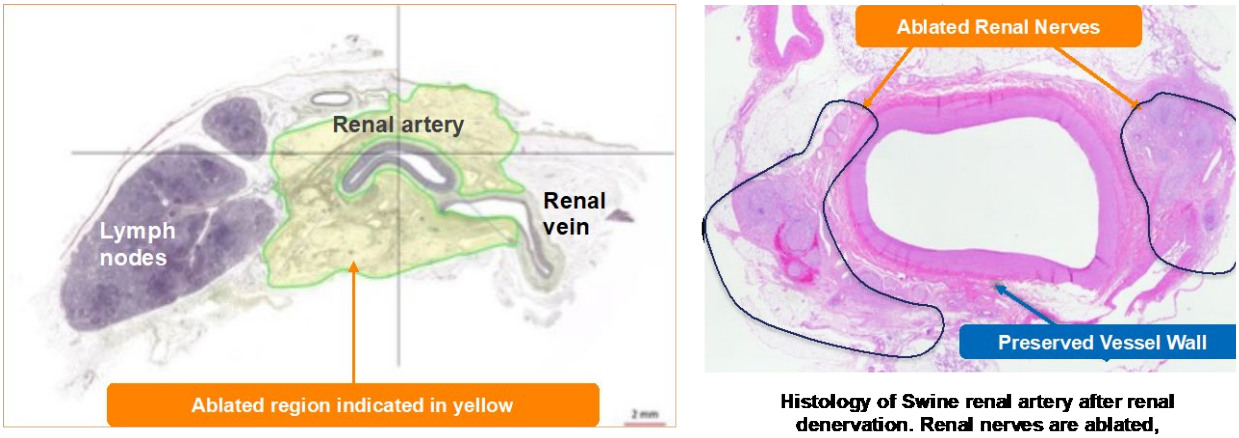
The selected target ablation region (1–6mm) is based on the detailed assessment describing the anatomic distribution of renal sympathetic nerves in humans published in JACC, 2014 by Sakakura et al (Sakakura et al 2014), and on the recent updated publication by Sato et al (Sato et al 2021).

ReCor conducted a series of non-clinical animal studies to select, characterize, and optimize the Paradise System ablation settings (acoustic power, time of energy delivery, and the cooling flow rate) to achieve a target ablation region for optimal nerve injury while protecting the renal arterial wall and protecting non-target tissues at depth.

Studies were conducted at 7 days, 28 days, and 90 days to evaluate histologically the extent of nerve injury following treatment with the Paradise System, as well as the safety of the system. Additionally, studies were conducted to assess the downstream effect of uRDN on norepinephrine levels to confirm that uRDN ablation results in a down-regulation of renal sympathetic nerve activity.

These preclinical studies demonstrated that the ablation settings (acoustic power, duration of energy delivery, and cooling flow rate) can be controlled and optimized to achieve a target tissue ablation region, with significant nerve injury within the target tissue ablation region (1–6mm, average, from the renal arterial lumen) (Figure 27). The coolant in the balloon is able to consistently and reproducibly protect the renal arterial wall from thermal injury. Additionally, the ablation settings can be controlled to minimize injury to non-target tissues at depth as well. The system can consistently, reliably, and significantly reduce norepinephrine levels in the kidney tissue following 2 to 3 emissions along the renal artery (Figure 28), which is the basis for the recommended treatment strategy (described in Section 3.2.2).

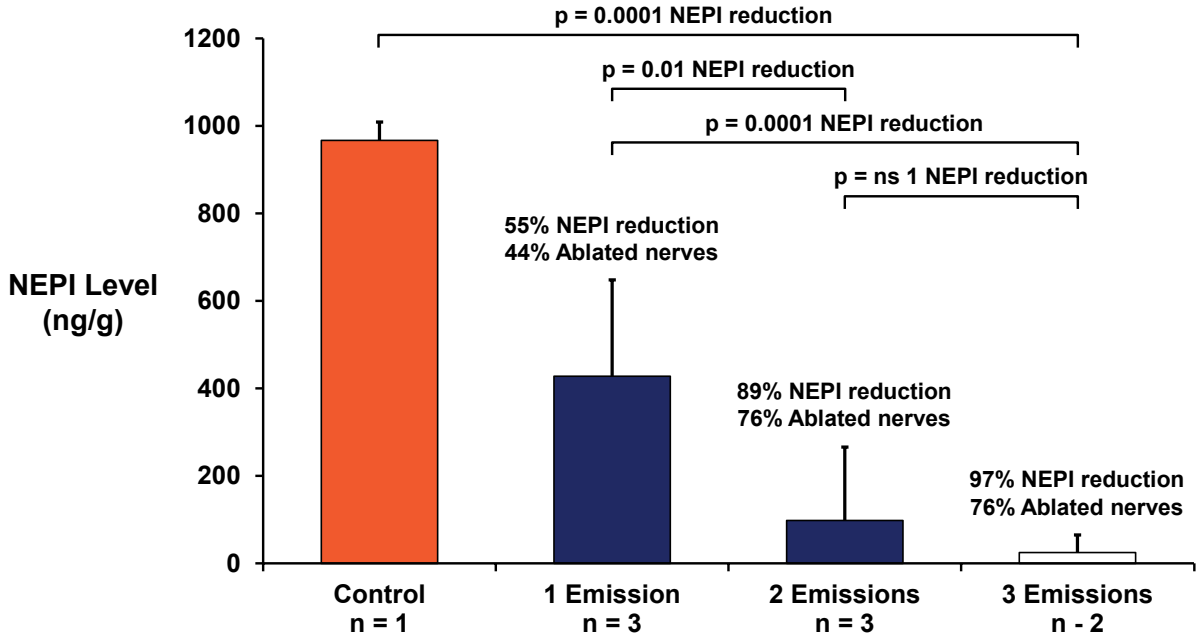
Figure 27: Porcine 7-Day Model of Ablated Renal Nerves



Histology of Swine renal artery after renal denervation. Renal nerves are ablated, yet arterial wall is preserved.

The tissue image on left shows target ablation region in yellow (target depth 1-6mm from the arterial lumen). The histologic image on right shows the renal arterial wall is protected from thermal injury and demonstrates the ablated renal nerves.

Figure 28: Porcine Model of Renal Norepinephrine Levels Following Ultrasound Emissions



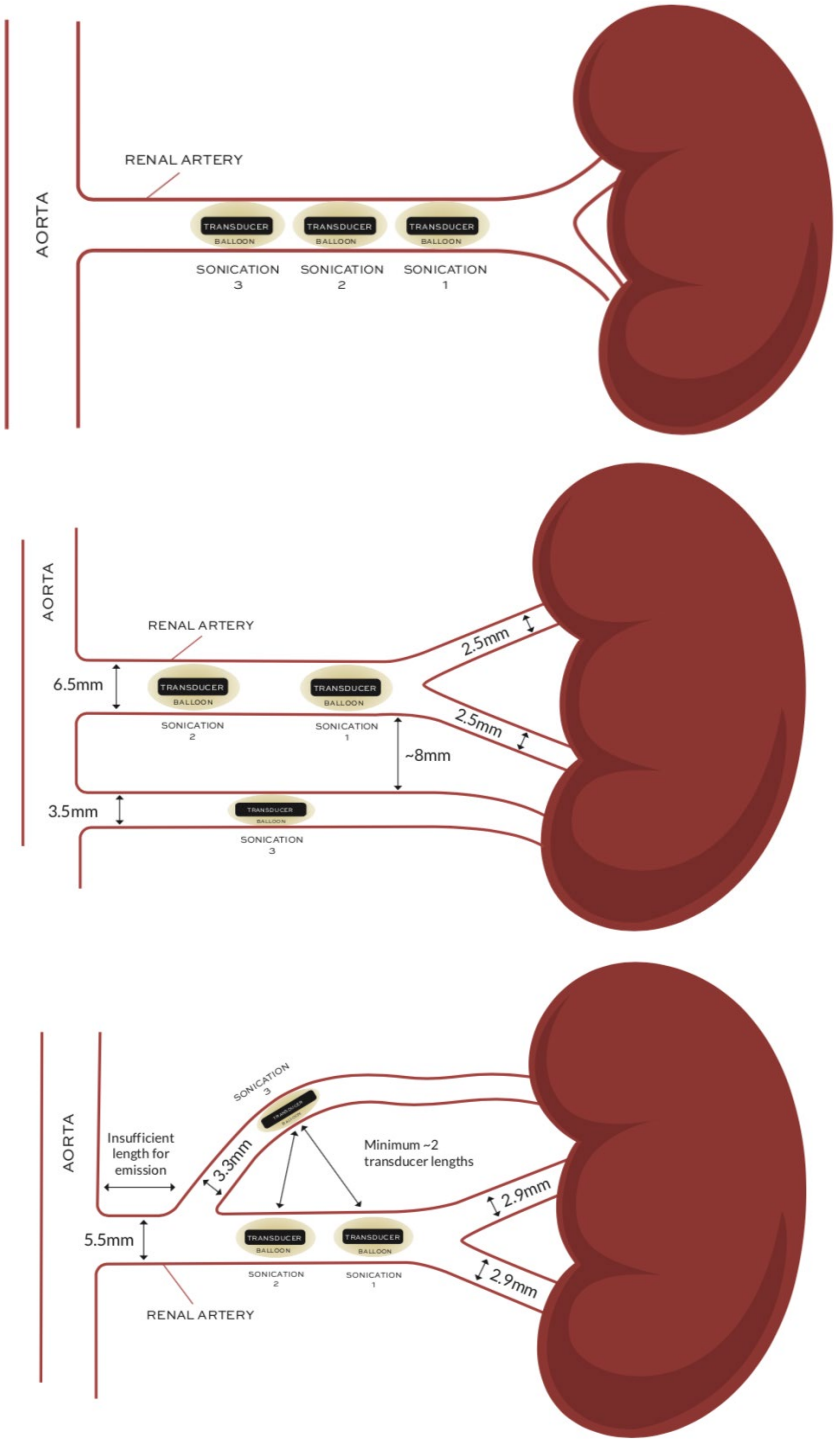
Renal Norepinephrine levels (porcine model) following 1, 2 or 3 ultrasound emissions. Significant reduction observed with 2 or 3 emissions.
Source: Pathak et al 2015

3.2.2 Treatment Strategy

To compensate for the presence of biological heat sinks (inferior vena cava, renal vein, and lymph nodes), which co-exist with the renal arteries in the peri-adventitial space, the recommended treatment strategy for use with the Paradise System includes delivery of 2–3 ultrasound emissions along each main renal artery, and 1 ultrasound emission along accessory arteries and proximal side branch arteries, when present. Emissions are to be delivered in a non-overlapping fashion; emissions are not delivered distally within the renal parenchyma.

The recommended treatment strategy is depicted in Figure 29. The top panel illustrates 3 emissions along a single main renal artery. The mid panel illustrates 2 emissions along a short main renal artery with one emission in an accessory artery. The bottom panel illustrates 2 emissions along a short main renal artery with 1 emission in a branch coming off the proximal portion of the main renal artery. While the treatment strategy may differ slightly depending on the specific anatomy, the basic principles depicted in Figure 29 apply.

Figure 29: Recommended Treatment Strategy



4 REGULATORY AND DEVELOPMENT HISTORY

Summary

- The Paradise System received Breakthrough designation in December 2020.
- The Paradise System clinical development program consisted of more than 500 patients from 3 randomized sham-controlled studies conducted in the United States and Europe:
    - RADIANCE II enrolled patients with mild -to moderate- hypertension
    - RANDIANCE-HTN, a 2-cohort study, included patients with mild-to-moderate hypertension in the SOLO study and patients with treatment-resistant hypertension on ≥ 3 antihypertensive medications in the TRIO study.
- Supportive evidence comes from a post-marketing study conducted in Europe (ACHIEVE).

4.1 Regulatory Milestones

ReCor Medical regulatory milestones include:

- The Paradise System received CE mark in 2012 for renal denervation in Europe.
- The original investigational device exemption (IDE) for RADIANCE-HTN SOLO and TRIO was approved in December 2015. Subsequently, the RADIANCE II pivotal study was approved in June 2018 under an IDE supplement.
- The Paradise System received Breakthrough designation in December 2020, for an indication to reduce BP in adult patients with uncontrolled hypertension, who may be inadequately responsive to, or who are intolerant to antihypertensive medications.
- The premarket approval (PMA) for the Paradise System was submitted on 26 October 2022.

4.2 Clinical Development Program

First in human evidence of the clinical safety and efficacy of a first generation uRDN system was evaluated in the REnal Denervation by Ultrasound transCatheter Emission (REDUCE) Trial, a single-center feasibility study initiated in 2011 and conducted in South Africa. Subsequently, the REALISE study was conducted in France, also on an earlier generation of the System. The ACHIEVE study, a multi-center study conducted

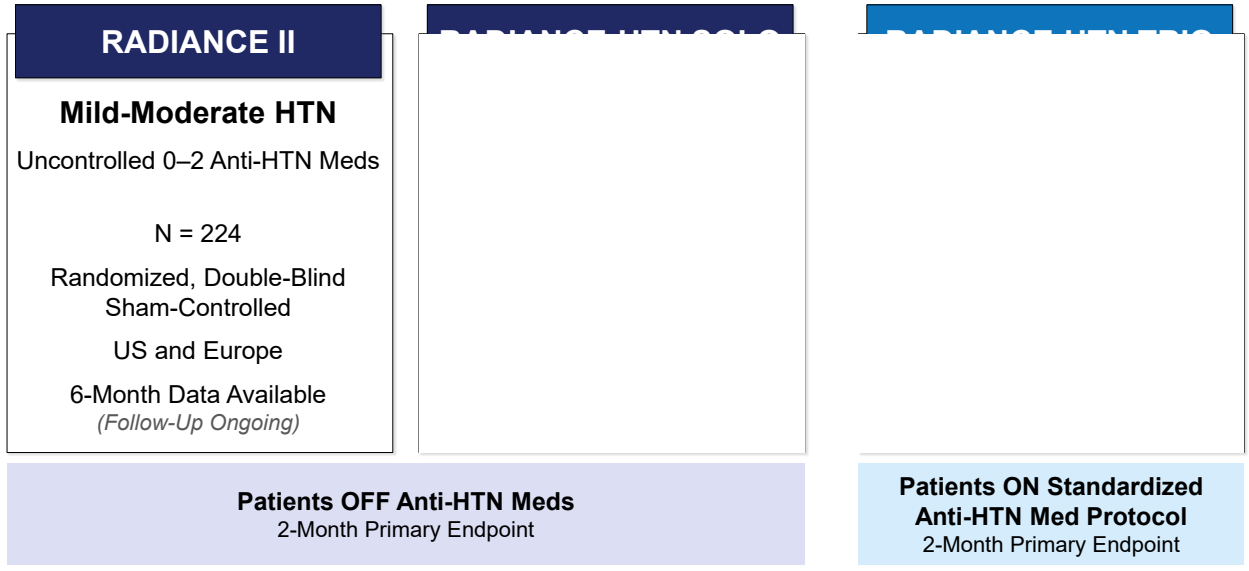
in Europe was initiated in 2013 and provides supportive evidence of the safety and effectiveness of the Paradise System.

In 2016, the RADIANCE-HTN Study, a randomized, double-blind, 2-cohort (SOLO and TRIO) study designed to evaluate the efficacy, and document the safety, of the Paradise System was initiated. This study included patients with mild-to-moderate hypertension washed out of antihypertensive medications (SOLO) and patients with treatment-resistant hypertension stabilized on a single triple antihypertensive medication pill (Amlodipine [10 mg], Valsartan [160 mg] or Olmesartan (40 mg), and Hydrochlorothiazide [25 mg]) (TRIO). The study design was based on the 2014 cardiovascular Think Tank co-sponsored by the American Society of Hypertension, the FDA, and the National Heart, Lung, and Blood Institute. SOLO has completed randomization and follow-up through 36 months, and TRIO has completed randomization and follow-up through 24 months.

In 2018, the RADIANCE II pivotal study was initiated to obtain additional data on the uRDN system to ensure an adequate sample size for a robust safety assessment. RADIANCE II is a randomized, sham-controlled study, which enrolled patients with mild-to-moderate hypertension. RADIANCE II has completed randomization and follow-up through 6-months.

Figure 30 provides an overview of the 3 studies considered part of the Paradise System clinical development program.

Figure 30: Paradise System Clinical Development Program



HTN=hypertension; US=United States.

5 STUDY DESIGNS

Summary

- RADIANCE II and SOLO enrolled patients with mild-to-moderate Stage 2 hypertension who were taking 0–2 antihypertensive medications; TRIO enrolled patients with uncontrolled hypertension despite the use of ≥ 3 antihypertensive medications.
- Patients in RADIANCE II and SOLO had to complete a 4-week wash-out of all antihypertensive medications because the primary endpoint in these studies was the efficacy of uRDN in the absence of antihypertensive medications.
- Patients in TRIO had all antihypertensive medications replaced with a single pill, which included a combination of 3 fixed-dose antihypertensive medications. Patients were stabilized for 4-weeks on the triple pill (Amlodipine [10 mg], Valsartan [160 mg] or Olmesartan (40 mg), and Hydrochlorothiazide [25 mg]).
- After 4 weeks, patients meeting the eligibility criteria were randomized (2:1 in RADIANCE II and 1:1 in SOLO and 1:1 in TRIO) to the Paradise System or sham (renal angiogram).
- The primary endpoint was the difference in the reduction in average daytime ambulatory SBP at 2 months post-procedure between uRDN and sham.
- Following the primary endpoint visit, patients were treated according to a standardized medication titration protocol with the goal of achieving BP control through 6 months post-procedure to assess the impact of the Paradise System in the presence of medications.
- After the 6-month follow-up visit in SOLO/TRIO and the 12-month follow-up visit in RADIANCE II, patients were unblinded.
- After the 6-month follow-up visit, patients were treated according to standard of care in all 3 studies.
- Long-term assessments were conducted at Months 12, 24, 36 and/or 48 and 60 months to evaluate the durability of the treatment effect.

RADIANCE II and RADIANCE-HTN were designed to assess the safety and efficacy of the Paradise System to reduce BP in patients 18–75 years of age with mild, moderate, and resistant forms of hypertension. These studies were designed in accordance with FDA guidance and had similar design features but were independently powered for effectiveness and are described separately below.

5.1 RADIANCE II

5.1.1 Study Design

RADIANCE II was a randomized, double-blind, sham-controlled, single cohort study designed to demonstrate the effectiveness and safety of the Paradise System in patients with Stage 2 hypertension on 0–2 antihypertensive medications of different classes. Patients meeting the enrollment criteria were randomized (2:1) to the Paradise System or sham procedure, which consisted of a renal angiogram procedure.

Eligible patients were required to stop taking all antihypertensive medications for a 4-week wash-out period at screening, and through the 2-month primary endpoint. For the period of wash-out through the 2-month primary efficacy endpoint visit, changes in medication could only occur:

- As required to facilitate antihypertensive drug wash-out per standard Institutional guidelines
- In the incidence of a BP emergency associated with clinical events believed to be related to persistent or elevated hypertension
- In the incidence of a clinical event that means a change in medication becomes necessary

Patients remained blinded up to the 12-month follow-up visit. Patients were blinded during the procedure by ensuring the patient was under conscious sedation and using standard Sponsor-provided headphones and eye covers. Study personnel responsible for the measurement and upload of ABP post-randomization were also blinded. A blinding index was used to evaluate the success of patient blinding post-procedure and at 2-, 6-, and 12-months.

Patients were required to remain free of antihypertensive medication through the 2-month primary efficacy endpoint visit. Between the 2-month and 6-month follow-up visits, a predefined protocol for escalation of antihypertensive medication was required for patients whose BP was not controlled. BP was evaluated at each follow-up visit between 2 and 6 months.

5.1.1.1 Blood Pressure Measurements

Office Blood Pressure: Measurement of office BP was done according to guidelines based on the 2017 ACC/AHA Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults. Patients were seated in a chair for > 5 min; were told to avoid caffeine, exercise, and smoking for ≥ 30 min before measurement; emptied his/her bladder; were told not to talk; and removed all clothing covering the location of cuff placement. At the first visit, BP was recorded in both arms, and the arm that gave the higher systolic reading was used for subsequent readings. Repeated measures were separated by 1–2 minutes.

Home Blood Pressure: All patients were provided with a validated home BP monitor with a cuff size appropriate to fit the arm. Patients were educated on the use of all the equipment necessary to record and report their home BP as well as the fact that individual BP readings may vary substantially. If differences were significant (> 10 mmHg), patients were instructed to use the arm with the higher systolic reading. Instructions for home BP measurement were similar to office BP measurement: take measurements in a quiet room; avoid smoking, caffeine, or exercise within 30 minutes of measuring BP, sit quietly for ≥ 5 min before measurement; ensure that the same arm is used for all home BP measurements; and take ≥ 2 BP measurements 1–2 minutes apart in the morning before taking medications and in the evening before dinner.

24-Hour Ambulatory Blood Pressure: All patients were provided with an ABP system with a cuff size appropriate to fit the arm. The ABP recording was done consistently at each timepoint, either during the week or on the weekend. Patients were advised to start and stop all ABP measurements at around the same time of day. Patients were advised not to remove the cuff during the 24-hour period of recording even when washing. During the period in which measurements occur, patients were instructed to relax their arm and try not to walk or speak. BP was measured every 20 minutes during daytime (07:00-22:00 hours) and every 30 min overnight (22:00-07:00 hours). The first hour of recordings were excluded as a “white coat window.” A time-weighted average was obtained (see List of Definitions).

5.1.1.2 Medication Escalation

Following the primary endpoint assessment at 2 months, if control was not achieved at any follow-up visit up to the 6-month follow-up visit, antihypertensive medication was started or escalated to the next step sequentially (see Table 6), unless otherwise medically indicated. The medication escalation started at the follow-up visit where a sustained elevation (≥ 135 mmHg SBP or ≥ 85 mmHg DBP) in average home BP was recorded and confirmed by an average office SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. Medication was recommended when elevated hypertension was sustained over 3 consecutive days. If an in-office BP was not obtained, the home BP diary was used to confirm the need for clinical intervention.

Table 6: RADIANCE II: Medication Escalation Protocol

Escalation Step	Drug Class	Recommended Drugs
1	Long acting dihydropyridine CCB: mid dose	Amlodipine: 5 mg
2	ARB or ACEi: full dose	ARB: Valsartan 160–320 mg; Olmesartan 20–40 mg ACEi: Ramipril 10–20 mg; Lisinopril 20–40 mg
3	Thiazide diuretic: low dose	HCTZ 12.5 mg
4	Thiazide diuretic: full dose	HCTZ 25 mg
5	Long acting dihydropyridine CCB: full dose	Amlodipine: 10 mg

ACEi=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; CCB=calcium channel blocker; HCTZ=hydrochlorothiazide.
Note: All recommended doses are once daily

Following at least 12 months of follow-up, patients randomized to the sham control group who met the eligibility criteria could cross-over and receive treatment.

5.1.2 Imaging Core Lab

An imaging core laboratory reviewed all follow-up CTA/MRA imaging. The core lab assessed the imaging studies submitted through the BioClinica image database called BioClinica SmartSubmit. The core lab reviewed images for evidence of renal artery injury and/or narrowing, and for evidence of renal injury. If any abnormalities were observed, the images were compared to baseline pre-procedure CTA/MRA and/or procedure angiographic imaging. The imaging core lab was not used to determine anatomic eligibility; eligibility was determined by the site.

5.1.3 Key Enrollment Criteria

Key inclusion criteria included:

- Age ≥ 18 and ≤ 75 years at time of consent
- Documented history of hypertension
- Previously or currently prescribed antihypertensive therapy
- Average seated office BP ≥ 140/90 mmHg < 180/120 mmHg at Screening Visit while stable for at least 4 weeks on 0–2 antihypertensive medications of different classes
- Documented daytime ABP ≥ 135/85 mmHg and < 170/105 mmHg at Baseline Visit after 4-week wash-out/run-in period
- Suitable renal anatomy compatible with the renal denervation procedure and documented by renal CTA or MRA of good quality performed within one year prior to consent (a CTA or MRA was obtained in patients without recent [≤ 1 year] cross-sectional renal imaging) and then confirmed by renal angiogram in patients that continue to procedure prior to randomization.

Key exclusion criteria included:

- Renal artery anatomy on either side ineligible for treatment
- Iliac/femoral artery stenosis precluding insertion of the Paradise Catheter
- Known, uncorrected causes of secondary hypertension other than sleep apnea
- Type I diabetes mellitus or uncontrolled Type II diabetes (defined as plasma HbA1c ≥ 9.0%)
- eGFR of < 40 mL/min/1.73 m^2
- Brachial circumference ≥ 42 cm

- Any history of cerebrovascular event (eg, stroke, transient ischemic event, cerebrovascular accident)
- Any history of severe cardiovascular event (eg, myocardial infarction, coronary artery bypass graft [CABG], acute heart failure requiring hospitalization [New York Heart Association (NYHA) class III-IV])
- Documented confirmed episode(s) of stable or unstable angina within 12 months prior to consent

5.1.4 Effectiveness Endpoints

The primary efficacy endpoint was the difference in average daytime ambulatory SBP between uRDN treatment with the Paradise System and sham control procedure (diagnostic renal angiogram) at 2 months post-procedure.

Secondary efficacy endpoints included the following, which were tested in hierarchical order:

- Reduction in average 24-hour ambulatory SBP at 2 months post procedure
- Reduction in average home SBP at 2 months post procedure
- Reduction in average office SBP at 2 months post procedure
- Reduction in average daytime ambulatory DBP at 2 months post procedure
- Reduction in average 24-hour ambulatory DBP at 2 months post procedure
- Reduction in average home DBP at 2 months post procedure
- Reduction in average office DBP at 2 months post procedure

Methods for BP measurements are described in Section 5.1.1.1.

5.1.5 Safety Endpoint

The primary safety endpoint was a composite of MAEs occurring within 30 days and new onset renal artery stenosis at 6 months.

5.1.5.1 Performance Goal

The primary safety endpoint was compared to a prespecified performance goal of 9.8%. The performance goal was derived from a review of AEs in studies of renal artery angioplasty or stenting, which was estimated to be 14.2% (ranging from 9.5% to 23.2%). Since there was precedent for use of this endpoint in another RDN trial that utilized 9.8% as a target, and this level fell within the range from the literature review), 9.8% was adopted as the performance goal. The estimated sample size of 128 treated patients provides 95% power for the performance goal if the population safety rate is approximately 3.0%.

5.1.6 Statistical Methods

5.1.6.1 Sample Size Calculation

The sample size for the study was based on a desire to compare randomized groups at the point of the Primary Efficacy Endpoint. Calculations were based on evaluating the treatment versus control groups.

Statistical analyses were performed at a two-sided 0.05 alpha level. Sample size calculations were based on a two-sample t-test. The planned analysis with the adjustment for baseline provided additional power beyond this, but the precise level depended on the correlation of the baseline value with the reduction during follow-up. Based on a 2:1 randomization, two-sample t-test, for an assumed mean ± standard deviation difference of 6±12 mmHg between uRDN and sham, a planned evaluable sample size of 192 patients was determined to provide 90% power.

5.1.6.2 Analysis Populations

The Intention-to-Treat (ITT) population consisted of all randomized patients analyzed according to their original randomization assignment.

The modified Intention-to-Treat (mITT) population consisted of all randomized patients analyzed according to their original randomization assignment, except excluded patients that met the protocol-defined criteria necessitating the restart of antihypertensive medication prior to the 2-month primary endpoint.

The Per-Protocol (PP) population consisted of all patients who were randomized, had treatment delivered successfully and were free from major issues which may have affected the assessment of the treatment:

- Baseline daytime ABP < 135/85mmHg or failure to obtain baseline ABP recording
- Renal artery anatomical exclusion deviations
- Failure to obtain 2-month follow-up ABP recording
- Patients restarting antihypertensive medication, for any reason, prior to the 2-month primary endpoint

The fully adherent population consisted of all patients who had no medications detected by urine adherence testing at both baseline and 2 months.

The complete ABP population consisted of only patients with complete ABP values at baseline and follow-up.

5.1.6.3 Methodology for Normality

The SAP for the RADIANCE studies prescribed prespecified analyses based on applying the ANCOVA model to ranked data to address issues with the normality

assumption of the primary endpoint model. A Shapiro-Wilk test for normality was performed at the 0.05 alpha level based on observed data. If there was significant evidence of non-normality, analyses were based on ranking the observations (with no imputation) and applying the ANCOVA model to the ranked data as described in Quade (1967), “Rank Analysis of Covariance”, Journal of the American Statistical Association, Vol 62, No 320.

5.1.6.4 Analyses of Efficacy Endpoints

The average difference between randomized groups for the change in daytime ambulatory SBP at 2 months post-procedure were compared by analysis of covariance (ANCOVA) adjusted for patients’ baseline daytime ambulatory SBP. Tests were performed at a 0.05 alpha level.

The statistical analysis of the secondary efficacy endpoints followed the methodology of the primary efficacy endpoint. For the purposes of controlling the type I error rate, a sequential gatekeeping procedure was employed. Hypotheses for the secondary endpoints were tested at the 0.05 level until a non-significant result was produced, in hierarchical order as shown in Section 5.1.4.

5.1.6.5 Data Handling

Multiple imputation was used for patients with missing 2-month follow-up BP values. The multiple imputation was based on a fully conditional specification using the following covariates for the imputation model: age, sex, and baseline ambulatory SBP.

For patients who met the protocol-defined criteria for medication changes, the last BP measurement prior to the medication change was used for the reduction in BP in the analysis.

5.2 RADIANCE-HTN (SOLO and TRIO Cohorts)

5.2.1 Study Design

RADIANCE-HTN was a randomized, double-blind, sham-controlled, 2-cohort study designed to demonstrate efficacy, and document safety, of the Paradise System in 2 distinct populations of patients with hypertension. These studies preceded the pivotal trial. The SOLO cohort included patients with essential hypertension controlled on 1 or 2 antihypertensive medications or uncontrolled on 0–2 antihypertensive medications. The TRIO cohort included patients with treatment-resistant hypertension on ≥ 3 different classes of antihypertensive medications including a diuretic.

5.2.1.1 SOLO

In SOLO, patients who were currently prescribed antihypertensive medication had their medication discontinued for a period of 4 weeks prior to reassessment for hypertension.

For the period of wash-out through the 2-month primary efficacy endpoint visit, changes in medication could not occur other than the scenarios described for RADIANCE II in Section 5.1.1.

Eligible patients were randomized (1:1) to receive renal denervation treatment with the Paradise System or a sham control (renal angiogram procedure). All patients remained blinded up to the 6-Month Follow-up visit. Patients were blinded during the procedure by ensuring the patient was sedated and using headphones and eye covers. Study personnel responsible for the measurement and upload of ABP post-randomization were also blinded. A blinding index was used to evaluate the success of patient blinding post-procedure and at 2 and 6 months.

Between the 2- and 6-month follow-up visits, predefined escalation of antihypertensive medication was strongly recommended (using the same escalation steps described for RADIANCE II in Table 6). The medication escalation started at the follow-up where a sustained elevation (≥ 135 mmHg systolic OR ≥ 85 mmHg diastolic) in 7-day home BP measurement was documented (confirmed by office SBP ≥ 140 mmHg or DBP ≥ 90 mmHg if required per Institutional practice). Drugs were added sequentially at each monthly follow-up in the event BP remained elevated. In the event BP remained < 135/85 mmHg, no action was required.

Following at least 6 months of follow-up post procedure and if the primary 2-month effectiveness endpoint was met for the cohort, eligible patients randomized to the sham control group could cross-over and receive treatment.

5.2.1.2 TRIO

In TRIO, patients had their current hypertensive regimen replaced with a single-pill, triple, fixed-dose antihypertensive combination of Amlodipine (10 mg), Valsartan (160 mg) or Olmesartan (40 mg), and Hydrochlorothiazide (25 mg) administered once daily during a 4-week stabilization period. This combination was to be taken at least through the 2-month primary efficacy endpoint follow-up visit. During this period, changes in antihypertensive medication could not occur unless in an emergency.

Eligible patients were randomized (1:1) to receive renal denervation treatment with the Paradise System or a sham control (renal angiogram procedure). All patients remained blinded up to the 6-month follow-up visit. Patients were blinded during the procedure by ensuring the patient was sedated and using headphones and eye covers. Study personnel responsible for the measurement and upload of ABP post-randomization were also blinded. A blinding index was used to evaluate the success of patient blinding post-procedure and at 2- and 6-months.

Introduction of additional antihypertensive therapy could occur as needed to achieve BP control following the measurement of the 2-month ABP. Introduction of antihypertensive medication was to occur sequentially as shown in Table 7.

Table 7: TRIO: Drug Escalation Protocol

Escalation Step	Drug Class	Recommended Drugs
1	Aldosterone agonist	Spironolactone: 25 mg
2	Long acting, cardio selective Beta-1 receptor blocker: full dose	Bisoprolol: 10 mg
3	Central alpha-2 receptor agonist: full dose	Clonidine: 0.1–0.2 mg; Rilmenidine: 1–2 mg; Moxonidine 0.2–0.4 mg
4	Long acting Alpha-1 receptor blocker: full dose	Slow release Prazosin 5–10 mg; Doxazosin 4–8 mg

Note: All recommended doses are once daily other than for clonidine, rilmenidine, or moxonidine which should be added twice daily at their higher doses

Following at least 6-months of follow-up post procedure, if the primary 2-month effectiveness endpoint was met for the cohort, eligible patients randomized to the sham control group could cross-over and receive treatment.

5.2.2 Key Enrollment Criteria

Key enrollment criteria for RADIANCE-HTN were identical to RADIANCE II (Section 5.1.3) except for the following:

- Background medications in the TRIO cohort
- Screening for secondary hypertension in the TRIO cohort
- TRIO had no upper limit on screening BP
- TRIO had different requirements regarding history of cardiovascular and cerebrovascular events

5.2.3 Endpoints

The primary efficacy endpoint was the difference in average daytime ambulatory SBP between uRDN treatment (renal denervation with the Paradise System) and sham control (renal angiogram) from baseline to 2 months post procedure.

Secondary efficacy endpoints included the following, in hierarchical order:

- Reduction in average 24-hour ambulatory SBP at 2 months post procedure
- Reduction in average 24-hour ambulatory DBP at 2 months post procedure
- Reduction in average nighttime ambulatory SBP at 2 months post procedure
- Reduction in average nighttime ambulatory DBP at 2 months post procedure

5.2.4 Statistical Methods

5.2.4.1 Sample Size Calculation

Statistical analyses were performed separately for the SOLO and TRIO cohorts, each at a two-sided 0.05 alpha level as there was independent interest in conclusions for each cohort separately. Conservatively, sample size calculations were based on a

two-sample t-test. The planned analysis with the adjustment for baseline could provide additional power beyond this, but the precise level depended on the correlation of the baseline value with the reduction during follow-up.

Assuming 80% power and a 2-sided 0.05 alpha, 64 randomized patients per group were calculated as required to detect an absolute difference in daytime ambulatory SBP change from baseline to 2 months of 6 ± 12 mmHg between Treatment and Control. The estimated minimum sample size to demonstrate efficacy was 128 patients. To account for an approximate 10% rate of premature withdrawal or failure to reach the primary endpoint measure, the total randomized per cohort was planned at 146 patients.

5.2.4.2 Analysis Populations

The ITT, mITT, PP, and complete ABP populations used the same definitions as in RADIANCE II (see Section 5.1.6.2). In SOLO, the fully adherent population consisted of all patients who had no medications detected by urine adherence testing at both baseline and 2 months. In TRIO, the fully adherent population consisted of all patients taking their prescribed medications detected by urine adherence testing at both baseline and follow-up.

5.2.4.3 Methodology for Normality

Testing for normality of data was conducted using the same methods as in RADIANCE II (see Section 5.1.6.3).

5.2.4.4 Analysis of Efficacy Endpoints

The primary efficacy endpoint was analyzed using the same methods as in RADIANCE II (see Section 5.1.6.4).

5.2.4.5 Data Handling

For patients missing the reduction in BP value, a value of zero was used for the reduction in BP in the analysis. For patients that met the protocol-defined criteria for medication changes, the last BP measurement prior to the medication change was used for the reduction in BP in the analysis.

6 CLINICAL EFFECTIVENESS

Summary

- All 3 clinical studies (RADIANCE II, SOLO, TRIO) met their primary endpoints demonstrating a significantly greater difference in average daytime ambulatory SBP between uRDN treatment with the Paradise System and sham control at 2 months after the procedure.
- The reduction in daytime ambulatory SBP following treatment with uRDN at 2 months was consistent across the three studies:
  - RADIANCE II = -7.9 mmHg
  - SOLO = -8.5 mmHg
  - TRIO = -8.0 mmHg
- The between-group differences (treatment vs sham) in daytime ambulatory SBP at 2 months were:
  - RADIANCE II = -6.3 mmHg
  - SOLO = -6.3 mmHg
  - TRIO = -4.5 mmHg
- Decreases were durable through at least 36 months.
  - In SOLO, patients had a mean decrease from baseline of -17.7±15.4 mmHg in office SBP and -11.3±9.3 in office DBP at 36 months.
  - In TRIO, patients had decreases from baseline of -9.3±23.3 and -5.0±14.7 for office SBP and DBP, respectively, at 24 months (the longest data reported in that study).
- More patients who received uRDN achieved their BP targets with fewer antihypertensive medications than sham.
- Results were consistent, regardless of patient demographics (eg, race and obesity), baseline disease states (eg, baseline SBP), and co-morbidities (eg. diabetes, chronic kidney disease).

6.1 Patient Populations

6.1.1 Patient Dispositions in Clinical Studies

6.1.1.1 RADIANCE II

A total of 1,038 patients were consented and screened for eligibility, and 259 underwent renal angiography. Of the 779 who were excluded prior to renal angiography, the majority did not meet office BP criteria (223), ABP criteria (199), or renal anatomic criteria on CT/MRA (114). Of the 259 who underwent renal angiography, 224 were randomized: 150 patients in the renal denervation group and 74 sham. The completion rate for the required 2-month BP follow-up was 97% (218/224); 5 in the uRDN group and 1 patient in the sham group did not complete the 2-month ABP. One patient

withdrew consent, 2 missed the visit, and 2 did not complete the 2-month ABP measurement in the uRDN group, and one patient did not complete 2-month ABP measurement in the sham group.

6.1.1.2 SOLO

A total of 804 patients were enrolled in SOLO, and 146 were randomized: 74 in the renal denervation group and 72 sham. Similar to RADIANCE II, the primary reasons for screen failure were ABP requirements not met after the 4-week wash-out period, renal anatomic criteria not met, and withdrawal of consent. Of the 146 patients, 1 in each group did not complete the 2-month ABP. A total of 51 patients in the uRDN group and 20 patients in the sham group had available office BP measurements at Month 36.

6.1.1.3 TRIO

ITT Population

A total of 990 patients were enrolled in TRIO, and 136 were randomized to either renal denervation (N=69) or sham control (N=67). The primary reason for screen failure was that the 24-hour ABP criteria was not met following the medication stabilization period (n=360). Standardization of antihypertensive medications to a triple pill allowed for daytime ABP to become controlled, demonstrating that many resistant hypertension patients were either not on optimized medical therapy or were likely not adherent to all their prescribed medications.

Per Protocol Population

Fourteen (14) patients were excluded from the ITT population in the uRDN group, and 10 were excluded from sham. In the uRDN group, the 14 exclusions included 3 who added antihypertensive medication before 2 months without meeting protocol-defined criteria; 2 with unsuccessful treatment; 2 with baseline daytime DBP lower than entry eligibility; 1 with ineligible anatomy; and 6 who did not complete ABP measurement. In the sham group, the 10 exclusions were due to 4 who added medications before 2 months according to the protocol-defined escape criteria, 4 added medications prior to 2 months without meeting protocol-defined criteria, and 2 had baseline daytime DBP lower than entry eligibility.

Complete 2-Month ABP Population

Of the 136 patients randomized, 63 in the uRDN group and 67 in the sham group completed 2-month ABP. Six patients in the uRDN group did not complete 2-month ABP: 1 missed visit due to COVID-19, 1 remote visit due to COVID-19, 1 non-procedure related death, 1 lost to follow-up, and 2 did not complete the ABP at the visit. A total of 51 patients in the uRDN group and 50 patients in the sham group had available office BP measurements at Month 24.

6.1.2 Baseline Demographics in Clinical Studies

The patient population was similar across studies and was predominantly male and Caucasian (Table 8). Black patients represented 14%–20% of randomized participants.

The mean age was mid-50s. The mean body mass index (BMI) was approximately 30 kg/m^2 across studies. Baseline office SBP ranged from 143–164 mmHg, and baseline office DBP ranged from 92–105 mmHg.

Table 8: RADIANCE Studies: Baseline Demographics and Health Characteristics

	RADIANCE II (N=224)		SOLO (N=146)		TRIO (N=136)	
Parameter, Mean±SD or n (%):	**uRDN (N=150)**	**Sham (N=74)**	**uRDN (N=74)**	**Sham (N=72)**	**uRDN (N=69)**	**Sham (N=67)**
Sex						
Male	103 (68.7)	57 (77.0)	46 (62.2)	39 (54.2)	56 (81.2)	53 (79.1)
Female	47 (31.3)	17 (23.0)	28 (37.8)	33 (45.8)	13 (18.8)	14 (20.9)
Age	55.1±9.9	54.9±7.9	54.4±10.2	53.8±10.0	52.3±7.5	52.8±9.1
Age ≥ 65 years	26 (17.3)	9 (12.2)	10 (13.5)	8 (11.1)	3 (4.4)	7 (10.5)
Race						
American Indian or Alaska Native	0	0	0	0	0	1 (1.5)
Asian	0	1 (1.4)	1 (1.4)	0	1 (1.5)	1 (1.5)
Black[a]	21 (14.0)	15 (20.3)	12 (16.2)	13 (18.1)	14 (20.3)	13 (19.4)
Caucasian/White	114 (76.0)	56 (75.7)	60 (81.1)	52 (72.2)	45 (65.2)	51 (76.1)
Hispanic or Latino	-	-	1 (1.4)	4 (5.6)	5 (7.3)	0
Other ethnicity not listed/mixed race	15 (10.0)	2 (2.7)	0	3 (4.2)	3 (4.4)	0
Unknown ethnicity	-	-	-	-	1 (1.5)	1 (1.5)
BMI[b]	30.1±5.2	30.6±5.2	29.9±5.9	29.0±5.0	32.8±5.7	32.6±5.4
Abdominal circumference (cm)	102.4±12.3	104.3±13.1	101.5±14.2	98.5±15.1	109.4±15.5	109.2±12.9
Left Brachial circumference (cm)	31.3±3.8	32.1±4.2	31.0±3.8	30.8±3.8	32.9±3.6	32.8±3.9
Right brachial circumference (cm)	31.5±3.9	32.2±4.1	31.0±3.8	30.8±3.8	32.9±3.6	32.8±3.9
Office SBP at screening (mmHg)[c]	155.8±11.1	154.3±10.6	142.6±14.7	144.6±15.9	161.9±15.5	163.6±16.8
Office DBP at screening (mmHg)[c]	101.3±6.7	99.1±5.6	92.3±10.1	93.6±8.3	105.1±11.6	103.3±12.7
Pulse[c] at screening	74.1±12.0	73.6±11.9	73.2±12.4	73.2±12.4	74.5±11.0	77.6±12.9
Pulse[c] at Baseline	74.3±11.3	72.5±11.5	72.0±12.1	72.6±12.3	76.9±12.2	82.0±12.1

BMI=body mass index; DBP=diastolic blood pressure; SBP=systolic blood pressure; SD=standard deviation; uRDN=ultrasound renal denervation.

a. Includes patients of African, Caribbean, and other heritages.

b. Measured in kg/m^2.

c. Average of 2 office measures, seated position.

6.1.3 Baseline Medical Characteristics in Clinical Studies

The baseline medical histories and comorbidities for patients in the clinical studies are presented in Table 9. As expected, patients in TRIO were more likely to have high risk characteristics than in RADIANCE II or SOLO, with more patients with type II diabetes, sleep apnea, and a history of hospitalization for hypertensive crisis.

Table 9: RADIANCE Studies: Baseline Medical Histories and Comorbidities

	RADIANCE II (N=224)		SOLO (N=146)		TRIO (N=136)	
Parameter, n (%):	**uRDN (N=150)**	**Sham (N=74)**	**uRDN (N=74)**	**Sham (N=72)**	**uRDN (N=69)**	**Sham (N=67)**
Hyperlipidemia	53 (35.3)	26 (35.1)	15 (20.3)	18 (25.0)	31 (44.9)	30 (44.8)
Sleep apnea	21 (14.0)	13 (17.6)	6 (8.1)	8 (11.1)	20 (29.0)	11 (16.4)
Obstructive sleep apnea	21/21 (100.0)	11/13 (84.6)	1/6 (16.7)	5/8 (62.5)	7/20 (35.0)	5/11 (45.5)
History of smoking[a]	47 (31.3)	27 (36.5)	N/A	N/A	N/A	N/A
Current smoker	13/47 (27.7)	4/27 (14.8)	N/A	N/A	N/A	N/A
Type II diabetes	9 (6.0)	5 (6.8)	2 (2.7)	5 (6.9)	21 (30.4)	17 (25.4)
Hospitalized for hypertensive crisis	9 (6.0)	3 (4.1)	2 (2.7)	2 (2.8)	15 (21.7)	11 (16.4)
Chronic kidney disease	8 (5.3)	3 (4.1)	0	0	4 (5.8)	4 (6.0)
Cerebrovascular event(s)	0	0	0	0	6 (8.7)	4 (6.0)
Bradycardia	2 (1.3)	3 (4.1)	1 (1.4)	2 (2.8)	1 (1.5)	0
Documented episodes of angina	1 (0.7)	2 (2.7)	0	0	4 (5.8)	1 (1.5)
Prior surgical coronary procedure	2 (1.3)	0	0	0	1 (1.5)	4 (6.0)
Coronary artery bypass surgery	0	0	0	0	0	2/4 (50.0)
Peripheral vascular disease	0	0	2 (2.7)	0	1 (1.5)	3 (4.5)
Prior myocardial infarction	0	0	0	0	2 (2.9)	4 (6.0)
History of heart failure	1 (0.7)	0	0	0	1 (1.5)	3 (4.5)
Ventricular arrhythmias	0	1 (1.4)	0	0	1 (1.5)	2 (3.0)
Atrial arrhythmias	0	0	0	0	0	3 (4.5)
Ischemic heart disease	0	0	0	0	2 (2.9)	1 (1.5)
History of alcohol or drug addiction	0	0	0	1 (1.4)	0	0
Polycystic kidney disease	0	0	0	0	0	1 (1.5)
Prior atrial ablation	1 (0.7)	0	0	0	0	1 (1.5)

uRDN=ultrasound renal denervation.
a. Includes current and former smokers.

6.1.3.1 Baseline Blood Pressure Measurements

Ambulatory, home, and office BP were obtained at baseline. Home BP measurements were obtained twice daily over a 7-day period prior to the clinic visit and reported as an average. Across the clinical studies, baseline BPs between the uRDN and sham groups were similar (Table 10). Daytime ABP had to be ≥ 135/85 mmHg to continue in the study. Mean daytime ambulatory SBP was 150–151 mmHg and mean daytime ambulatory DBP was 93–95 mmHg across groups and studies.

Table 10: RADIANCE Studies: Baseline Blood Pressure Readings

Blood Pressure (mmHg), Mean±SD Median:	RADIANCE II (N=224)		SOLO (N=146)		TRIO (N=136)	
	uRDN (N=150)	Sham (N=74)	uRDN (N=74)	Sham (N=72)	uRDN (N=69)	Sham (N=67)
Daytime ambulatory SBP	150.3±8.6	151.2±9.0	150.3±7.8	150.0±9.8	150.0±11.9	151.1±12.6
Daytime ambulatory DBP	93.8±5.2	93.2±5.5	93.1±4.8	93.5±5.5	93.8±7.7	94.6±9.1
24-hour ambulatory SBP	143.4±8.9	144.6±9.6	142.6±8.1	143.8±10.4	143.9±13.4	145.4±14.0
24-hour ambulatory DBP	88.4±5.8	88.3±5.9	87.3±5.0	88.6±5.7	88.9±8.2	89.5±9.5
Nighttime ambulatory SBP	132.2±12.5	134.1±13.3	130.3±11.9	132.5±13.7 [a]	134.4±18.0	136.4±18.6
Nighttime ambulatory DBP	79.9±8.2	80.5±8.4	78.2±8.0	80.0±8.1	81.3±10.7	81.3±12.1
Home SBP	152.6±9.6 [c]	150.1±10.4 [d]	147.6±8.7	147.7±12.3	153.6±16.2 [b]	153.4±17.0
Home DBP	98.0±6.5 [c]	96.0±7.5 [d]	95.2±7.0	94.6±7.0	97.1±10.9 [b]	96.9±11.3
Office SBP*	156.9±13.1	156.3±12.8	154.5±12.4	153.6±15.7	155.2±16.8	155.1±16.8
Office DBP*	102.3±7.6	101.0±7.5	99.7±7.7	99.1±9.4	101.3±11.7	99.6±10.9

BP=blood pressure; DBP=diastolic blood pressure; SBP=systolic blood pressure; SD=standard deviation; uRDN=ultrasound renal denervation.

* Average of 2 office measures, seated position.

a. Based on 71 patients with nighttime BP readings.

b. Based on 67 patients with home BP readings.

c. Based on 148 patients with home BP readings.

d. Based on 73 patients with home BP readings.

6.1.3.2 Antihypertension Medications

Per protocol in the clinical studies, patients self-reported the number of antihypertensive medications they were taking at the screening visit (Table 11). According to protocol inclusion criteria, patients in TRIO were taking more antihypertensive medications (3 or more) than patients in RADIANCE II or SOLO, who were required to be taking 2 or fewer antihypertensive medications at screening. All but 3 patients in RADIANCE II and SOLO were taking 0–2 medications at screening.

Table 11: RADIANCE Studies: Number of Antihypertensive Medications at Screening

Number of Antihypertensive Medications, n (%):	RADIANCE II (N=224)		SOLO (N=146)		TRIO (N=136)	
	uRDN (N=150)	Sham (N=74)	uRDN (N=74)	Sham (N=72)	uRDN (N=69)	Sham (N=67)
0	54 (36.0)	23 (31.1)	12 (16.2)	16 (22.2)	0	0
1	52 (34.7)	25 (33.8)	33 (44.6)	28 (38.9)	0	0
2	44 (29.3)	25 (33.8)	28 (37.8)	27 (37.5)	0	0
3	0	0	1 (1.4)[a]	1 (1.4)[a]	27 (39.1)	28 (41.8)
4	0	1 (1.4)[a]	0	0	20 (29.0)	24 (35.8)
5	0	0	0	0	16 (23.2)	10 (14.9)
6+	0	0	0	0	6 (8.7)	5 (7.5)

uRDN=ultrasound renal denervation.
[a]Protocol deviations were noted for these patients.

Following the screening visit in RADIANCE II and SOLO, patients were instructed to discontinue antihypertensive medications for 4 weeks during a wash-out period. In TRIO, patients were started on a single pill, triple antihypertensive therapy (Amlodipine [10 mg], Valsartan [160 mg] or Olmesartan (40 mg), and Hydrochlorothiazide [25 mg]) and stabilized for 4 weeks.

6.1.3.3 Treatment and Procedure Characteristics

As expected, the average study procedure lasted longer for renal denervation than sham. The mean total procedure time, including angiography, was approximately 72–83 minutes for renal denervation compared to 38–44 minutes for sham (Table 12). Among patients who received uRDN, the mean device time (defined as the total time the catheter was inserted) ranged from 33–40 minutes. Across the clinical studies, 96% of patients had a successful procedure. In the uRDN groups, a total of 7 patients did not receive the minimum of 2 successful ultrasound emissions; 5 of these cases were due to anatomical reasons, 1 did not receive denervation due to a generator that was determined to be non-functional following randomization but prior to insertion of the Paradise Catheter, and 1 was manually randomized to the incorrect arm due to lack of availability of the electronic database during the procedure.

Table 12: RADIANCE Studies: Treatment and Procedure Characteristics

Procedure Characteristic, Mean±SD Median or n (%):	RADIANCE II (N=224)		SOLO (N=146)		TRIO (N=136)	
	uRDN (N=150)	Sham (N=74)	uRDN (N=74)	Sham (N=72)	uRDN (N=69)	Sham (N=67)
Procedure time (min)[a]	76.7±25.2 73.0	43.9±16.6 40.5	72.3±23.3 67.0	38.1±12.6 38.5	83.0 [69.0, 99.0]	41.0 [33.0, 50.0]
Device time (min)[b]	33.4±18.7 29.0	NA	34.8±19.9[f] 31.5[f]	NA	39.7±22.7 37.0	NA
Total emission time (seconds)	38.9±7.3 42.0	NA	37.4±8.0[e] 35.0[e]	NA	40.7±8.1 42.0	NA
Sedation/anesthesia						
Conscious sedation	114 (76.0)	57 (78.1)[e]	62 (83.8)	58 (80.6)	44 (63.8)	41 (61.2)
General anesthesia	17 (11.3)	6 (8.2)[e]	12 (16.2)	14 (19.4)	8 (11.6)	10 (14.9)
Monitored anesthesia care	19 (12.7)	10 (13.7)[e]	-	-	17 (24.6)	16 (23.9)
Contrast volume (cc)[d]	135.7±67.4 120.0	64.6±30.4[e] 60.0[e]	140.7±68.8[f] 120.0[f]	78.7±41.1[g] 78.0[g]	176.9±77.0 -	80.0±40.1 -
Fluoroscopy exposure (min)[d]	15.9±8.6 14.0	4.2±4.6[f] 3.0[f]	13.9±7.0[g] 12.6[g]	4.8±12.3[g] 2.9[g]	19.0±11.5 -	4.1±3.6 -
Total number of emissions	5.6±1.0 6.0	NA	5.3±1.1[e] 5.0[e]	NA	5.8±1.2 6.0	NA
Left	2.7±0.7 3.0	NA	2.5±0.8[e] 3.0[e]	NA	2.8±0.6 3.0	NA
Right	2.8±0.7 3.0	NA	2.8±0.6[e] 3.0[e]	NA	3.0±0.8 3.0	NA
Total number of pts with accessory and/or proximal side branch emissions	30 (20.0)	NA	9 (12.2)	NA	17 (24.6)	NA
Treatment successfully delivered[c]	148 (98.7)	NA	71 (96.0)	NA	67 (97.1)	NA

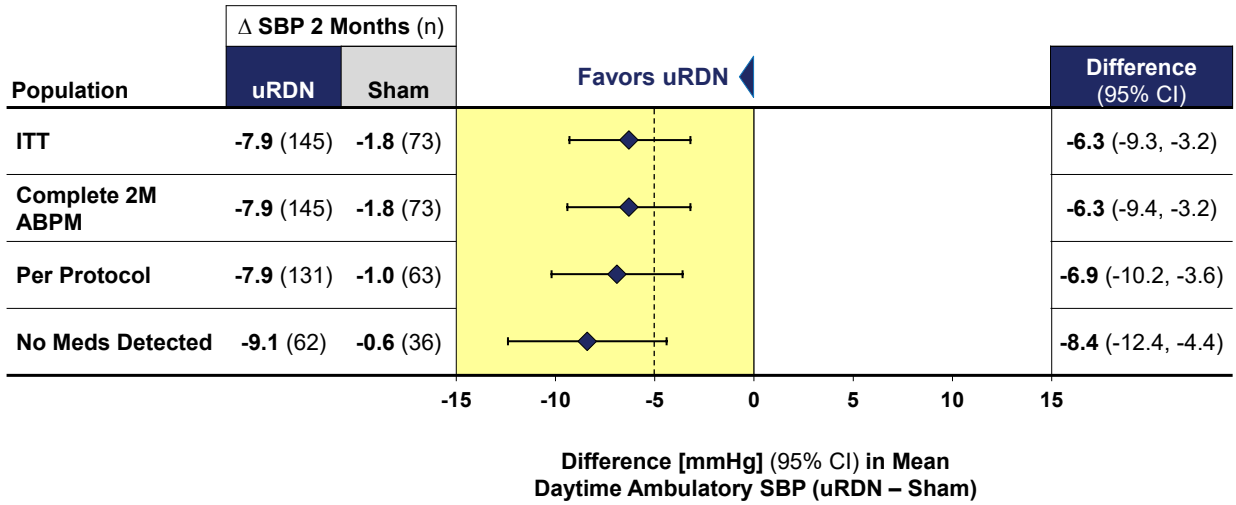
Min=minutes; NA=not applicable; pts=patients; SD=standard deviation; uRDN=ultrasound renal denervation.
a. Encompasses time of sheath removal minus time of sheath insertion; data in TRIO presented as median [interquartile range].
b. Encompasses time of catheter removal minus time of catheter insertion
c. Minimum of 2 missions bilateral.
d. Median contrast volume and fluoroscopy exposure not reported in TRIO.
e. Based on N=73 patients.
f. Based on N=72 patients.
g. Based on N=71 patients.

6.2 RADIANCE II Results

6.2.1 Primary Effectiveness Results: Change from Baseline in Average Daytime Ambulatory SBP at 2 Months Post-Procedure

RADIANCE II met its primary effectiveness endpoint, showing a statistically significant and clinically meaningful reduction in daytime ambulatory SBP in the uRDN group compared to sham. As previously defined, the primary efficacy endpoint was the difference in average daytime ambulatory SBP between renal denervation treatment with the Paradise System and sham control procedure (diagnostic renal angiogram) from baseline to 2 months post-procedure. Results were consistent across the ITT and PP populations (Figure 31).

Figure 31: RADIANCE II: Change from Baseline in Average Daytime Ambulatory SBP at 2 Months



ABPM=ambulatory blood pressure measurement; CI=confidence interval; ITT=intention-to-treat; SBP=systolic blood pressure; uRDN=ultrasound renal denervation

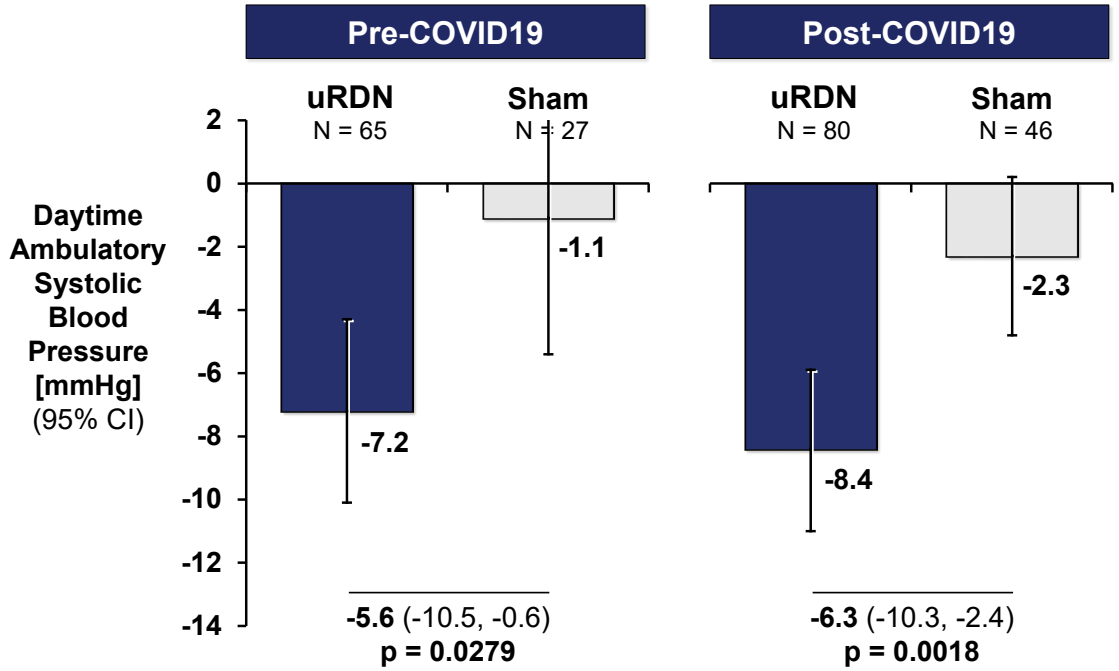
6.2.1.1 COVID-19 Impact

RADIANCE II was temporarily paused in March 2020 due to the COVID public health emergency; enrollment resumed in June 2020. Ninety-five patients were randomized before the enrollment pause and 129 patients were randomized when enrollment resumed. Analyses investigating how COVID-19 might affect patient populations and evaluations of efficacy revealed:

1. Baseline characteristics of patients enrolled pre- and post-pause were similar
2. Baseline BPs were similar for patients enrolled pre- and post-pause
3. There was no difference in the primary efficacy endpoint results between patients randomized before vs after COVID-19 pause (Figure 32)

4. Neither enrollment stoppage nor changes in operational aspects of the trial, such as remote BP recording, related to the COVID-19 pandemic impacted the outcome of the study.

Figure 32: RADIANCE II: Daytime Ambulatory Systolic Blood Pressure Pre- and Post-COVID-19 Pause



CI=confidence interval; uRDN=ultrasound renal denervation.

6.2.1.2 Sensitivity Analysis of Primary Endpoint

Results of the tipping-point analysis demonstrated the primary endpoint data to be robust (Table 13). The tipping-point analysis evaluated best-case, worst-case, and multiple cases in between. Missing data were imputed from a range of that patient's treatment group BP reduction percentile value: 0% (minimum), 25%, 50%, 75%, 100% (maximum).

Table 13: RADIANCE II: Primary Endpoint Tipping-Point Analysis (ITT Population)

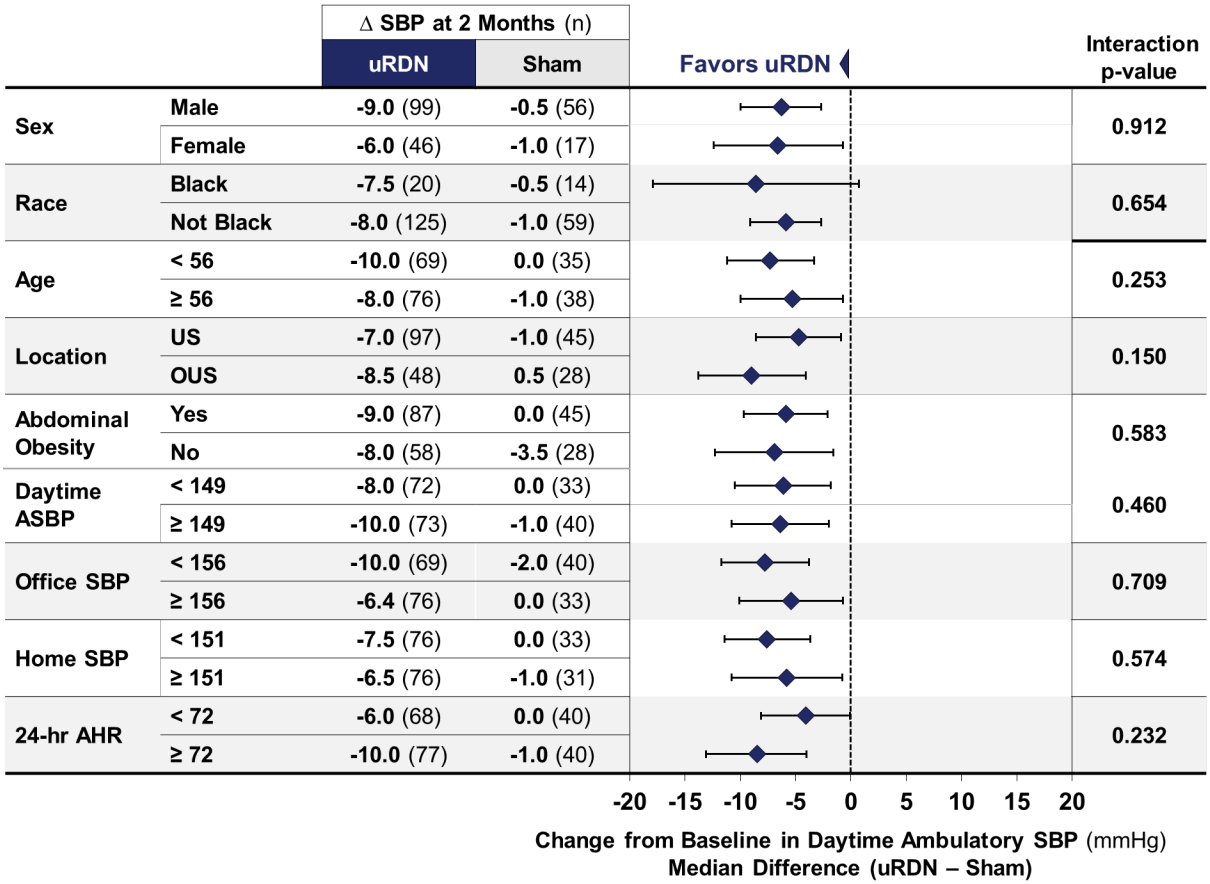
	Control				
Treatment:	**0% (-41 mmHg)**	**25% (-15 mmHg)**	**50% (-9 mmHg)**	**75% (-1 mmHg)**	**100% (26 mmHg)**
0% (-30 mmHg)	<0.0001 (<0.0001*)	0.0001 (<0.0001*)	0.0002 (<0.0001*)	0.0004 (<0.0001*)	0.0064 (0.0002*)
25% (-7 mmHg)	<0.0001 (<0.0001*)	<0.0001 (<0.0001*)	<0.0001 (<0.0001*)	0.0001 (<0.0001*)	0.0033 (<0.0001*)
50% (-1 mmHg)	<0.0001 (<0.0001*)	<0.0001 (<0.0001*)	<0.0001 (<0.0001*)	0.0001 (<0.0001*)	0.0028 (<0.0001*)
75% (5 mmHg)	<0.0001 (<0.0001*)	<0.0001 (<0.0001*)	<0.0001 (<0.0001*)	<0.0001 (<0.0001*)	0.0024 (<0.0001*)
100% (26 mmHg)	<0.0001 (<0.0001*)	<0.0001 (<0.0001*)	<0.0001 (<0.0001*)	<0.0001 (<0.0001*)	0.0015 (<0.0001*)

Adj=adjusted; ANCOVA=analysis of covariance; BL=baseline; ITT=intention-to-treat.
Note: p-value from ANCOVA, adjusting for baseline value. The p-value (*) from a baseline-adjusted ANCOVA on the ranks is also provided.

6.2.1.3 Subgroup Analyses of Primary Endpoint

Treatment interactions were assessed with linear regression models adjusting for baseline daytime ambulatory SBP for subgroups prespecified in the statistical analysis plan: sex, race, age, location, and abdominal obesity. Across all subgroups, the primary efficacy endpoint findings favored the uRDN group (Figure 33). Additional prespecified analyses assessed: baseline daytime ambulatory SBP, office SBP, home SBP and 24-hour ambulatory heart rate. Across these additional subgroups, the primary efficacy endpoint findings favored the uRDN group.

Figure 33: RADIANCE II: Subgroup Analysis of Primary Efficacy— Mean Changes in Daytime Ambulatory SBP by Patient Characteristics (ITT Population)



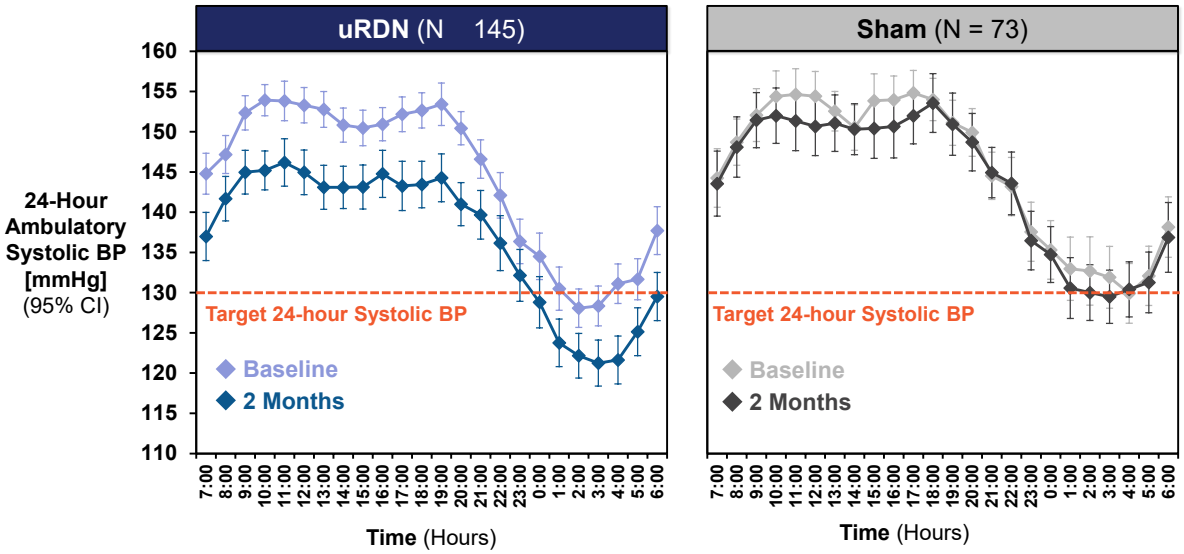
AHR=ambulatory heart rate; OUS=outside United States; SBP=systolic blood pressure; uRDN=ultrasound renal denervation, US=United States

6.2.2 Secondary Endpoint Results

6.2.2.1 24-Hour Ambulatory Systolic Blood Pressure

Comprehensive evaluation of the 24-hour ABP profiles highlights the consistently lower SBP throughout the circadian cycle after 2 months in the uRDN group while the sham control group showed little change from baseline (Figure 34).

Figure 34: RADIANCE II: 24-Hour Ambulatory Systolic Blood Pressure at Baseline and 2 Months after Procedure for Renal Denervation and Sham

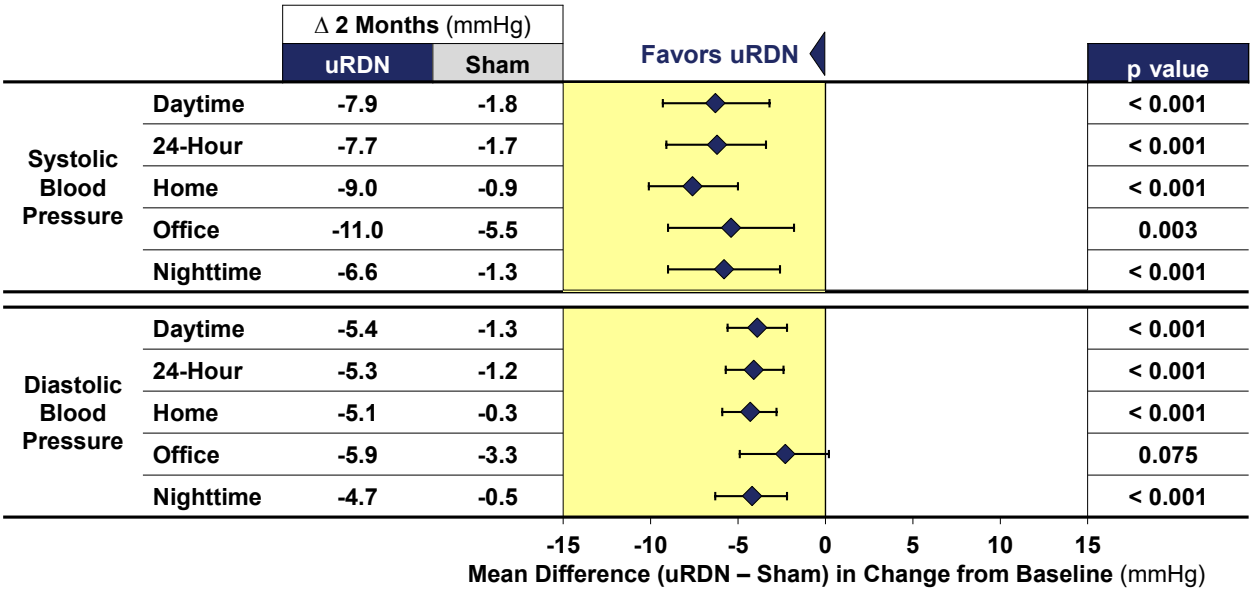


CI=confidence interval; BP=blood pressure; uRDN=ultrasound renal denervation.

6.2.2.2 Additional Systolic and Diastolic Blood Pressure Measurements

Prespecified secondary endpoints included 24-hour, home, and office SBP at 2 months. Nighttime ABP was not a secondary endpoint in this study but is included within this section for completeness. Consistent with daytime ABP results, patients who received renal denervation experienced significantly greater reductions across all SBP measurements (Figure 35). Prespecified secondary endpoints also included daytime, 24-hour, home, and office DBP at 2 months. Results for DBP consistently favored renal denervation over sham, with patients experiencing an average of 4.7–5.9 mmHg lower DBP across different measures.

Figure 35: RADIANCE II: Systolic and Diastolic Blood Pressure Measurements (ITT Population)



Δ=change; ITT=Intention-to-Treat; uRDN=ultrasound renal denervation.

6.2.3 Observational Efficacy Assessments at 2 Months after Procedure

6.2.3.1 Antihypertension Medication Dose Burden

Following their procedure, patients were required to remain free of antihypertensive medication at least through the 2-month follow-up visit, unless required in the event of a BP emergency. The majority of patients (90%) remained off medications at the time of the 2-month visit. Table 14 provides an overview of patients who started medications prior to 2 months whether or not they met protocol-defined criteria.

Table 14: RADIANCE II: Antihypertensive Medication Restart Prior to 2-Months after Procedure (ITT Population)

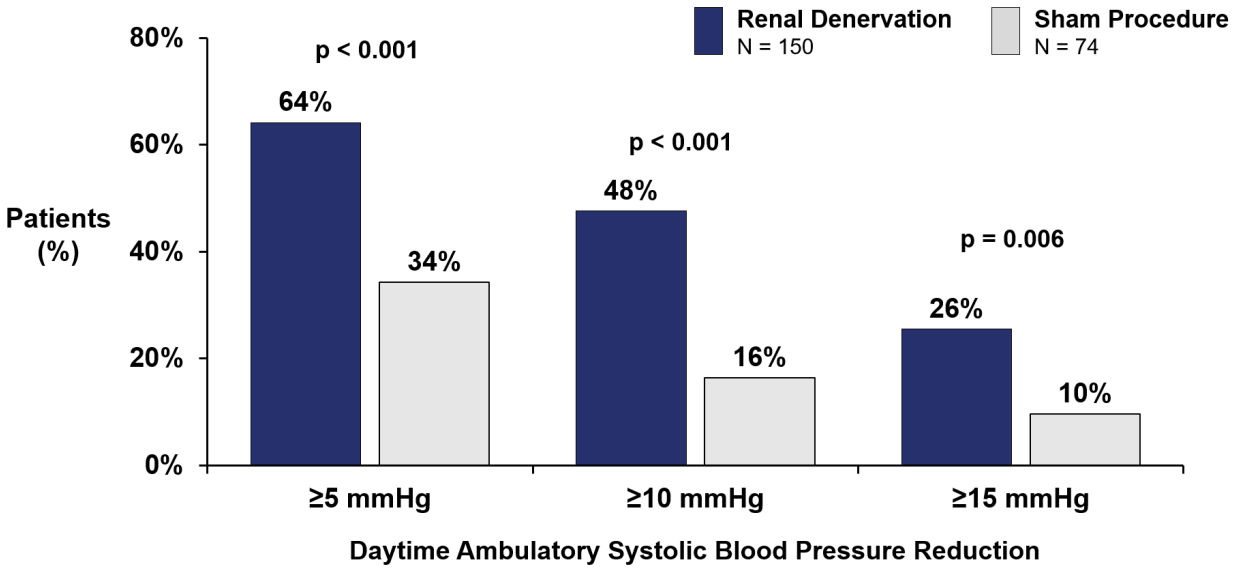
Circumstances and Timing of Antihypertensive Medication Restart, n (%)	uRDN (N=150)	Sham (N=74)	p-value
Total patients receiving additional antihypertensive medications prior to 2-month ABP measurement	12 (8.0)	10 (13.5)	0.1922
Protocol-defined criteria	4 (2.7)	6 (8.1)	0.0853
Physician decision or patient preference	8 (5.3)	4 (5.4)	1.0000

ABP=ambulatory blood pressure; BP=blood pressure; ITT=Intention-to-Treat; uRDN=ultrasound renal denervation
Note: p-value from Chi-square or Fisher's exact test, as appropriate, comparing treatment arm to sham arm.

6.2.3.2 *Blood Pressure Reduction Magnitude and Blood Pressure Targets*

Two months after the procedure, significantly more patients had a decrease of ≥ 5 mmHg, ≥ 10 mmHg, or ≥ 15 mmHg in daytime ambulatory SBP in the renal denervation group compared with sham (Figure 36).

Figure 36: RADIANCE II: Observational Efficacy Assessment – Blood Pressure Reduction Magnitude (ITT Population)



ITT=intention-to-treat

Additionally, more patients who received renal denervation met prespecified BP targets (without assistance from antihypertensive medication) compared with sham (Table 15).

Table 15: RADIANCE II: Control of Hypertension at 2 Months, per Protocol-Defined Targets, without Antihypertensive Medication (ITT Population)

Definition, n/N (%):	uRDN (N=138)	Sham (N=64)	p-value
Daytime ABP < 135/85 mmHg	25/133 (18.8)	3/63 (4.8)	0.0087
24-hour ABP < 130/80 mmHg	31/132 (23.5)	3/63 (4.8)	0.0013
Nighttime ABP < 120/70 mmHg	32/132 (24.2)	5/63 (7.9)	0.0066
Home BP < 135/85 mmHg	15/129 (11.6)	0/59	0.0033
Office BP* < 140/90 mmHg	29/125 (23.2)	13/61 (21.3)	0.7724

ABP=ambulatory blood pressure; BP=blood pressure; ITT=Intention-to-Treat; uRDN=ultrasound renal denervation.
* Average of 2 office measures, taken in the seated position.

6.2.4 Effectiveness Results at 6 Months

The 6-month data show continued lowering of BP (Table 16) and a numerically lower, but not statistically significant, medication burden in uRDN-treated patients compared with sham (Table 17). Medication dose burden was assessed by both defined daily

dose and medication load index. Defined daily dose was calculated using the World Health Organization's Defined Daily Dose for a given drug class, which is the assumed average maintenance dose per day for a drug used for its main indication in adults (World Health Organization 2018), and the total defined daily dose for each medication was added together for each patient. The medication load index was calculated as described in Wan et al 2009. For this method of medication burden, the percentage of the maximum labeled daily dose for each agent was calculated for each medication a patient was taking and then added together. Both the Defined Daily Dose and the medication index load were lower among patients who received renal denervation compared to sham.

Table 16: RADIANCE II Change in Daytime Ambulatory Blood Pressure from Baseline to 6 Months

	Renal Denervation (n=143)			Sham Procedure (n=67)			Baseline Adjusted		Baseline and Medication Adjusted	
	Baseline	6 months	Change	Baseline	6 months	Change	Difference[1]	p[2]	Difference[3]	p[4]
Daytime Ambulatory systolic blood pressure (mmHg)	143 150.2 ± 8.5 149.0 [135.0, 169.0]	143 132.7 ± 11.9 131.0 [111.0, 180.0]	143 -17.5 ± 11.4 -18.0 [-45.0, 16.0] (-19.4, -15.6)	67 150.9 ± 9.1 150.0 [136.0, 170.0]	67 133.5 ± 12.4 132.0 [111.0, 167.0]	67 -17.4 ± 14.0 -19.0 [-53.0, 12.0] (-20.8, -14.0)	-0.5 [-3.8, 2.8]	0.7739	-1.3 (-4.3, 1.8)	0.4135
24 Hour Ambulatory systolic blood pressure (mmHg)	141 143.1 ± 9.0 142.0 [126.0, 168.0]	141 126.8 ± 11.9 125.0 [105.0, 185.0]	141 -16.3 ± 10.8 -17.0 [-45.0, 17.0] (-18.1, -14.5)	66 144.4 ± 9.7 145.5 [126.0, 164.0]	66 128.0 ± 12.1 126.0 [104.0, 162.0]	66 -16.4 ± 13.5 -18.0 [-53.0, 11.0] (-19.7, -13.1)	-0.4 [-3.7, 2.8]	0.7869	-1.1 (-4.0, 1.9)	0.4664
Home systolic blood pressure (mmHg)	136 152.5 ± 9.8 152.2 [126.1, 181.1]	136 132.3 ± 10.4 130.5 [105.4, 167.3]	136 -20.2 ± 10.7 -20.2 [-55.0, 6.4] (-22.0, -18.4)	64 149.6 ± 10.5 148.9 [127.8, 172.6]	64 132.9 ± 10.3 132.3 [114.7, 157.5]	64 -16.7 ± 12.5 -17.8 [-45.5, 10.9] (-19.8, -13.5)	-1.8 [-4.7, 1.1]	0.2206	-2.6 (-5.4, 0.2)	0.0676
Office systolic blood pressure (mmHg)	135 156.7 ± 13.4 157.0 [121.5, 201.0]	135 135.8 ± 13.6 136.0 [103.5, 171.0]	135 -20.9 ± 14.8 -20.5 [-63.5, 12.5] (-23.4, -18.4)	57 156.7 ± 12.5 154.5 [134.5, 192.0]	57 136.5 ± 12.8 135.0 [100.5, 164.0]	57 -20.2 ± 16.4 -20.5 [-69.5, 18.5] (-24.5, -15.9)	-0.7 [-4.6, 3.2]	0.7236	-1.7 (-5.6, 2.2)	0.3915
Daytime Ambulatory diastolic blood pressure (mmHg)	143 93.7 ± 5.2 93.0 [84.0, 105.0]	143 82.3 ± 7.6 82.0 [66.0, 107.0]	143 -11.4 ± 7.2 -12.0 [-29.0, 8.0] (-12.6, -10.2)	67 93.0 ± 5.6 93.0 [85.0, 114.0]	67 82.0 ± 8.8 82.0 [66.0, 102.0]	67 -11.0 ± 9.3 -11.0 [-36.0, 8.0] (-13.3, -8.7)	-0.1 [-2.3, 2.1]	0.9206	-0.7 (-2.7, 1.4)	0.5215
24 Hour Ambulatory diastolic blood pressure (mmHg)	141 88.3 ± 5.8 87.0 [75.0, 105.0]	141 77.6 ± 7.4 77.0 [63.0, 107.0]	141 -10.7 ± 6.8 -10.0 [-29.0, 7.0] (-11.8, -9.6)	66 88.2 ± 6.0 89.0 [77.0, 104.0]	66 77.7 ± 8.0 77.5 [65.0, 96.0]	66 -10.6 ± 8.8 -11.0 [-32.0, 7.0] (-12.7, -8.4)	-0.1 [-2.2, 1.9]	0.9100	-0.6 (-2.4, 1.3)	0.5623
Home diastolic blood pressure (mmHg)	136 97.7 ± 6.5 97.3 [82.4, 114.3]	136 84.8 ± 6.8 83.8 [69.4, 113.9]	136 -12.8 ± 7.0 -13.0 [-35.2, 1.4] (-14.0, -11.7)	64 95.4 ± 7.6 94.8 [76.7, 117.8]	64 86.0 ± 7.5 85.5 [69.5, 106.5]	64 -9.4 ± 8.1 -9.2 [-36.5, 10.7] (-11.5, -7.4)	-2.2 [-4.1, -0.2] (-3.4 [-5.7, -1.1]*)	0.0277 (0.0507*)	-2.6 (-4.5, -0.7)	0.0066 (0.0129*)
Office diastolic blood pressure (mmHg)	135 101.9 ± 7.7 102.0 [82.5, 123.0]	135 89.6 ± 8.6 88.5 [69.5, 112.0]	135 -12.3 ± 9.2 -12.5 [-35.0, 17.5] (-13.8, -10.7)	57 101.0 ± 7.2 101.0 [84.5, 118.5]	57 89.0 ± 8.4 89.0 [63.5, 108.5]	57 -12.0 ± 9.6 -11.5 [-35.5, 10.5] (-14.6, -9.5)	0.3 [-2.2, 2.8]	0.8221	-0.4 (-2.9, 2.1)	0.7710
Nighttime Ambulatory systolic blood pressure (mmHg)	141 132.1 ± 12.7 131.0 [95.0, 174.0]	141 117.6 ± 14.0 117.0 [91.0, 191.0]	141 -14.5 ± 13.5 -14.0 [-53.0, 19.0] (-16.7, -12.2)	66 133.9 ± 13.7 135.0 [106.0, 163.0]	66 119.0 ± 14.1 117.0 [90.0, 156.0]	66 -14.9 ± 14.8 -13.0 [-53.0, 14.0] (-18.5, -11.2)	-0.5 [-4.1, 3.2]	0.8026	-1.0 (-4.5, 2.4)	0.5523

	Renal Denervation (n=143)			Sham Procedure (n=67)			Baseline Adjusted		Baseline and Medication Adjusted	
	Baseline	**6 months**	**Change**	**Baseline**	**6 months**	**Change**	**Difference[1]**	**p[2]**	**Difference[3]**	**p[4]**
Nighttime Ambulatory diastolic blood pressure (mmHg)	141 79.8 ± 8.3 79.0 [57.0, 104.0]	141 70.1 ± 9.1 70.0 [48.0, 104.0]	141 -9.7 ± 8.7 -9.0 [-32.0, 10.0] (-11.1, -8.2)	66 80.5 ± 8.7 81.0 [63.0, 105.0]	66 70.8 ± 9.2 69.0 [48.0, 94.0]	66 -9.7 ± 9.3 -9.0 [-34.0, 7.0] (-12.0, -7.4)	-0.3 [-2.6, 2.1]	0.8096	-0.6 (-2.8, 1.6)	0.5809

ANCOVA=Analysis of Covariance; CI=confidence interval
Note: Data displayed as Mean±SD, Median [Range], and 95% CI for change. Change is calculated as 6 Months – Baseline
[1]Estimate of treatment difference, from baseline adjusted ANCOVA. In the event that change from baseline in either cohort is non-normal, the Hodges-Lehmann estimator of location shift and associated 95% confidence interval (*) (observed data) is also provided.
[2]p-value from baseline adjusted ANCOVA. In the event that change from baseline in either cohort is non-normal, the p-value (*) from a baseline adjusted ANCOVA on the ranks (observed data) is also provided.
[3]Estimate of treatment difference, from baseline and medication adjusted ANCOVA. In the event that change from baseline in either cohort is non-normal, the Hodges-Lehmann estimator of location shift and associated 95% confidence interval (*) (observed data) is also provided.
[4]p-value value from baseline and medication adjusted ANCOVA. In the event that change from baseline in either cohort is non-normal, the p-value (*) from a baseline and medication adjusted ANCOVA on the ranks (observed data) is also provided.

Table 17: RADIANCE II: Number and Type of Antihypertensive Medications, Defined Daily Dose, and Antihypertensive Medication Load at 6 Months (Complete 6M ABP Population)

Characteristic, Mean±SD or n (%)	Renal Denervation (N = 143)	Sham Procedure (N = 67)	P Value
Total number of antihypertensive medications at 6 months	1.3 ± 1.0	1.5 ± 1.0	0.331
Number of antihypertensive medications at 6 months, n/N (%)			0.2297
0	35 (24.5)	11 (16.4)	
1	42 (29.4)	22 (32.8)	
2	48 (33.6)	25 (37.3)	
3	18 (12.6)	7 (10.4)	
4	0 (0.0)	2 (3.0)	
Medication dose burden			
Defined Daily Dose	1.9 ± 1.7	2.2 ± 1.7	0.175
Antihypertensive medication load index	0.7 ± 0.6	0.8 ± 0.6	0.357

Note: P-value from students t-test or Wilcoxon rank sum test for continuous variables and Chi-square or Fishers exact F test for categorical variables as appropriate comparing treatment arm to sham arm.

In RADIANCE II, a linear mixed model adjusting for baseline BP and number of medications including the interaction term, showed that home SBP was 4.6 mmHg lower with uRDN than with sham (95% CI: 2.1 to 7.1 mmHg, p <0.001) (Table 18). The benefit seen in home BP through 6 months reflects the benefit obtained with uRDN in an out-of-office setting when patients are taking their medications as they normally would over a one-week period. The adjustment for post-randomization medication was motivated by clinical considerations, and the results should be interpreted only in terms of correlations or associations, not in terms of causal statements.

Table 18: RADIANCE II: Liner Mixed Model for Repeated Measures including Baseline and Months 2–6 Home SBP (Complete 6-Month ABP Population)

	Mean (95% CI)	p-value
Treatment difference (mmHg)	-4.94 [-7.56, -2.33]	< 0.001
Treatment difference: model including visit by arm interaction term (mmHg)	-4.63 [-7.12, -2.13]	< 0.001
Treatment difference: 2 months (mmHg)*	-6.77 [-11.48, -2.05]	< 0.001
Treatment difference: 3 months (mmHg)*	-5.05 [-9.75, -0.34]	0.0243
Treatment difference: 4 months (mmHg)*	-4.17 [-8.86, 0.52]	0.1317
Treatment difference: 5 months (mmHg)*	-3.62 [-8.34, 1.09]	0.305
Treatment difference: 6 months (mmHg)*	-3.53 [-8.25, 1.19]	0.3441

Note: Models adjusted for baseline home systolic BP and number of medications at visit. Observed values at 2 months, rather than imputed values at 2 months were used in this analysis.
ABP=ambulatory blood pressure; BP=blood pressure; CI: confidence interval; SBP=systolic blood pressure
*p-value adjusted for multiple comparisons (Tukey-Kramer)

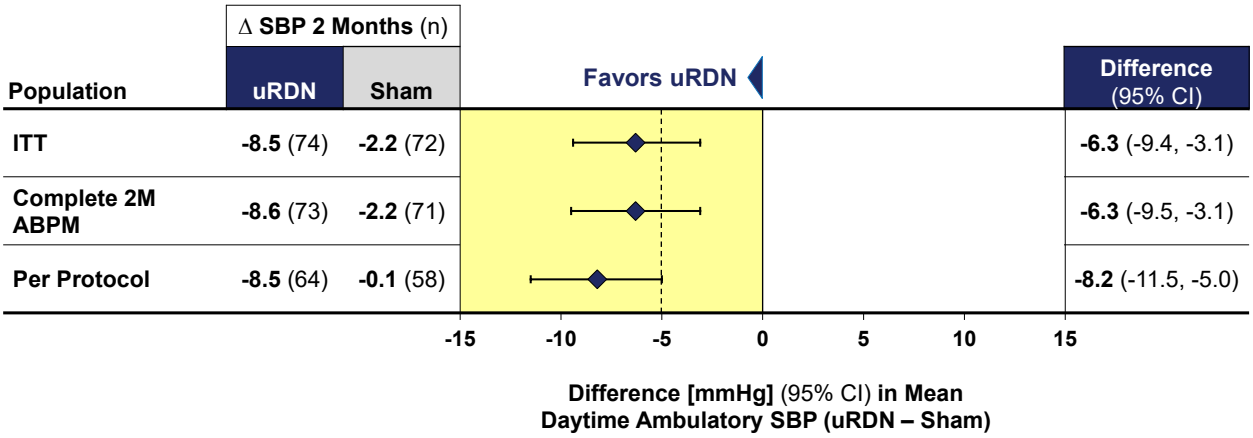
6.3 RADIANCE-SOLO Results

6.3.1 Primary Endpoint Results: Change from Baseline in Average Daytime Ambulatory SBP at 2 Months Post-Procedure

Similar to RADIANCE II, SOLO met its primary endpoint, showing a statistically significant and clinically meaningful reduction in daytime ambulatory SBP in the renal denervation group compared with sham (Figure 37).

Twenty-four (24) patients were excluded from the PP Population for not following protocol requirements. In the uRDN group, 10 patients were excluded for the following reasons: 5 for receiving antihypertensive medication before the 2-month follow-up visit; 2 with baseline ABP lower than entry eligibility; 1 having pre-existing ostial renal artery stenosis; 1 with unilateral renal denervation; and 1 not completing ABP measurement. In the sham group, 14 patients were excluded for the following reasons: 13 for receiving antihypertensive medication and 1 for not completing the ABP measurement. Similar to the ITT Population, there was a significant difference seen in daytime ambulatory SBP between the renal denervation and sham groups at 2 months in the PP Population.

Figure 37: SOLO: Change from Baseline in Average Daytime Ambulatory SBP at 2 Months



2M=2-month; ABPM=ambulatory blood pressure measurement; CI=confidence interval; ITT=intention-to-treat; SBP=systolic blood pressure; uRDN=ultrasound renal denervation

6.3.1.1 Sensitivity Analysis of Primary Endpoint

As with RADIANCE II, a tipping-point analysis supported the robustness of the primary endpoint results in SOLO. In all scenarios, no points were identified where the primary analysis result became non-significant (Table 19). Details on the conduct of the tipping-point analysis are provided in Section 6.2.1.2.

Table 19: SOLO: Primary Endpoint Tipping-Point Analysis (ITT Population)

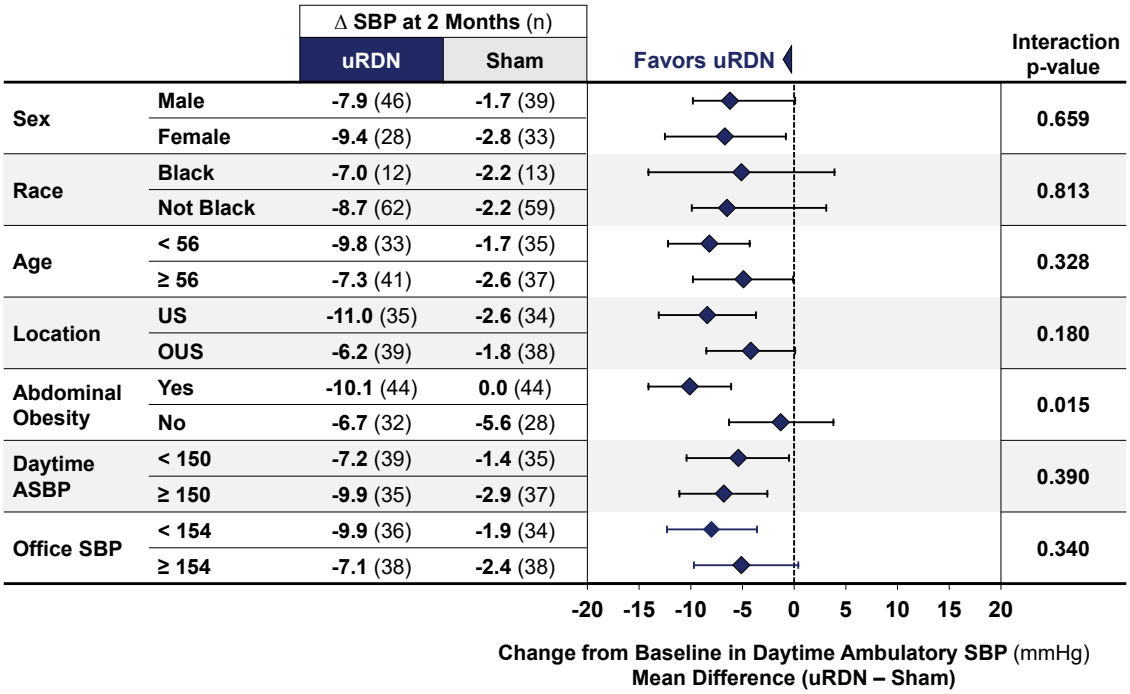
	Control				
Treatment:	**0%**	**25%**	**50%**	**75%**	**100%**
0%	0.0058 (0.0005*)	< .0001	< 0.0001	< 0.0001	< 0.0001
25%	0.0088 (0.0006*)	0.0002	< 0.0001	< 0.0001	< 0.0001
50%	0.0113 (0.0007*)	0.0002	< 0.0001	< 0.0001	< 0.0001
75%	0.0142 (0.0010*)	0.0003	0.0001	< 0.0001	< 0.0001
100%	0.0322 (0.0031*)	0.0013	0.0006	0.0003	< 0.0001

ANCOVA=analysis of covariance; ITT=Intention-to-Treat
*p-value from ANCOVA, adjusting for baseline value. The p-value (*) from a baseline-adjusted ANCOVA on the ranks is also provided.

6.3.1.2 Subgroup Analyses of Primary Endpoint

Across subgroups, the primary efficacy endpoint findings favored the renal denervation group (Figure 38).

Figure 38: SOLO: Subgroup Analysis of Primary Efficacy – Mean Changes in Daytime Ambulatory SBP by Patient Characteristics (ITT Population)



Δ=change; ITT=intention-to-treat; OUS=outside United States; SBP=systolic blood pressure; uRDN=ultrasound renal denervation, US=United States

6.3.2 Secondary Endpoint Results

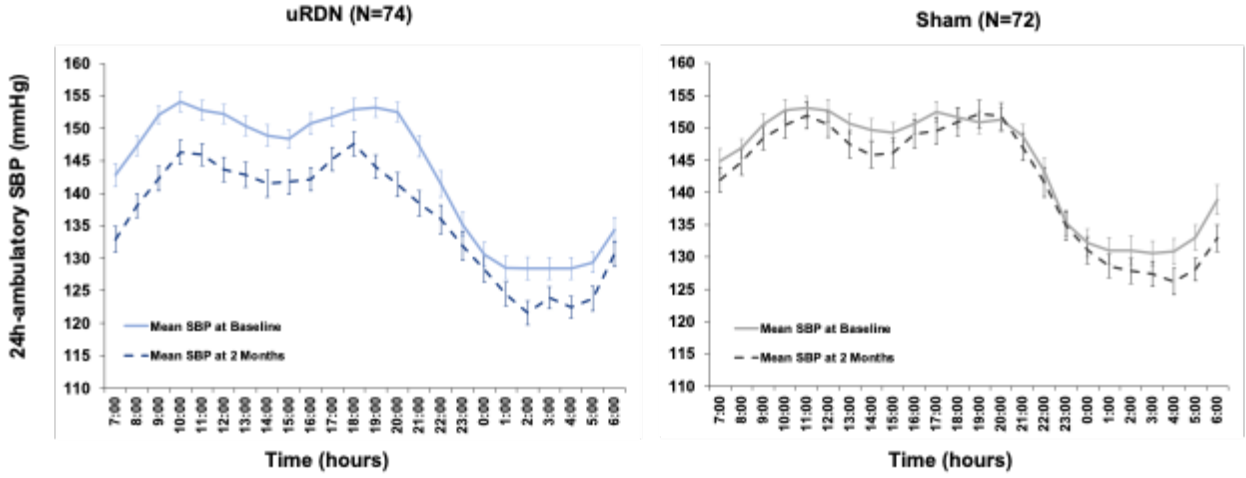
Changes in daytime ambulatory DBP, 24-hour ambulatory, and nighttime ABPs at 2 months in SOLO are shown in Table 20. Significant decreases between renal denervation and sham were observed in 24-hour ambulatory SBP (Figure 39) and daytime ambulatory DBP. Although not statistically significant, a larger difference between groups for nighttime measures was also observed in the renal denervation group in SOLO.

Table 20: SOLO: Secondary Endpoint Results (ITT Population)

BP (mmHg) Mean±SD Median:	uRDN (N=74)			Sham (N=72)			Baseline Adjusted	
	Baseline	2-month	Difference (95% CI)	Baseline	2-month	Difference (95% CI)	Mean Diff (95% CI)	p-value[a]
24-hour ambulatory SBP	142.6 ± 8.1 141.8	135.6 ± 11.4 135.6	-7.0 ± 8.6 -6.8	143.8±10.4 142.8	140.7±11.8 140.8	-3.1±9.7 -1.7	-4.1 (-7.1, -1.2)	0.0061
24-hour ambulatory DBP	87.3±5.0 87.5	83.0 ± 6.8 82.7	-4.4 ± 5.8 -3.8 (-5.7, -3.0)	88.6±5.7 88.0	85.7±7.1 85.4	-3.0±6.1 -2.8 (-4.4, -1.5)	-1.8 (-3.7, 0.2)	0.0715
Nighttime ambulatory SBP	130.3 ± 11.9 130.1	125.6 ± 12.8 125.6	-4.8±11.7 -4.5 (-7.5, -2.1)	132.5±13.7 131.2	129.4±13.1 129.8	-3.1±11.5 -2.2 (-5.8, -0.4)	-2.5 (-6.0, 0.9)	0.1534
Nighttime ambulatory DBP	78.2 ± 8.0 79.2	74.8 ± 8.5 74.4	-3.3±8.5 -1.6 (-5.3, -1.4)	80.0±8.1 80.1	77.3±8.5 76.7	-2.7±7.3 -2.7 (-4.4, -1.0)	-1.4 (-3.8, 1.0)	0.2492
Daytime ambulatory DBP	93.1 ± 4.8 93.4	87.9 ± 7.1 88.6	-5.1±5.9 -4.9 (-6.5, -3.8)	93.5±5.5 93.1	90.9±7.9 91.0	-2.6±6.5 -1.4 (-4.1, -1.1)	-2.6 (-4.6, 0.6)	0.0118 (0.0060*)

ANCOVA=analysis of covariance; BP=blood pressure; CI=confidence interval; DBP=diastolic blood pressure; Diff=difference; ITT=Intention-to-Treat; SBP=systolic blood pressure; SD=standard deviation; uRDN=ultrasound renal denervation.
a. Mean difference with 95% CI and p-value from ANCOVA, adjusting for baseline value. In the event that the change from baseline in either cohort is non-normal, the p-value (*) from a baseline-adjusted ANCOVA on the ranks is also provided.

Figure 39: SOLO: 24-Hour Ambulatory SBP



6.3.3 Observational Endpoint Results

Changes in home and office BP were included as observational endpoints in SOLO. For all measures, a statistically significant reduction of BP was seen for uRDN-treated patients compared to sham patients (Table 21). Home systolic BP reductions were similar in magnitude as those obtained during the daytime ambulatory recordings.

Table 21: SOLO: Change from Baseline to 2 Months in Office and Home Blood Pressure

BP (mmHg) Mean±SD Median:	uRDN (N=74)			Sham (N=72)			Baseline Adjusted	
	Baseline	2-month	Difference (95% CI)	Baseline	2-month	Difference (95% CI)	Mean Diff (95% CI)	p-value[a]
Office SBP	154.5 ± 12.4 154.0	143.7 ± 16.1 141.0	-10.8 ± 13.6 -10.5 (-14.0, -7.7)	153.6±15.7 154.5	149.7±17.4 150.0	-3.9±17.4 -2.5 (-8.0, 0.2)	-6.5 (-11.3, -1.8)	0.0073
Office DBP	99.7 ± 7.7 100.0	94.2 ± 10.0 94.0	-5.5 ± 8.4 -5.0 (-7.5, -3.6)	99.1 ± 9.4 99.5	98.0 ± 10.0 98.0	-1.2±10.0 0.0 (-3.5, 1.2)	-4.1 (-7.0, -1.3)	0.0045
Home SBP	147.5 ± 8.8 148.0	139.4 ± 11.7 140.0	-8.1 ± 9.7 -9.0 (-10.4, -5.8)	147.7 ± 12.3 131.2	146.6 ± 15.4 145.0	-1.1±10.6 1.0 (-3.6, 1.4)	-7.1 (-10.4, -3.8)	< 0.0001
Home DBP	94.8 ± 6.9 96.0	89.9 ± 7.8 89.0	-4.9 ± 6.7 -5.0 (-6.5, -3.3)	94.6 ± 7.0 95.0	93.3 ± 8.5 92.0	-1.3±6.2 -1.0 (-2.7, 0.2)	-3.6 (-5.6, 1.5)	0.0009

BP=blood pressure; CI=confidence interval; DBP=diastolic blood pressure; Diff=difference; SBP=systolic blood pressure; SD=standard deviation; uRDN=ultrasound renal denervation

a. Mean difference with 95% CI and p-value from ANCOVA, adjusting for baseline value. In the event that the change from baseline in either cohort is non-normal.

6.3.4 Effectiveness Results at 6 Months

Favorable decreases in both systolic and DBP continued through 6 months in SOLO (Table 22). Patients who received renal denervation consistently had larger SBP and DBP decreases from baseline than sham.

Table 22: SOLO: Changes from Baseline in Systolic and Diastolic Blood Pressure at 6 Months (ABP Population)

	Renal Denervation (n=69)			Sham Procedure (n=71)			Baseline Adjusted		Baseline and Medication Adjusted	
	Baseline	6 months	Difference	Baseline	6 months	Difference	Mean Difference (95% CI) (RDN – Sham)[1]	p[1]	Mean Difference (95% CI) (RDN – Sham)[2]	p[2]
Daytime Ambulatory systolic blood pressure (mmHg)	69 150.2 ± 7.9 148.8 [134.8, 165.8]	69 132.2 ± 12.1 130.2 [103.6, 167.5]	69 -18.1 ± 12.2 -19.6 [-45.2, 20.8] (-21.0, -15.1)	71 149.9 ± 9.8 150.1 [134.5, 176.7]	71 134.3 ± 11.2 133.5 [105.8, 163.5]	71 -15.6 ± 13.2 -13.7 [-52.5, 13.0] (-18.7, -12.4)	-2.3 (-6.0, 1.5)	0.2418	-4.2 (-7.8, -0.5)	0.0254
Daytime Ambulatory diastolic blood pressure (mmHg)	69 93.0 ± 4.6 93.4 [82.6, 102.5]	69 82.3 ± 7.5 82.0 [65.8, 98.9]	69 -10.7 ± 7.8 -10.7 [-26.1, 9.3] (-12.6, -8.8)	71 93.4 ± 5.4 92.6 [85.1, 107.6]	71 83.7 ± 7.9 83.9 [64.7, 108.4]	71 -9.7 ± 8.1 -9.6 [-31.5, 10.3] (-11.6, -7.7)	-1.3 (-3.7, 1.2)	0.3210	-2.6 (-5.0, -0.3)	0.0249
24 Hour Ambulatory systolic blood pressure (mmHg)	69 142.4 ± 8.2 141.7 [123.3, 161.6]	69 126.0 ± 11.2 125.0 [99.7, 160.1]	69 -16.5 ± 11.8 -17.2 [-48.2, 16.0] (-19.3, -13.6)	71 143.7 ± 10.4 142.5 [124.4, 176.7]	71 128.8 ± 10.6 128.9 [104.7, 158.1]	71 -14.9 ± 12.8 -12.1 [-52.5, 13.7] (-17.9, -11.9)	-2.4 (-6.0, 1.1)	0.1783 (0.1080*)	-4.2 (-7.5, -0.9)	0.0136 (0.0068*)
24 Hour Ambulatory diastolic blood pressure (mmHg)	69 87.3 ± 4.9 87.5 [75.0, 98.6]	69 77.6 ± 7.0 76.9 [65.3, 92.7]	69 -9.7 ± 7.3 -9.1 [-26.2, 6.8] (-11.4, -7.9)	71 88.5 ± 5.7 87.9 [78.9, 106.3]	71 79.2 ± 7.4 79.0 [61.8, 99.6]	71 -9.4 ± 7.8 -8.3 [-32.8, 8.2] (-11.2, -7.5)	-1.0 (-3.3, 1.3)	0.3833 (0.2510*)	-2.4 (-4.5, -0.3)	0.0223 (0.0125*)
Nighttime Ambulatory systolic blood pressure (mmHg)	69 130.0 ± 12.0 129.8 [96.7, 161.0]	69 116.1 ± 12.0 116.2 [90.9, 151.7]	69 -13.9 ± 13.6 -13.4 [-67.0, 15.2] (-17.2, -10.7)	70 132.5 ± 13.7 131.2 [105.2, 168.3]	70 119.7 ± 12.1 119.0 [94.7, 146.7]	70 -12.8 ± 13.5 -10.8 [-45.6, 17.2] (-16.0, -9.5)	-2.7 (-6.4, 1.0)	0.1565 (0.1803*)	-4.6 (-8.0, -1.1)	0.0106 (0.0147*)
Nighttime Ambulatory diastolic blood pressure (mmHg)	69 78.1 ± 8.1 78.7 [57.7, 94.6]	69 70.2 ± 8.1 69.6 [54.4, 92.3]	69 -7.9 ± 9.1 -7.7 [-36.5, 11.6] (-10.1, -5.7)	70 80.0 ± 8.2 79.9 [60.0, 107.1]	70 71.7 ± 8.0 71.0 [55.7, 90.9]	70 -8.3 ± 8.7 -7.2 [-37.5, 12.8] (-10.3, -6.2)	-0.8 (-3.3, 1.7)	0.5335	-2.3 (-4.5, -0.0)	0.0485

Data displayed as Mean±SD, Median [Range], and 95% CI for change. Change is calculated as 6 Months - Baseline

[1]Mean difference with 95% CI and p-value value from ANCOVA, adjusting for baseline value. In the event that the change from baseline in either cohort is non-normal, the p-value (*) from a baseline adjusted ANCOVA on the ranks is also provided.

[2]Mean difference with 95% CI and p-value value from ANCOVA, adjusting for baseline value and number of medications at visit. In the event that the change from baseline in either cohort is nonnormal, the p-value (*) from a baseline and number of medications adjusted ANCOVA on the ranks is also provided.

Additionally, patients who received renal denervation required fewer antihypertensive medications at 6 months after the procedure than sham (Table 23).

Table 23: SOLO: Antihypertensive Medications Taken at 6 Months after Procedure (ABP Population)

Characteristic, Mean±SD or n (%)	SOLO		
	uRDN (N=69)	Sham (N=71)	p-value
Total number of antihypertensive medications at 6 months	1.0±0.9	1.3±0.9	0.020
Number of antihypertensive medications at 6 months			0.0736
0	25 (36.2)	12 (16.9)	
1	26 (37.7)	33 (46.5)	
2	14 (20.3)	19 (26.8)	
3	4 (5.8)	7 (9.9)	
Medication dose burden			
Defined daily dose	1.1±1.2	1.8±1.4	0.005
Antihypertensive medication load index	0.5±0.4	0.7±0.5	0.006

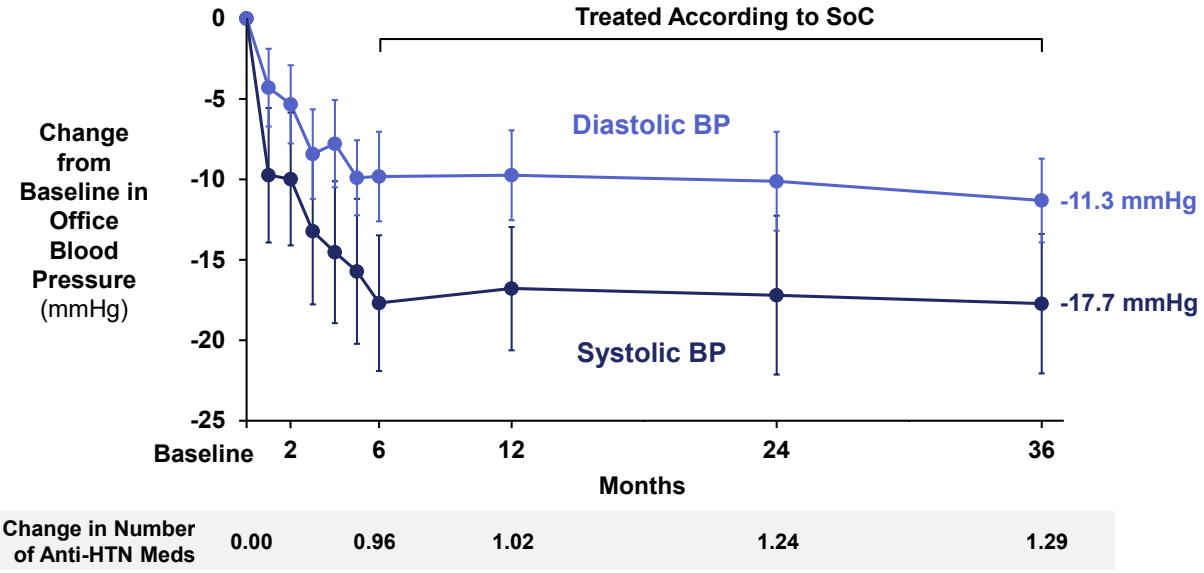
ABP=ambulatory blood pressure; SD=standard deviation; uRDN=ultrasound renal denervation.
Note: Medication dose burden at 12 months expressed as the sum of defined daily dose of each individual antihypertensive medication. Defined daily dose calculated as the assumed average maintenance dose per day for a drug used for its main indication in adults (WHO 2018). For medication load index, the percentage of the maximum labeled daily dose for each agent was calculated for each medication a patient was taking and then added together (Wan et al 2009). P-value from students t-test or Wilcoxon rank sum test for continuous variables and Chi-square or Fishers exact test for categorical variables as appropriate comparing treatment arm to sham arm.

6.3.5 Long-Term Effectiveness

After completing their 12-month follow-up visit, patients returned once per year for office BP measurements at their primary care provider's office. Given the study design limitations at longer-term follow-up (patients were unblinded after 6 months, patients who received sham began to cross-over following the 12-month visit, and the study was not powered to measure differences in office BP between groups at the 24- and 36-month timepoints), the long-term durability is focused only on patients who initially received renal denervation.

In SOLO, reductions in office SBP and DBP among patients who received uRDN were sustained through 36 months (Figure 40).

Figure 40: SOLO: Change from Baseline in Office Blood Pressure Through 36 Months



BP=blood pressure; HTN=hypertension; SoC=standard of care.

Additional analyses were conducted to evaluate office BP and number of antihypertensive medications at screening and 36 months. In SOLO, 51 patients treated with uRDN had an office blood pressure measurement at screening and have reached the 36-month follow-up visit. Reductions in office systolic and diastolic BP compared to screening were -8.4 mmHg and -4.4 mmHg, respectively with patients on a similar number of antihypertensive medications (Table 24).

Table 24: SOLO: Office Blood Pressure and Number of Antihypertensive Medications at Screening and 36 Months

Measurement Mean ±SD, Median [Range] 95% CI	SOLO		
	Office Systolic BP	Office Diastolic BP	Anti-HTN Medications
Screening (N=51)	144.5 ± 13.6 144.0 [121.0, 176.0] 140.73 to 148.37	92.1 ± 10.4 92.0 [65.0, 109.0] 89.22 to 95.05	1.2 ± 0.7 1.0 [0.0, 2.0] 0.98 to 1.37
Month 36 (N=51)	136.2 ± 14.4 136.0 [104.0, 189.0] 132.11 to 140.20	87.7 ± 9.7 88.0 [65.0, 113.0] 85.01 to 90.48	1.3 ± 0.8 1.0 [0.0, 3.0] 1.07 to 1.52
Change (36 Months – Screening)	-8.4 ± 16.6 -8.0 [-39.0, 32.0] -13.07 to -3.71	-4.4 ± 10.5 -4.0 [-25.0, 17.0] -7.35 to -1.44	0.1 ± 1.0 0.0 [-2.0, 2.0] -0.17 to 0.41

BP=blood pressure; CI=confidence interval; HTN=hypertensive

As a reminder, SOLO enrolled patients were either controlled on 1-2 antihypertensive medications or uncontrolled on 0-2 antihypertensive medications at screening. Because

of this, a subset analysis of patients who were uncontrolled at screening and reached the 36-month follow-up visit was conducted. Overall, SOLO included 27 uRDN patients who were uncontrolled at screening, who had a screening office blood pressure and have reached the 36-month follow-up visit. This population aligns with the proposed indication.

While an increase in antihypertensive medications from 0.9 to 1.4 (difference 0.5) was observed in uRDN-treated patients, reductions in office SBP and DBP were more pronounced among patients who had uncontrolled hypertension at baseline, where SBP was reduced by 15.1 mmHg and DBP was reduced by 10.1 mmHg compared to screening.

Table 25: SOLO: Office Blood Pressure and Number of Antihypertensive Medications at Screening and 36 Months in uRDN Patients with Screening Office Blood Pressure Uncontrolled at Screening

Measurement Mean ±SD, Median [Range] 95% CI	SOLO		
	Office Systolic BP	Office Diastolic BP	Anti-HTN Medications
Screening (N=27)	153.9 ± 8.9 154.0 [141.0, 176.0] 150.39 to 157.39	99.9 ± 6.2 101.0 [90.0, 109.0] 97.41 to 102.30	0.9 ± 0.7 1.0 [0.0, 2.0] 0.61 to 1.17
Month 36	138.8 ± 14.0 136.0 [117.0, 189.0] 133.22 to 144.33	89.8 ± 8.9 89.0 [70.0, 113.0] 86.27 to 93.29	1.4 ± 0.9 1.0 [0.0, 3.0] 1.02 to 1.72
Change (36 Months – Screening)	-15.1 ± 15.7 -15.0 [-39.0, 28.0] -21.31 to -8.91	-10.1 ± 8.7 -9.0 [-25.0, 8.0] -13.50 to -6.65	0.5 ± 1.1 1.0 [-2.0, 2.0] 0.04 to 0.93

BP=blood pressure; CI=confidence interval; HTN=hypertensive

6.4 RADIANCE-TRIO Results

6.4.1 Primary Endpoint Results: Change from Baseline in Average Daytime Ambulatory SBP at 2 Months Post-Procedure

TRIO also met its primary endpoint, showing a significant and clinically meaningful reduction in daytime ambulatory SBP in the uRDN group compared with sham in patients with uncontrolled hypertension, despite the use of ≥ 3 antihypertensive medications (Figure 41). Similar to the ITT Population, there was a more pronounced reduction in daytime ambulatory SBP at 2 months with renal denervation compared with sham in the PP analysis.

The between-group difference was slightly smaller in TRIO (4.5 mmHg) in the ITT population compared to the 6.3 mmHg difference in daytime ASBP in SOLO and RADIANCE II. The key factor that contributes to this observed difference was the

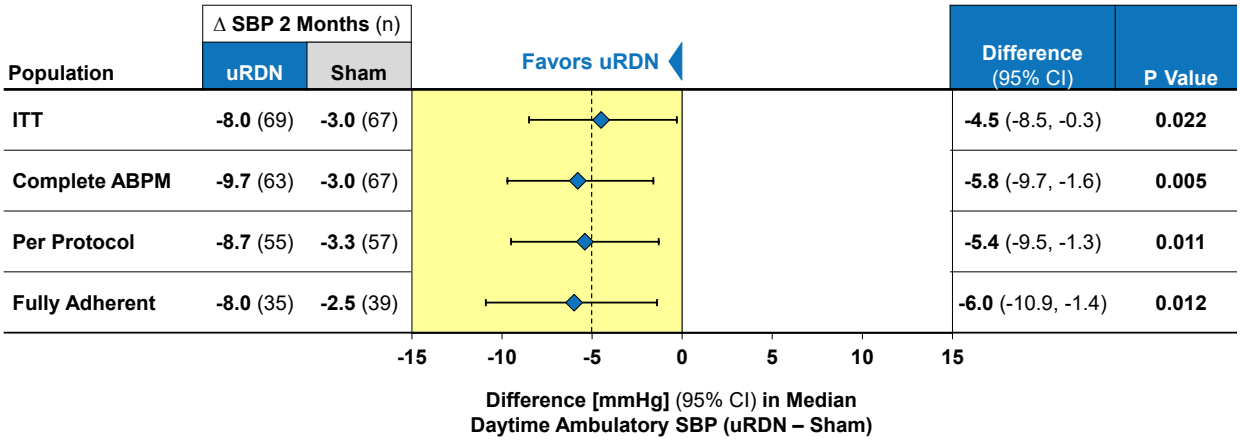
imbalance of missing data between the uRDN and sham groups at 2 months in TRIO and the handling of missing data in the intention-to-treat population.

Per the SAP, if an ABPM was missing at 2 months, a conservative approach was utilized to account for these missing values. For patients with missing values, it was assumed there was no change in BP from baseline and a value of zero was imputed. In addition, if a patient added medications prior to 2 months and met escape criteria (with demonstrated increased BP) their 2-month results were also imputed to baseline values.

In TRIO, 6 uRDN patients (8.7%) compared with 0 sham patients (0%) had missing ABPM values at 2 months; thus, more patients in the uRDN group had their ABPM imputed at 2 months to baseline values (no change) due to missing data. When accounting for this imbalance in missing data and assessing only patients with complete ambulatory BP values, the median between group difference in daytime ASBP was -5.8 mmHg and the mean between-group difference was -5.3 mmHg.

Importantly, the complete ABP and fully adherent analyses in TRIO demonstrated a mean between group difference of -5.3 mmHg and -5.5 mmHg, respectively, similar to the mean between-group difference observed in SOLO and RADIANCE II of -6.3 mmHg. Therefore, the treatment effect observed in TRIO exceeds the 5-mmHg threshold deemed to be clinically important during the December 2018 Circulatory System Devices Panel of the Medical Device Advisory Committee (Circulatory System Devices Panel of the Medical Devices Advisory Committee December 2018).

Figure 41: TRIO: Change in Ambulatory Systolic Blood Pressure from Baseline to 2 Months by Population



ABPM=ambulatory blood pressure measurement; CI=confidence interval; ITT=intent to treat

6.4.1.1 Sensitivity Analysis of Primary Endpoint

As with RADIANCE II, a tipping-point sensitivity analysis demonstrated the primary endpoint data to be robust (Table 26). Details on the conduct of the tipping-point analysis are provided in Section 6.2.1.2.

Table 26: TRIO: Primary Endpoint Tipping-Point Analysis (ITT Population)

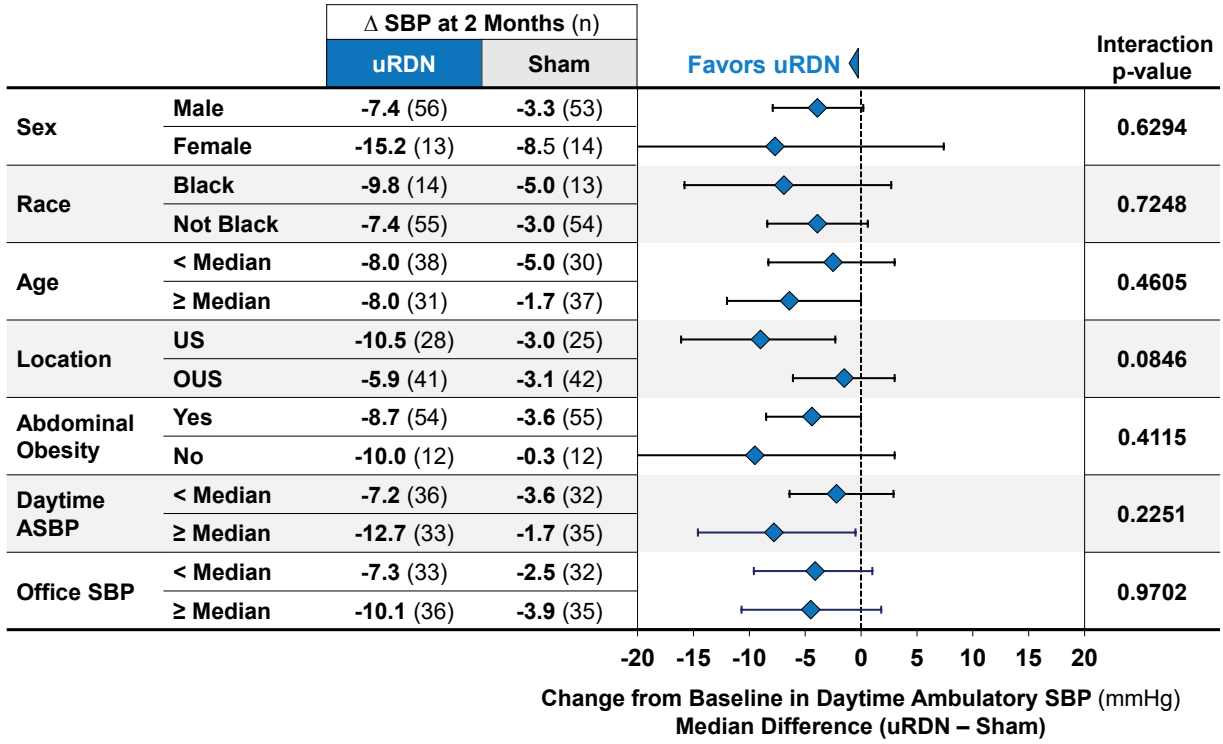
	Control				
uRDN	**0%**	**25%**	**50%**	**75%**	**100%**
0%	0.10042 (0.01184*)	0.00406 (0.00205*)	0.00262 (0.00070*)	0.00196 (0.00040*)	0.00048 (0.00020*)
25%	0.49648 (0.02092*)	0.03871 (0.00406*)	0.02533 (0.00148*)	0.01905 (0.00088*)	0.00435 (0.00047*)
50%	0.63433 (0.03862*)	0.06655 (0.01160*)	0.04489 (0.00335*)	0.03433 (0.00206*)	0.00782 (0.00115*)
75%	0.80891 (0.14482*)	0.12107 (0.05620*)	0.08518 (0.02702*)	0.06676 (0.01380*)	0.01551 (0.00852*)
100%	0.62392 (0.36113*)	0.56481 (0.17298*)	0.46339 (0.09622*)	0.40036 (0.07038*)	0.12345 (0.03751*)

ANCOVA=analysis of covariance; ITT=Intention-to-Treat; uRDN=ultrasound renal denervation.
*p-value value from ANCOVA, adjusting for baseline value. The p-value (*) from a baseline-adjusted ANCOVA on the ranks is also provided.

6.4.1.2 Subgroup Analyses of Primary Endpoint

Across subgroups, the primary efficacy endpoint findings favored the uRDN group (Figure 42).

Figure 42: TRIO: Subgroup Analysis of Primary Efficacy – Median Changes in Daytime Ambulatory SBP by Patient Characteristics (ITT Population)



ASBP=ambulatory systolic blood pressure; ITT=intention-to-treat; SBP=systolic blood pressure

6.4.2 Secondary Endpoint Results

Changes in daytime ambulatory DBP, 24-hour ambulatory, and nighttime ABPs at 2 months in TRIO are shown in Table 27. The results in TRIO directionally favored the uRDN group, although the differences were not statistically significant. Changes in 24-hour and nighttime ambulatory SBP parameters were consistent with daytime ambulatory favoring renal denervation, which supports the "always-on" effect of renal denervation.

Table 27: TRIO: Secondary Endpoint Results (ITT Population)

	uRDN (N=69)			Sham (N=67)			Baseline Adjusted	
BP (mmHg) Mean±SD Median:	Baseline	2-month	Difference (95% CI)	Baseline	2-month	Difference (95% CI)	Mean Diff (95% CI)	p-value[a]
24-hour ambulatory SBP	143.9±13.4 139.9	135.2±16.0 133.4	-8.7±13.9 -8.5	145.4±14.0 142.4	140.5±18.7 138.2	-4.8±16.5 -2.9	-4.3 (-9.3, 0.7)	0.0895 (0.0162*)
24-hour ambulatory DBP	88.9±8.2 87.6	83.6±10.9 82.8	-5.2±8.7 -5.4 (-7.3, -3.2)	89.5±9.5 87.2	85.8±12.0 84.6	-3.7±10.8 -2.4 (-6.4, -1.1)	-1.7 (-4.9, 1.5)	0.3054 (0.1228*)
Nighttime ambulatory SBP	134.4±18.0 130.1	126.3±18.4 125.1	-8.1±15.7 -8.3 (-11.9, -4.3)	136.4±18.6 132.4	131.9±20.9 129.9	-4.5±19.5 -1.8 (-9.3, 0.2)	-4.4 (-9.9, 1.2)	0.1213 (0.0441*)
Nighttime ambulatory DBP	81.3 ± 10.7 79.8	76.2 ± 12.2 74.8	-5.1 ± 10.0 -5.1	81.3 ± 12.1 80.3	78.4 ± 13.2 77.0	-2.8 ± 12.9 -2.0 (-6.0, 0.3)	-2.2 (-5.8, 1.4)	0.2242 (0.0534*)
Daytime ambulatory DBP	93.8 ± 7.7 91.6	88.5 ± 11.6 86.4	-5.3 ± 9.2 -4.9	94.6 ± 9.1 91.6	90.7 ± 12.2 89.5	-3.9 ± 10.5 -2.0 (-6.5, -1.3)	-1.6 (-4.9, 1.7)	0.3415 (0.1835*)

ANCOVA=analysis of covariance; CI=confidence interval; DBP=diastolic blood pressure; Diff=difference; ITT=Intention-to-Treat; SD=standard deviation; uRDN=ultrasound renal denervation.

a. Mean difference with 95% CI and p-value from ANCOVA, adjusting for baseline value. In the event that the change from baseline in either cohort is non-normal, the p-value (*) from a baseline-adjusted ANCOVA on the ranks is also provided.

6.4.3 Observational Endpoint Results

Changes in home and office BP were included as observational endpoints in TRIO. The treatment effect of uRDN was consistent for office and home BP with a larger BP lowering effect in the uRDN group (Table 28). The homogeneity of the BP lowering effect of RDN independently of the BP measurement method reinforces the strength of the results.

Table 28: TRIO: Change from Baseline to 2 Months in Office and Home Blood Pressure

BP (mmHg) Mean±SD Median:	uRDN (N=74)			Sham (N=72)			Baseline Adjusted	
	Baseline	2-month	Difference (95% CI)	Baseline	2-month	Difference (95% CI)	Mean Diff (95% CI)	p-value[a]
Office SBP	155.6 ± 16.7 155.5	147.1 ± 20.3 146.0	-8.5 ± 19.1 -9.0 (-13.3, -3.7)	154.9 ± 16.8 155.0	152.1 ± 22.0 146.5	-2.8 ± 20.7 -4.0 (-7.9, 2.3)	-5.4 (-11.9, 1.1)	0.1042
Office DBP	101.4 ± 11.6 101.0	96.6 ± 13.9 95.0	-4.8 ± 13.7 -5.0 (-8.2, -1.4)	99.4 ± 10.9 99.5	98.7 ± 13.8 97.0	-0.7 ± 12.7 -1.0 (-3.9, 2.4)	-3.2 (-7.5, 1.1)	0.1375
Home SBP	152.0 ± 16.2 149.5	144.6 ± 18.2 146.0	-7.4 ± 15.0 -6.0 (-11.2, -3.5)	153.1 ± 17.0 153.5	149.9 ± 18.9 146.5	-3.2 ± 9.3 -2.0 (-5.6, -0.9)	-4.3 (-8.6, 0.0)	0.0524
Home DBP	96.5 ± 11.2 93.0	93.2 ± 14.7 90.0	-3.3 ± 8.2 -4.0 (-5.4, -1.2)	96.7 ± 11.4 94.0	96.0 ± 12.8 93.0	-0.7 ± 6.4 -1.0 (-2.3, -0.9)	-2.6 (-5.2, 0.0)	0.0527

ANCOVA=analysis of covariance; BP=blood pressure; CI=confidence interval; DBP=diastolic blood pressure; Diff=difference; ITT=Intention-to-Treat; SBP=systolic blood pressure; SD=standard deviation; uRDN=ultrasound renal denervation.
a. Mean difference with 95% CI and p-value from ANCOVA, adjusting for baseline value.

6.4.4 Effectiveness Results at 6 Months

Favorable decreases in both systolic and DBP continued through 6 months in TRIO (Table 29).

Table 29: TRIO: Changes from Baseline in Systolic and Diastolic Blood Pressure after 6 Months (ABP Population)

	Renal Denervation (n=65)			Sham Procedure (n=64)			Unadjusted	Baseline Adjusted		Baseline and Medication Adjusted	
	Baseline	6 months	Difference	Baseline	6 months	Difference	Median Difference (95% CI) (RDN – Sham)[1]	Mean Difference (95% CI) (RDN – Sham)[2]	p[2]	Mean Difference (95% CI) (RDN – Sham)[3]	p[3]
Daytime Ambulatory systolic blood pressure (mmHg)	65 150.1 ± 12.2 147.1 [134.5, 179.8]	65 138.3 ± 15.1 137.6 [110.1, 171.1]	65 -11.8 ± 14.2 -9.2 [-56.2, 26.3] (-15.3, -8.3)	64 151.3 ± 12.7 149.0 [133.8, 202.0]	64 139.0 ± 14.3 136.1 [109.0, 194.9]	64 -12.3 ± 14.2 -12.4 [-46.7, 42.6] (-15.8, -8.7)	1.5 [-3.0, 5.8]	-0.0 (-4.6, 4.5)	0.9835 (0.6467*)	1.0 (-3.6, 5.6)	0.6796 (0.4792*)
Daytime Ambulatory diastolic blood pressure (mmHg)	65 93.9 ± 7.8 91.6 [82.6, 112.6]	65 86.0 ± 10.2 85.7 [62.2, 103.6]	65 -7.9 ± 9.1 -7.7 [-36.3, 20.6] (-10.2, -5.7)	64 94.6 ± 9.0 91.8 [82.9, 136.1]	64 86.1 ± 10.2 86.9 [68.6, 125.0]	64 -8.4 ± 9.7 -7.6 [-31.9, 30.8] (-10.9, -6.0)	0.6 [-2.5, 3.5]	0.3 (-2.8, 3.4)	0.8669 (0.7909*)	0.8 (-2.4, 3.9)	0.6278 (0.7912*)
24 Hour Ambulatory systolic blood pressure (mmHg)	65 144.1 ± 13.7 139.9 [123.3, 180.1]	65 132.7 ± 15.7 130.0 [104.7, 167.8]	65 -11.4 ± 14.1 -9.8 [-57.4, 28.7] (-14.9, -7.9)	64 145.5 ± 13.8 142.8 [125.0, 201.6]	64 133.3 ± 13.4 131.0 [109.0, 183.9]	64 -12.1 ± 14.5 -12.3 [-46.2, 48.1] (-15.8, -8.5)	1.2 [-3.3, 6.0]	0.1 (-4.3, 4.6)	0.9545 (0.8474*)	1.1 (-3.4, 5.6)	0.6390 (0.6878*)
24 Hour Ambulatory diastolic blood pressure (mmHg)	65 89.2 ± 8.3 87.6 [75.6, 113.1]	65 81.2 ± 10.4 80.2 [60.4, 102.3]	65 -8.0 ± 8.9 -7.3 [-36.1, 21.1] (-10.2, -5.8)	64 89.4 ± 9.3 87.3 [77.1, 131.8]	64 81.2 ± 9.7 80.5 [65.2, 116.0]	64 -8.3 ± 9.2 -8.3 [-31.5, 31.9] (-10.6, -6.0)	0.5 [-2.4, 3.3]	0.2 (-2.8, 3.1)	0.9043 (0.7372*)	0.6 (-2.4, 3.6)	0.6995 (0.7767*)
Nighttime Ambulatory systolic blood pressure (mmHg)	65 134.6 ± 18.2 130.1 [104.7, 181.2]	65 124.4 ± 18.3 122.0 [92.4, 168.2]	65 -10.3 ± 17.2 -9.8 [-60.1, 32.2] (-14.5, -6.0)	64 136.4 ± 18.1 132.6 [100.5, 199.4]	64 124.8 ± 15.6 121.5 [94.6, 174.3]	64 -11.6 ± 18.3 -12.4 [-53.1, 59.1] (-16.1, -7.0)	1.7 [-4.5, 7.5]	0.3 (-4.8, 5.5)	0.8940 (0.8103*)	1.5 (-3.7, 6.8)	0.5715 (0.6411*)

Note: Data displayed as Mean±SD, Median [Range], and 95% CI for change. Change is calculated as 6 Months - Baseline

[1]Hodges-Lehmann estimate of location shift and 95% asymptotic CI.

[2]Mean difference with 95% CI and p-value value from ANCOVA, adjusting for baseline value. In the event that the change from baseline in either cohort is non-normal, the p-value (*) from a baseline adjusted ANCOVA on the ranks is also provided.

[3]Mean difference with 95% CI and p-value value from ANCOVA, adjusting for baseline value and number of medications at visit. In the event that the change from baseline in either cohort is non-normal, the p-value (*) from a baseline and number of medications adjusted ANCOVA on the ranks is also provided.

Additionally, patients who received uRDN required numerically fewer (not statistically significant) antihypertensive medications at 6 months after the procedure than sham (Table 30). The medication dose burden, assessed by both defined daily dose and medication load index, was lower among patients who received renal denervation compared to sham.

Table 30: TRIO: Antihypertensive Medications Taken at 6 Months after Procedure (ABP Population)

Characteristic, Mean±SD or n (%)	uRDN (N=65)	Sham (N=64)	p-value
Total number of antihypertensive medications at 6 months	3.8±1.0	4.1±1.1	0.086
Number of antihypertensive medications at 6 months			0.2416
0	0	0	
1	1 (1.5)	0	
2	2 (3.1)	1 (1.6)	
3	26 (40.0)	22 (34.4)	
4	22 (33.8)	19 (29.7)	
5	12 (18.5)	13 (20.3)	
6 or more	2 (3.1)	9 (14.1)	
Medication dose burden			
Defined daily dose ± SD	5.2±1.3	5.7±1.5	0.131
Antihypertensive medication load index ± SD	2.3±0.6	2.4±0.6	0.139

ABP=ambulatory blood pressure; SD=standard deviation; uRDN=ultrasound renal denervation.
Note: P-value from students t-test or Wilcoxon rank sum test for continuous variables and Chi-square or Fishers exact test for categorical variables as appropriate comparing treatment arm to sham arm.

Further, the use of aldosterone antagonists (the first step in the standardized stepped-care antihypertensive treatment protocol) was significantly less in the uRDN group (40.0% for uRDN vs 59.4% for sham; p=0.028) (Table 31).

Table 31: TRIO: Aldosterone Antagonists Taken at 6 Months after Procedure (ABP Population)

Type of Medication	TRIO		
	uRDN (N=65)	Sham (N=64)	p-value
Standardized triple pill[a]			
Renin angiotensin system blockers	97%	100%	0.496
Calcium channel blocker	99%	98%	1.000
Diuretic	95%	95%	1.000
Standardized treatment escalation protocol			
Aldosterone antagonist	40%	59%	0.028
Alpha-1 receptor blocker	5%	6%	0.718
Beta blocker	34%	39%	0.538
Centrally acting alpha-2 agonist or imidazoline receptor agonist	5%	9%	0.324
Vasodilator	2%	2%	1.000

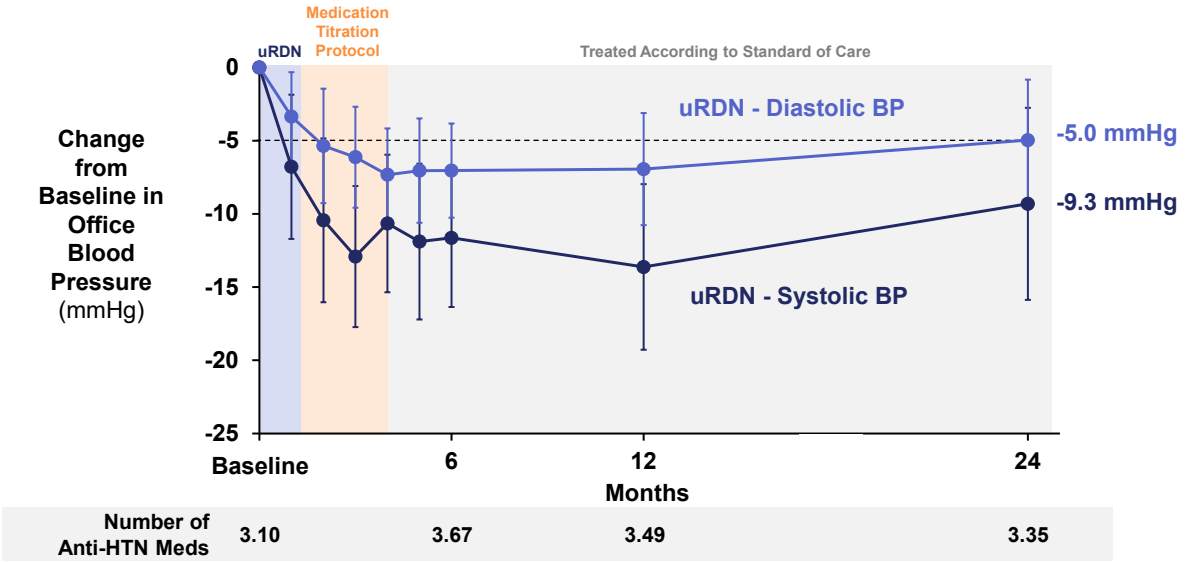
uRDN=ultrasound renal denervation
[a] Amlodipine [10 mg], Valsartan [160 mg] or Olmesartan (40 mg), and Hydrochlorothiazide [25 mg]

6.4.5 Long-Term Effectiveness

As in SOLO, after completing their 12-month follow-up visit, patients returned once per year for office BP measurements at their primary care provider's office. Given the study design limitations at longer-term follow-up (patients were unblinded after 6 months, patients who received sham began to cross-over following the 12-month visit, and the study was not powered to measure differences in office BP between groups at the 24- and 36-month timepoints), the long-term durability is focused only on patients who initially received renal denervation.

As shown in Figure 43, change from baseline in office BP reduction was sustained after the 6-month follow-up visit. Of note, the overall medication burden shows attrition in medical treatment among these patients already on multiple medications for BP control.

Figure 43: TRIO: Change from Baseline in Office Blood Pressure Over 24 Months



Additional analyses were conducted to evaluate office BP and number of antihypertensive medications at screening and 24 months in TRIO (Table 32). Reductions in office BP were observed in TRIO when comparing Month 24 results to screening. Systolic office BP was reduced by 14.6 mmHg and diastolic office BP was reduced by 8.4 mmHg. Furthermore, uRDN-treated patients required fewer antihypertensive medications at Month 24 compared with screening.

Table 32: TRIO: Office Blood Pressure Change from Screening to 24 months (uRDN)

Measurement Mean ±SD, Median [Range] 95% CI	TRIO		
	Office Systolic BP	Office Diastolic BP	Anti-HTN Medications
Screening (N=51)	159.8 ± 14.9 159.0 [150.0, 168.0] 136.0, 207.0	103.5 ± 10.7 100.0 [95.0, 113.0] 90.0, 129.0	3.9 ± 1.0 4.0 [3.0, 7,0] 3.7, 4.2
Month 24 (N=51)	145.2 ± 19.5 140.0 [128.0, 161.0] 118.0, 190.0	95.1 ± 14.7 90.0 [84.0, 102.0] 75.0, 132.0	3.4 ± 1.5 3.0 [0.0, 7.0] 2.9, 3.8
Change (24 Months - Screening)	-14.6 ± 20.8 -21.0 [-28.0, 1.0] -60.0, 30.0	-8.4 ± 12.8 -10.0 [-18.0, 1.0] -32.0, 25.0	-0.6 ± 1.5 0.0 [-5.0, 3.0] -1.0, -0.2

Abbreviations: BP=blood pressure; CI=confidence interval; HTN=hypertension; SD=standard deviation

6.5 Supportive Clinical Data

The ACHIEVE Study, conducted in Europe, treated 96 patients with resistant hypertension on a mean of 5 antihypertensive medications with the Paradise System. The study was designed with one-year follow-up. A mean change in 24-hour ambulatory SBP of -7.46 ± 18.29 mmHg (p=0.0007), office SBP of -15.0 ± 27.0 mmHg (p= 0.0033), and home SBP of -12.30 ± 19.75 mmHg (p=0.0033) from baseline to one year post procedure with no change in the number of medications was observed.

Longer-term follow-up data (8 years post procedure) on a subset of patients (n=20) that re-consented in an investigator sponsored study, demonstrated a persistent reduction in 24-hour ambulatory systolic BP after RDN of -20.6 ± 19.8 mmHg (p=0.0004). The total number of antihypertensive medications per patient decreased between baseline and the long-term follow-up (4.9 ± 2.3 vs. 3.5 ± 1.5 respectively, p=0.034).

RADIOSOUND-HTN, an investigator sponsored study conducted in Germany, compared the effectiveness of uRDN versus radiofrequency RDN in the main+branches and radiofrequency RDN in the main artery. Long-term follow-up data were recently published showing a durable effect of uRDN through 6 months on stable medications (Fengler et al 2023). The change in 24-hour ambulatory SBP was significantly greater in the uRDN group (-12.1 mmHg) than the 2 active comparators.

REQUIRE, which was sponsored and conducted by Otsuka Medical Devices in Japan and Korea, evaluated uRDN in patients with treatment-resistant hypertension. The study did not meet its primary endpoint due to limitations in study design including numerous methodological biases such as poor control of medication adherence and inadequate blinding. A post-hoc analysis evaluated available urine samples for medication adherence at baseline and 3 months. This analysis demonstrated that in patients with good baseline and follow-up adherence, the reduction in 24-hour ASBP was similar to other uRDN studies (-10.1 mmHg in uRDN vs. -1.9 mmHg in sham) (Kario et al 2023).

7 CLINICAL SAFETY

Summary

- The Paradise System has a favorable safety profile, with no significant risks identified either acutely or during long-term follow-up.
  - The Paradise System met its primary safety endpoint with no MAEs in the RADIANCE II study.
  - The composite MAE rate was 1.1% across all 3 RADIANCE studies with a total of 6 MAEs reported.
  - All MAEs were independently assessed by a CEC as either unrelated or likely unrelated to study procedure.
- AEs and SAEs occurred at similar rates between treatment and sham groups across the studies.
- Serious AEs and serious ADEs were low and comparable between treatment and sham groups.
  - Few procedure- or device-related SAEs were reported.
  - Most serious ADEs (SADEs) resolved within 30 days, resulting in no long-term sequelae.
- Extensive imaging confirmed safety of the kidneys and renal arteries.
  - There was no evidence of renal injury from the uRDN procedure.
  - No clinically meaningful new onset renal artery stenosis was observed.

7.1 Treatment Exposure

Across the clinical development program, 367 patients received renal denervation treatment with the Paradise System (Table 33). Safety data for the cross-over patients are provided in Appendix 12.1.

Table 33: RADIANCE Studies: Treatment Exposure

Clinical Study	Total Patients Randomized (N=506)	Patients Receiving uRDN (N=367)
SOLO	146	72
SOLO cross-over	-	37
TRIO	136	69
TRIO cross-over	-	21
RADIANCE II	224	149
RADIANCE II cross-over	-	19

uRDN=ultrasound renal denervation

7.2 Adverse Events

7.2.1 Summary of Adverse Events

AEs in all clinical studies were collected throughout the duration of each study. Across the clinical program, rates of ADEs were higher among patients who received renal denervation, compared to sham, while rates of SAEs were similar to patients in the sham group. Rates of SADEs were low and consistent across the clinical program (Table 34).

Table 34: RADIANCE Studies: Summary of Adverse Events

	RADIANCE II (N=224)		SOLO (N=146)		TRIO (N=136)	
Adverse Events: m, n (%)	**uRDN (N=150)**	**Sham (N=74)**	**uRDN (N=74)**	**Sham (N=72)**	**uRDN (N=69)**	**Sham (N=67)**
Any AE	321, 114 (76.0)	147, 50 (67.6)	169, 53 (71.6)	182, 55 (76.4)	215, 59 (85.5)	216, 54 (80.6)
Serious AE	14, 13 (8.7)	7, 7 (9.5)	12, 8 (10.8)	10, 8 (11.1)	36, 18 (26.1)	33, 16 (23.9)
ADE	134, 91 (60.7)	49, 35 (47.3)	67, 41 (55.4)	30, 23 (31.9)	68, 37 (53.6)	27, 21 (31.3)
Serious ADE	12, 11 (7.3)	1, 1 (1.4)	5, 5 (6.8)	0	5, 3 (4.4)	2, 2 (3.0)
Unexpected ADE	0	0	0	0	0	0
Unexpected serious ADE	0	0	0	0	0	0
Deaths[a]	1 (0.7)	1 (1.4)	0	1 (1.4)	1 (1.4)	3 (4.5)

AE=adverse event; ADE=adverse device event; m=number of events; n=number of patients with an event; uRDN=ultrasound renal denervation; %=percent of patients with an event.

a. One patient died while enrolled in TRIO but who was not randomized to either renal denervation or sham due to screening failure and therefore is not included in this table.

7.2.2 Adverse Events within 30 Days of Procedure

There were few serious events during the post-procedure period in any clinical study (Table 35). Importantly, most ADEs (60-70%) in the clinical studies resolved in ≤ 2 weeks with no long-term sequelae.

Table 35: RADIANCE Studies: Summary of Adverse Events Occurring within 30 Days of Procedure in Any Study

Adverse Events: m, n (%)	RADIANCE II (N=224)		SOLO (N=146)		TRIO (N=136)	
	uRDN (N=150)	Sham (N=74)	uRDN (N=74)	Sham (N=72)	uRDN (N=69)	Sham (N=67)
Any AE	88, 50 (33.3)	37, 19 (25.7)	35, 28 (37.8)	58, 29 (40.3)	50, 31 (44.9)	49, 32 (47.8)
Serious AE	1, 1 (0.7)	0	1, 1 (1.4)	1, 1 (1.4)	6, 4 (5.8)	0
ADE	128, 89 (59.3)	48, 35 (47.3)	64, 38 (51.4)	29, 23 (31.9)	64, 36 (52.2)	26, 20 (29.9)
Serious ADE	11, 10 (6.7)	1, 1 (1.4)	5, 5 (6.8)	0	5, 3 (4.4)	1, 1 (1.5)
Unexpected ADE	0	0	0	0	0	0
Unexpected serious ADE	0	0	0	0	0	0

AE=adverse event; ADE=adverse device event; m=number of events; n=number of patients with an event; uRDN=ultrasound renal denervation; %=percent of patients with an event.

7.2.3 Adverse Events > 30 Days after Procedure

Across the clinical program, rates of ADEs occurring > 30 days after the procedure were low and similar (Table 36). Only 1 patient who received renal denervation in any study (RADIANCE II) experienced a SADE > 30 days after the procedure. The event was asymptomatic aortic dissection in the lower abdomen, an incidental finding in the 6-month follow-up CTA, which did not involve the renal artery or emission sites and did not require intervention.

Table 36: RADIANCE Studies: Summary of Adverse Events Occurring > 30 Days after Procedure in Any Study

AEs > 30 Days Post-Procedure, m n (%):	RADIANCE II (N=224)		SOLO (N=146)		TRIO (N=136)	
	uRDN (N=150)	Sham (N=74)	uRDN (N=74)	Sham (N=72)	uRDN (N=69)	Sham (N=67)
Any AE	233, 104 (69.3)	110, 45 (60.8)	134, 46 (62.2)	124, 48 (66.7)	165, 49 (71.0)	167, 50 (74.6)
Serious AE	13, 12 (8.0)	7, 7 (9.5)	11, 8 (10.8)	9, 8 (11.1)	30, 16 (23.2)	33, 16 (23.9)
ADE	6, 5 (3.3)	1, 1 (1.4)	3, 3 (4.1)	1, 1 (1.4)	4, 3 (4.4)	1, 1 (1.5)
Serious ADE	1, 1 (0.7)	0	0	0	0	1, 1 (1.5)
Unexpected ADE	0	0	0	0	0	0
Unexpected serious ADE	0	0	0	0	0	0

AE=adverse event; ADE=adverse device event; m=number of events; n=number of patients with an event; uRDN=ultrasound renal denervation; %=percent of patients with an event.

7.2.4 Common Adverse Events

Rates of the most frequently reported AEs occurring at any timepoint were generally similar between the renal denervation and sham treatment arms across the clinical program (Table 37). The most common AEs affecting patients who received renal denervation were viral upper-respiratory tract infection, adverse drug reactions, headache, and positive testing for coronavirus.

Table 37: RADIANCE Studies: Common Adverse Events Affecting ≥ 3% of Patients Receiving Renal Denervation in Any Study

	RADIANCE II (N=224)		SOLO (N=146)		TRIO (N=136)	
Adverse Events, m (% patients):	**uRDN (N=150)**	**Sham (N=74)**	**uRDN (N=74)**	**Sham (N=72)**	**uRDN (N=69)**	**Sham (N=67)**
Viral upper-respiratory tract infection	-	-	10 (13.5)	9 (11.1)	6 (7.3)	6 (7.5)
ADR, any	26 (13.3)	21 (14.9)	7 (9.5)	8 (9.7)	15 (20.3)	15 (20.9)
Headache	20 (12.0)	8 (9.5)	8 (10.8)	19 (16.7)	9 (10.1)	7 (10.5)
Coronavirus test positive	16 (10.7)	12 (13.5)	2 (2.7)	1 (1.4)	7 (10.1)	5 (6.0)
Arthralgia	-	-	3 (4.1)	2 (2.8)	7 (10.1)	3 (4.5)
Hypertension, condition aggravated	10 (6.7)	10 (12.2)	6 (8.1)	16 (16.7)	11 (5.8)	20 (22.4)
Dizziness	6 (4.0)	0	5 (5.4)	3 (4.2)	5 (7.3)	5 (7.5)
Peripheral edema	-	-	3 (4.1)	4 (5.6)	6 (7.3)	3 (4.5)
Back pain	8 (4.7)	1 (1.4)	2 (2.7)	2 (2.8)	6 (5.8)	6 (7.5)
Hypotension	2 (1.3)	1 (1.4)	2 (1.4)	5 (6.9)	4 (5.8)	6 (7.5)
Gout	0	1 (1.4)	0	2 (2.8)	5 (5.8)	4 (6.0)
Urinary tract infection	-	-	5 (5.4)	2 (2.8)	4 (5.8)	3 (3.0)
Blood potassium decreased	-	-	0	3 (4.2)	5 (4.4)	7 (9.0)
Blood uric acid increased	0	1 (1.4)	-	-	3 (4.4)	3 (4.5)
Chest pain	1 (0.7)	1 (1.4)	3 (4.1)	0	3 (4.4)	3 (4.5)
Herpes zoster	-	-	3 (1.4)	-	3 (4.4)	2 (3.0)
Hypertension	2 (1.3)	2 (2.7)	1 (1.4)	2 (2.8)	3 (4.4)	1 (1.5)
Pain in extremity	1 (0.7)	0	3 (4.1)	1 (1.4)	4 (5.8)	1 (1.5)
Syncope	-	-	3 (4.1)	1 (1.4)	2 (2.9)	1 (1.5)
Cataract operation	-	-	4 (4.1)	0	-	-

ADR=adverse drug reaction; m=number of events; uRDN=ultrasound renal denervation; %=percent of patients with an event.
Note: ADR includes total number of all drug reaction

7.2.5 Serious Adverse Events

Across the clinical program, SAEs occurred infrequently overall and with similar frequencies in the uRDN and sham groups (Table 34). Table 38 summarizes 9 SAEs which occurred ≥ 2 times in any of the studies. Note that certain events occurred more than once in a single patient (uRDN or sham), as reflected by the (%) in the table. In

RADIANCE II, there were no patients with SAE types that occurred more than once. In SOLO, SAEs of cholelithiasis occurred twice in a single uRDN patient and SAEs of hypertensive crisis occurred twice in a single sham patient. In TRIO, 1 SAE type (hypertensive crisis) occurred in 5 patients – 3 events in uRDN and 2 events in sham groups. Additional events in TRIO that occurred 2 or 3 times occurred in 1 or 2 patients in both uRDN and sham (Table 38).

Table 38 RADIANCE Studies: Serious Adverse Events Occurring ≥ 2 Times in Any Study

	RADIANCE II (N=224)		SOLO (N=146)		TRIO (N=136)	
Adverse Events, m (% patients):	**uRDN (N=150)**	**Sham (N=74)**	**uRDN (N=74)**	**Sham (N=72)**	**uRDN (N=69)**	**Sham (N=67)**
Any SAE	18 (10.0)	8 (9.5)	12 (10.8)	10 (11.1)	36 (26.1)	33 (23.9)
Hypertension, hypertensive crisis	1 (0.7)	0	0	2 (1.4)	3 (4.4)	2 (3.0)
Ventricular tachycardia	0	0	0	0	3 (2.9)	0
Cholelithiasis	0	0	2 (1.4)	0	1 (1.5)	0
Deep vein thrombosis	0	0	0	0	2 (2.9)	1 (1.5)
Cardiac failure	0	0	0	0	2 (1.5)	0
Infection	0	0	0	0	2 (1.5)	0
Cardiac failure, congestive	0	0	0	0	2 (1.5)	0
Cerebrovascular accident	0	0	0	0	0	2 (3.0)
Pneumonia	0	0	0	0	1 (1.5)	3 (3.0)

m=number of events; SAE=serious adverse event; uRDN=ultrasound renal denervation; %=percent of patients with an event.

7.2.6 Adverse Events Leading to Discontinuation

Of the 506 patients randomized into treatment across the clinical development program, 2 (0.4%) had AEs leading to withdrawal: 1 in the renal denervation arm of RADIANCE II and 1 in the sham arm of TRIO. No patients withdrew due to an AE in SOLO.

The patient in RADIANCE II, who received renal denervation, had an AE of intentional self-injury and was hospitalized for suicidal ideations. The patient has a history of depression and anxiety; due to family and financial conditions, the patient became severely depressed and ultimately withdrew from the study. The patient in TRIO, who received sham procedure, had an AE of “hypertension, condition aggravated” approximately 1.5 years (552 days) after the procedure. At that time, the patient had a BP of approximately 190/120 and withdrew from the study based on the severity of hypertension. The patient was not hospitalized.

7.2.7 Device-Related Adverse Events

7.2.7.1 Overview of Device-Related Adverse Events

The most frequently reported device- and procedure-related AEs included transient vasospasm and access site complications (Table 39). Transient vasospasm was observed in a small number of patients and generally resolved within 10 minutes either with or without the delivery of intra-arterial nitroglycerin, with full vessel patency and no sequelae. Vascular access site pain and vascular access site hematoma occurred at a similar rate across treatment groups. These events generally resolved quickly and did not require intervention beyond standard medical care.

Table 39: RADIANCE Studies: Adverse Device Events Affecting ≥ 2% of Patients Receiving Renal Denervation in Any Study

	RADIANCE II (N=224)		SOLO (N=146)		TRIO (N=136)	
Adverse Event, m (% patients):	**uRDN (N=150)**	**Sham (N=74)**	**uRDN (N=74)**	**Sham (N=72)**	**uRDN (N=69)**	**Sham (N=67)**
Vasospasm	7 (4.7)	0	15 (20.3)	0	13 (18.8)	1 (1.5)
Vascular access site pain	16 (10.7)	11 (14.9)	13 (17.6)	10 (13.9)	9 (13.0)	9 (13.4)
Vascular access site hematoma	13 (8.7)	6 (8.1)	11 (14.9)	13 (18.1)	10 (14.5)	5 (7.5)
Bradycardia	3 (2.0)	0	2 (2.7)	0	7 (10.1)	0
Back pain	12 (8.0)	3 (4.1)	4 (5.4)	0	4 (5.8)	3 (4.5)
Post-procedural pain	11 (7.3)	0	-	-	-	-
Vasospasm, drug therapy	-	-	5 (6.8)	0	3 (4.4)	0
Hypotension	1 (0.7)	0	1 (1.4)	0	4 (5.8)	0
Groin pain	8 (5.3)	3 (4.1)	-	-	-	-
Lower-back pain	6 (4.0)	1 (1.4)	-	-	-	-
Post-procedural complication	0	2 (2.7)	0	1 (1.4)	2 (2.9)	0
Post-procedural nausea	5 (2.7)	1 (1.4)	-	-	-	-
Post-procedural headache	4 (2.7)	3 (4.1)	-	-	-	-
Inguinal pain	4 (2.7)	0	-	-	-	-
Post-procedural vomiting	4 (2.7)	0	-	-	-	-
Orthostatic hypotension	1 (0.7)	0	2 (2.7)	0	-	-
Vomiting	-	-	2 (2.7)	0	1 (1.5)	0
Loin pain	3 (2.0)	0	-	-	-	-

m=number of events; uRDN=ultrasound renal denervation; %=percentage of patients with an event.

7.2.7.2 Device-Related Serious Adverse Events

The number and rate of SADEs across the clinical program was very low, with only 1 SADE affecting > 1 patient (vascular access site hematoma [4 patients]; Table 40).

None of the 4 vascular access site hematoma patients required blood transfusion or surgical repair, and all events resolved without sequelae.

Table 40: RADIANCE Studies: Serious Adverse Device Events Affecting ≥ 1% of Patients Receiving Renal Denervation in Any Study

	RADIANCE II (N=224)		SOLO (N=146)		TRIO (N=136)	
Serious Adverse Device Event m (%):	uRDN (N=150)	Sham (N=74)	uRDN (N=74)	Sham (N=72)	uRDN (N=69)	Sham (N=67)
Vascular access site hematoma	3 (2.0)	0	0	0	1 (1.5)	0
Hypotension	0	0	0	0	1 (1.5)	0
Infection	0	0	0	0	1 (1.5)	0
Sedation complication, drug therapy	0	0	0	0	1 (1.5)	0
Atrial fibrillation	0	0	1 (1.4)	0	0	0
Atrioventricular block, drug therapy	0	0	1 (1.4)	0	0	0
Bradycardia, drug therapy	0	0	2 (2.7)	0	0	0
Presyncope, drug therapy	0	0	1 (1.4)	0	0	0

m=number of events; uRDN=ultrasound renal denervation; %=percentage of patients with an event.

7.2.8 Deaths

A total of 8 patients died during the clinical development program.

In SOLO, 1 patient in the sham group died from suicide 241 days post-procedure. The death was determined unrelated to the procedure.

In TRIO, 4 deaths were reported in the randomized patient population, and 1 death occurred during screening prior to randomization:

- Two deaths occurred in the sham group, 1 due to each of: suicide 530 days after procedure; and interstitial lung disease diagnosed 793 days after procedure and death occurred 822 days post procedure.
- One death occurred in a uRDN patient 21 days after procedure; the patient was found dead at home. The patient had been diagnosed with prostate cancer 13 days before death. No further information about the cause of death was available and an autopsy was not performed.
- One death occurred 21 days post cross-over procedure; natural cause of death per death certificate. No further information is available, and autopsy report is not available.
- One additional death occurred during the screening phase of the study prior to randomization due to pancreatic cancer.

In RADIANCE II, 2 deaths occurred in study participants, 1 in the sham group, and 1 in the treatment group. The patient who received sham experienced an ST elevation

resulting in myocardial infarction and death 840 days after procedure. The uRDN patient was diagnosed with metastatic pancreatic cancer and died 97 days post procedure.

7.2.9 Post-Procedural Pain

In RADIANCE II, 53/224 patients experienced procedure-related pain for longer than 2 days (duration of 4–61 days): 40 in the renal denervation group and 13 in the sham group (Table 41). Most events were vascular access site pain, and 42 of 44 events resolved without sequelae.

Table 41: RADIANCE II: Incidence of Post-Procedural Pain Lasting > 2 Days

Patients with, m (%) (95% CI):	uRDN (N=150)	Sham (N=74)
Procedure-related pain lasting for > 2 days	40 (25.3) (18.6%, 33.1%)	13 (16.2) (8.7%, 26.6%)

CI=confidence interval; m=number of events; uRDN=ultrasound renal denervation; %=percentage of patients with an event.

The 2 patients who had post-procedural pain ongoing at the time of data cutoff were both in the renal denervation treatment group. One had back pain, reported as lumbar pain in a standing position, that was assessed as probably related to the device by the principal investigator. The other patient had vascular access site pain, reported as increased pain perception, that was assessed as not related to the device by the principal investigator.

7.3 Additional Safety Analyses

7.3.1 Prespecified Safety Events

Table 42 and Table 43 show the incidence of specific prespecified safety events within 30 days and > 30 days post-procedure, respectively. Overall, the rates of events were low and similar across groups and studies. Within 30 days post-procedure, procedure-related pain lasting for > 2 days occurred in 14–25% of patients in the uRDN groups and 6–17% of patients in the sham groups. All other events occurred in < 2% of patients.

Table 42: Incidence of Specific Events Within 30 Days Post-Procedure

	SOLO		TRIO		RADIANCE II	
Number of Events (% Subjects with Event) 95%CI[1]	**RDN (n=74)**	**Sham (n=72)**	**RDN (n=69)**	**Sham (n=67)**	**RDN (n=150)**	**Sham (n=74)**
All-cause mortality	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	1 (1.45%) 0.04% - 7.81%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Hypertensive emergency resulting in hospitalization	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	0 (0.00%) 0.00% - 5.36%	1 (0.67%) 0.02% - 3.66%	1 (1.35%) 0.03% - 7.30%
Hospitalization for heart failure	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Stroke, transient ischemic attack, cerebrovascular accident	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Acute myocardial infarction (STEMI/non-STEMI)	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Any coronary revascularization	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
End stage renal disease, the need for permanent renal replacement therapy (i.e. the need for dialysis); doubling of plasma creatinine	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	1 (1.45%) 0.04% - 7.81%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Any renal artery complication requiring intervention (e.g. dissection; perforation)	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Major access site complications requiring intervention	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	1 (1.45%) 0.04% - 7.81%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Significant embolic events resulting in end organ damage	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Procedure-related pain lasting for > 2 days	10 (13.51%) 6.68% - 23.45%	4 (5.56%) 1.53% - 13.62%	12 (17.39%) 9.32% - 28.41%	10 (14.93%) 7.40% - 25.74%	40 (25.33%) 18.59% - 33.07%	13 (16.22%) 8.67% - 26.61%
Acute renal injury	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Significant (>50%) and severe (>75%) new onset renal stenosis as diagnosed by duplex ultrasound and confirmed by renal CTA/MRA or as diagnosed/confirmed by renal CTA/MRA	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%

	SOLO		TRIO		RADIANCE II	
Number of Events (% Subjects with Event) 95%CI[1]	**RDN (n=74)**	**Sham (n=72)**	**RDN (n=69)**	**Sham (n=67)**	**RDN (n=150)**	**Sham (n=74)**
Need for renal artery angioplasty or stenting	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%

Table excludes events occurring post-crossover in subjects who cross-over. See separate tables for events occurring post cross-over in cross-over subjects.
[1]Exact 95% confidence interval.

Table 43: Incidence of Specific Events > 30 Days Post-Procedure

	SOLO		TRIO		RADIANCE II	
Number of Events (% Subjects with Event) 95%CI[1]	**RDN (n=74)**	**Sham (n=72)**	**RDN (n=69)**	**Sham (n=67)**	**RDN (n=150)**	**Sham (n=74)**
All-cause mortality	0 (0.00%) 0.00% - 4.86%	1 (1.39%) 0.04% - 7.50%	0 (0.00%) 0.00% - 5.21%	1 (1.49%) 0.04% - 8.04%	1 (0.67%) 0.02% - 3.66%	1 (1.35%) 0.03% - 7.30%
Hypertensive emergency resulting in hospitalization	1 (1.35%) 0.03% - 7.30%	2 (1.39%) 0.04% - 7.50%	3 (4.35%) 0.91% - 12.18%	2 (2.99%) 0.36% - 10.37%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Hospitalization for heart failure	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	4 (1.45%) 0.04% - 7.81%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Stroke, transient ischemic attack, cerebrovascular accident	1 (1.35%) 0.03% - 7.30%	1 (1.39%) 0.04% - 7.50%	0 (0.00%) 0.00% - 5.21%	2 (2.99%) 0.36% - 10.37%	2 (1.33%) 0.16% - 4.73%	1 (1.35%) 0.03% - 7.30%
Acute myocardial infarction (STEMI/non-STEMI)	0 (0.00%) 0.00% - 4.86%	1 (1.39%) 0.04% - 7.50%	2 (2.90%) 0.35% - 10.08%	1 (1.49%) 0.04% - 8.04%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Any coronary revascularization	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	2 (2.90%) 0.35% - 10.08%	1 (1.49%) 0.04% - 8.04%	2 (1.33%) 0.16% - 4.73%	0 (0.00%) 0.00% - 4.86%
End stage renal disease, the need for permanent renal replacement therapy (i.e. the need for dialysis); doubling of plasma creatinine	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	1 (1.45%) 0.04% - 7.81%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Any renal artery complication requiring intervention (e.g. dissection; perforation)	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Major access site complications requiring intervention	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	1 (1.49%) 0.04% - 8.04%	1 (0.67%) 0.02% - 3.66%	0 (0.00%) 0.00% - 4.86%
Significant embolic events resulting in end organ damage	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	1 (1.45%) 0.04% - 7.81%	1 (1.49%) 0.04% - 8.04%	1 (0.67%) 0.02% - 3.66%	1 (1.35%) 0.03% - 7.30%

	SOLO		TRIO		RADIANCE II	
Number of Events (% Subjects with Event) 95%CI[1]	**RDN (n=74)**	**Sham (n=72)**	**RDN (n=69)**	**Sham (n=67)**	**RDN (n=150)**	**Sham (n=74)**
Procedure-related pain lasting for > 2 days	2 (2.70%) 0.33% - 9.42%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Acute renal injury	0 (0.00%) 0.00% - 4.86%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Significant (>50%) and severe (>75%) new onset renal stenosis as diagnosed by duplex ultrasound and confirmed by renal CTA/MRA or as diagnosed/confirmed by renal CTA/MRA	1 (1.35%) 0.03% - 7.30%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%
Need for renal artery angioplasty or stenting	1 (1.35%) 0.03% - 7.30%	0 (0.00%) 0.00% - 4.99%	0 (0.00%) 0.00% - 5.21%	0 (0.00%) 0.00% - 5.36%	0 (0.00%) 0.00% - 2.43%	0 (0.00%) 0.00% - 4.86%

Table excludes events occurring post-crossover in subjects who cross-over. See separate tables for events occurring post cross-over in cross-over subjects.
[1]Exact 95% confidence interval.

7.3.2 New Onset Orthostatic Hypotension

Across all clinical studies, 3 patients experienced onset of new orthostatic hypotension after receiving renal denervation treatment; one patient in the sham group had new onset of orthostatic hypotension (Table 44). Three events occurred within ≤ 2 days of procedure. One event (in the renal denervation group of RADIANCE II) occurred 221 days after the procedure. All 4 events resolved on their own without sequalae.

Table 44: RADIANCE Studies: Incidence of New Onset Orthostatic Hypotension after Procedure

Parameter, m (%) (95% CI):	RADIANCE II (N=224)		SOLO (N=146)		TRIO (N=136)	
	uRDN (N=150)	Sham (N=74)	uRDN (N=74)	Sham (N=72)	uRDN (N=69)	Sham (N=67)
New onset orthostatic hypotension	1 (0.7) (0.0 – 3.7%)	0 (0.0 – 4.9%)	2 (2.7) (0.3 – 9.4%)	0 (0.0 – 5.0%)	0 (0.0 – 5.2%)	1 (1.5) (0.0 – 8.0%)

CI=confidence interval; m=number of events; uRDN=ultrasound renal denervation; %=percentage of patients with an event.

7.3.3 Laboratory Evaluations: Serum Creatinine, eGFR, and UPCR

In all 3 clinical studies, serum creatinine and eGFR were assessed at baseline, then again at 2 months and 12 months after post-procedure to determine whether the renal denervation procedure has any negative impact on kidney function. Both parameters remained within normal ranges in both treatment groups across the clinical studies, and no clinically meaningful changes were observed, indicating no change in renal function after procedure (Table 45). The 12-month data for RADIANCE II are not yet complete.

Table 45: RADIANCE Studies: eGFR and Serum Creatinine Changes from Baseline to 2-Months and 12-Months after Procedure

Parameter, Mean±SD Median [Range]:	uRDN		Sham	
	Baseline	Change (95% CI)	Baseline	Change (95% CI)
2 Months				
SOLO	N=73		N=69	
eGFR	84.7±16.2 82.4 [55.5, 136.7]	1.3±13.1 0.8 [-48.7, 36.1] (-1.8, 4.3)	83.2±16.1 79.1 [48.2, 128.7]	2.4±11.7 2.3 [-32.6, 29.9] (-0.5, 5.2)
Serum creatinine	0.9±0.2 0.9 [0.5, 1.6]	0.0±0.1 0.0 [-0.6, 0.3] (0.0, 0.0)	0.9±0.2 0.9 [0.6, 1.5]	0.0±0.1 0.0 [-0.4, 0.2] (0.0, 0.0)
TRIO	N=69[1]		N=67[2]	
eGFR	87.9±24.9 87.5 [40.0, 192.0]	-1.2±12.6 0.0 [-43.6, 32.3] (-4.4, 2.0)	82.1±19.2 81.4 [40.2, 129.2]	-0.7±8.1 0.0 [-20.4, 17.4] (-2.7, 1.4)
Serum creatinine	1.0±0.3 0.9 [0.4, 1.8]	0.0±0.1 0.0 [-0.5, 0.3] (0.0, 0.0)	1.0±0.3 1.0 [0.6, 2.2]	0.0±0.1 0.0 [-0.3, 0.3] (0.0, 0.0)
RADIANCE II	N=136		N=72	
eGFR	81.4±14.6 81.3 [51.6, 152.8]	1.1±8.2 0.0 [-21.6, 24.5] (-0.3, 2.5)	81.8±14.6 81.8 [52.7, 118.7]	-0.1±8.0 0.0 [-16.6, 19.9] (-1.9, 1.8)
Serum creatinine	0.9±0.2 0.9 [0.5, 1.4]	0.0±0.1 0.0 [-0.3, 0.2] (0.0, 0.0)	1.0±0.2 0.9 [0.7, 1.3]	0.0±0.1 0.0 [-0.2, 0.2] (0.0, 0.0)
12 Months[3]				
SOLO	N=68		N=67	
eGFR	84.5±16.5 82.2 [55.5, 136.7]	-1.0±11.2 0.0 [-31.1, 30.4] (-3.7, 1.7)	82.2±15.8 78.3 [48.2, 128.7]	3.4±11.5 2.2 [-29.6, 37.6] (0.6, 6.2)
Serum creatinine	0.9±0.2 0.9 [0.5, 1.6]	0.0±0.1 0.0 [-0.3, 0.3] (0.0, 0.0)	0.9±0.2 0.9 [0.6, 1.5]	0.0±0.1 0.0 [-0.5, 0.2] (-0.1, 0.0)
TRIO	N=69[4]		N=67[5]	
eGFR	85.9±24.8 86.6 [40.0, 192.0]	-4.7±13.2 -5.3 [-38.7, 27.7] (-8.1, 1.3)	82.6±18.6 80.8 [42.7, 129.2]	-2.9±14.1 -1.5 [-39.5, 42.9] (-6.7, 0.8)
Serum creatinine	1.0±0.3 1.0 [0.4, 1.8]	0±0.2 0.0 [-0.4, 0.4] (0.0, 0.1)	1.0±0.2 1.0 [0.6, 1.4]	0.0±0.1 0.0 [-0.2, 0.5] (0.0, 0.1)

CI=confidence interval; eGFR=estimated glomerular filtration rate; SD=standard deviation; uRDN=ultrasound renal denervation.

[1]n=63 for eGFR and n=64 for creatinine

[2]n=65 for eGFR and n=66 for creatinine

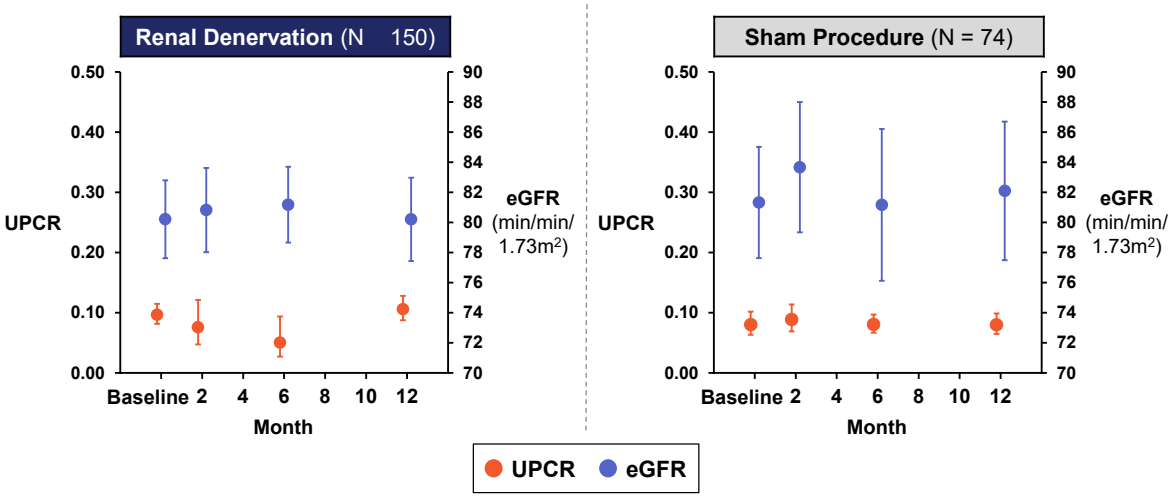
[3]12-month data for RADIANCE II were not available at the time of data cutoff.

[4]n=60 for eGFR and n=61 for creatinine

[5]n=58 for eGFR and n=59 for creatinine

Given the importance of proteinuria as a proxy of kidney damage, proteinuria (estimated by the urine protein creatinine ratio [UPCR] in gram per gram) was assessed along with the serum creatinine and corresponding estimated GFR at baseline and Months 2, 6, and 12. There were no meaningful differences over time or between groups (Figure 44).

Figure 44: RADIANCE II: Urinary Protein-to-Creatinine Ratio (UPCR) and estimated Glomerular Filtration Rate (eGFR) Over Time



7.4 Device Deficiencies

No AEs due to a device deficiency were reported in any of the clinical studies. The majority of deficiencies reported by the clinical sites were detected during prep, and the device was exchanged, resulting in a minimal delay in procedure time. A summary of deficiencies is presented in Table 46.

Table 46: RADIANCE Studies: Summary of Device Deficiencies

	RADIANCE II (N=224)		SOLO (N=146)		TRIO (N=136)	
Deficiency Classification, n (%):	**Events (N=24)**	**Pts with Deficiency (N=19)**	**Events (N=25)**	**Pts with Deficiency (N=21)**	**Events (N=18)**	**Pts with Deficiency (N=12)**
Paradise catheter	13 (54.2)	12 (63.2)	15 (60.0)	14 (66.7)	11 (61.1)	9 (75.0)
Paradise cartridge	5 (20.8)	4 (21.1)	6 (24.0)	6 (28.6)	6 (33.3)	5 (41.7)
Paradise generator	4 (16.7)	4 (21.1)	1 (4.0)	1 (4.8)	-	-
Paradise connection cable	1 (4.2)	1 (5.3)	3 (12.0)	3 (14.3)	-	-
Other	1 (4.2)	1 (5.3)	-	-	1 (5.6)	1 (8.3)

Pts=patients.

7.5 Imaging Results

In each of the RADIANCE studies, all patients were required to undergo CTA or MRA to assess anatomical eligibility pre-procedure.

In RADIANCE II, all patients were required to obtain CTA or MRA at 6 months and patients who received uRDN were required to obtain CTA or MRA at 12 months post-procedure. An independent core lab reviewed all imaging and reported on any renal injury, renal artery injury and provided an estimate (in percent) of narrowing if there was any renal artery narrowing detected. No incidences of clinically meaningful (> 70%) renal artery stenosis (as defined in the clinical protocol) have been observed, with nearly all patients experiencing no measurable stenosis (Table 47).

Table 47: RADIANCE II: Summary of CT/MRA Imaging Observations by Core Lab Assessment at 6 and 12 Months after Procedure

Visit, % (n)	Total N of Pts	No Measurable Stenosis	1–30% Stenosis	31–50% Stenosis	51–70% Stenosis	71–99% Stenosis	Renal Artery Occlusion
6-mo FU	195	97.4% (190)	1.0% (2)	1.5% (3)	0.0% (0)	0.0% (0)	0.0% (0)
Treatment	137	97.8% (134)	1.5% (2)	0.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Control	58	96.6% (56)	0.0% (0)	3.4% (2)	0.0% (0)	0.0% (0)	0.0% (0)
12-mo FU	126	93.7% (118)	2.4% (3)	2.4% (3)	1.6% (2)	0.0% (0)	0.0% (0)
Treatment	112	92.9% (104)	2.7% (3)	2.7% (3)	1.8% (2)	0.0% (0)	0.0% (0)

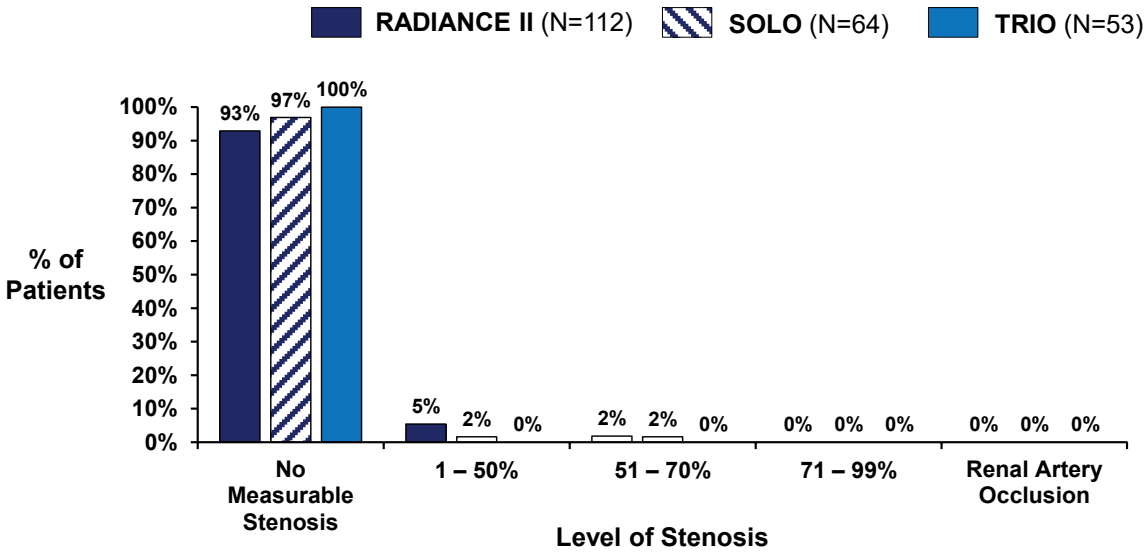
CT=computed tomography; FU=follow-up; mo=month; MRA=magnetic resonance angiography; Pts=patients.

Follow-up imaging protocols in SOLO and TRIO differed from those in RADIANCE II. At Month 2 and Month 6, renal duplex ultrasound imaging was performed to assess flow and changes in velocity which might indicate narrowing. If specific duplex ultrasound parameters[1] were exceeded, a CTA/MRA was performed. At Month 12, CTA or MRA was required for all patients who received renal denervation. Independent diagnostic radiologists reported on any injury to, or narrowing of, the renal artery and/or injury to the kidney. In addition, all 12-month images were reviewed by the Imaging Core Lab.

All available 12-month imaging from RADIANCE II, SOLO, and TRIO were reviewed by the Imaging Core Lab to ensure consistent assessment of all follow-up CTA/MRA studies. The 12-month imaging evaluations showed no evidence of renal injury in the uRDN-treated patients across the RADIANCE studies (Figure 45). Based on core lab adjudication, no patients demonstrated newly recognized renal artery stenosis of more than 70%.

[1] Peak Systolic Velocity (PSV) along any portion of the renal arteries > 180cm/sec, renal to aortic peak systolic velocity ratio ≥ 3.5, or complete lack of Doppler signal in any portion of the main or accessory renal artery

Figure 45: RADIANCE Studies: Summary of 12-Month CTA/MRA Observations (Core Lab Adjudicated)



CTA=computed tomography angiography; MRA=magnetic resonance angiography

7.6 Pooled Safety Analysis

A pooled analysis of MAEs in RADIANCE II, SOLO, and TRIO was conducted to further characterize the safety profile of renal denervation with the Paradise System. This safety analysis was discussed with the FDA and was considered appropriate as the design and procedures were similar across the studies. The pooled MAE analysis included 367 patients who received renal denervation in the Paradise System clinical studies. The composite MAE event rate was compared to a prespecified performance goal of 9.8%. The events were all adjudicated using the same definitions across studies by an independent CEC.

Overall, 6 events in 4 patients met the definition for MAEs: 2 deaths, 2 major vascular complications, 1 hospitalization for hypotensive crisis, and 1 hospitalization for major cardiovascular event. The overall composite rate was 1.1%, which was significantly lower than the prespecified performance goal of 9.8%. Additionally, there was no new onset of renal artery stenosis greater than 70% at 6 months.

8 PATIENT PREFERENCE RESULTS — PREFER STUDY

8.1 PREFER Study Overview

To better understand patients' preferences for a renal denervation procedure with the Paradise System compared to current standard of care medications given to manage uncontrolled hypertension, ReCor performed the RADIANCE PREFER Study. The choice between medication and renal denervation to treat hypertension involves trading-off pill burden, minimally invasive procedures, cardiovascular outcomes, and treatment risks. This study quantified how patients make those trade-offs. PREFER was a cross-sectional, discrete-choice study of US patients with uncontrolled hypertension who were taking at least 1 antihypertensive medication. Potential participants were identified through a combination of databases, physician referrals, patient advocacy groups, associations, and patient social media networks using standardized, institutional review board-approved recruitment materials. The study sought to enroll patients with a similar background to those enrolled in the RADIANCE studies.

Primary objectives in PREFER were:

1. To quantify preferences of patients for the attributes of hypertension treatment
2. To establish the maximum acceptable risk that patients will tolerate and minimum acceptable benefit that patients will require to prefer the Paradise System over standard antihypertensive medications
3. To estimate the likelihood that patients will prefer the Paradise System over standard antihypertensive medications

8.2 PREFER Results

Participants (n=258) were 62% female, 40% non-white, and from multiple regions of the US, with a majority from the South (63%). Mean (SD) age was 53 (12) years and BMI was 33(10) kg/m2. The most frequently used antihypertensive was amlodipine (35%). Many participants reported that they received their hypertension diagnosis less than 6 years ago (n=120, 46.5%), and almost all reported a family history of hypertension.

Numeracy, literacy, and internal validity tests suggest the preference data was good quality. Most participants had high health literacy (n=248, 96%) and numeracy (n=244, 95%) and passed the stability test (n=233, 90%) and dominance test (n=246, 95%). The mean survey completion time was 11.9 min. While 61% of participants did not make choices based on a single attribute, one third of the participants made choices predominantly based on 10-year cardiovascular risk.

When choosing between treatment options patients put most weight on reducing 10-year cardiovascular risk (relative attribute importance=33%), followed by reducing risk of mild-to-moderate side effects (19%), and reducing number of pills (16%). Participants were least likely to consider reducing risk of serious side effects requiring a procedure (7%) and avoiding a minimally invasive procedure (7%), followed by reducing the risk of

serious side effects requiring hospitalization (9%) and extending treatment durability (9%). As hypertension affects a broad range of patients with different disease profiles, there was not unexpectedly, variation in patient preferences depending on the patient profile.

Given the same number of pills, 42% would choose an interventional treatment if it reduced their 10-year cardiovascular risk by 5% more than medication alone. In addition, 42% of patients would prefer a one-time invasive procedure versus taking an additional pill if the procedure had the same effect on cardiovascular risk as medication alone.

Based on the results of PREFER, it was concluded that:

1. Patients are willing to make the trade-offs associated with renal denervation — being willing to tolerate a minimally invasive procedure in exchange of adding another pill or reducing cardiovascular risk.
2. The willingness to make these trade-offs varied between patients:
    a. Patients who took ≥ 3 medications put significantly more weight on reducing cardiovascular risk and reducing pill burden.
    b. Patients who had a history of major adverse cardiac event (MACE) put more weight on reducing cardiovascular risk.
    c. Patients who sometimes forgot to take medications put more weight on reducing pill burden.

While uncertainty in real-world outcomes prohibits the estimation of precise uptake rates, scenario analyses suggest a substantial number of patients taking medication for hypertension would be willing to undergo renal denervation to reduce their cardiovascular risk or to avoid an increase in their pill burden.

9 POST-MARKETING PLAN

ReCor is committed to patient safety and has a multi-component plan to continue to collect data post-approval. ReCor will continue to follow patients enrolled in the SOLO and TRIO cohorts of RADIANCE-HTN for 3 years, or 5 years for those who consent to longer-term follow-up.

ReCor also plans to initiate a US arm of the Global Paradise System (US-GPS) Registry to continue to collect additional data on the Paradise System post-approval. The GPS registry is currently ongoing in Europe and the UK. The US-GPS Registry will include patients currently enrolled in the RADIANCE Continued Access Protocol as well as de novo patients who will be enrolled and treated according to the approved labeling of the Paradise System. The registry will include up to 500 patients at up to 100 clinical sites with 5 years of follow-up. Inclusion and exclusion criteria will support the proposed labelling: patients will have a documented history of hypertension, uncontrolled BP at screening, and evidence of an attempt to manage their BP with medications. Patients who are pregnant, allergic to contrast medium, and with other renal anatomy exclusions that would make them unsuitable for treatment will be excluded. The primary measure of BP reduction in the US-GPS Registry will be home BP, which was shown to correlate with ABP in the RADIANCE studies. Patients will be provided with a telemetric home BP system that can automatically transmit BP data allowing for remote patient data collection.

To ensure proper use of the Paradise System, ReCor has developed a robust training and education program for physicians. This program consists of didactic training classes and hands-on training for clinical staff as well as case support and proctoring for at least the first 5 procedures. Once completed, training accreditation, and documentation thereof, will be issued by the ReCor training staff.

10 BENEFIT-RISK CONCLUSIONS

Hypertension is one of the most important risk factors for cardiovascular diseases, is life-threatening, and is a significant cause of morbidity and mortality worldwide. Control of hypertension is a global unmet need, and the currently available options are limited to lifestyle modifications and medications which present challenges with non-adherence and side effects associated with drug therapies.

Catheter-based renal denervation is an adherence-independent alternative that offers a viable option to the hypertensive population, that is complementary to available medications and to lifestyle changes, and provides an additive effect which can provide a clinically meaningful reduction in BP.

The Paradise System can effectively and safely ablate the renal nerves without causing injury to the renal arterial wall, as demonstrated in preclinical animal models. The data from three independent, statistically powered, well-controlled, randomized, blinded, sham-controlled RADIANCE clinical studies indicate the Paradise System can safely, effectively, and reproducibly lower blood pressure in patients with a range of hypertension.

Catheter-based renal denervation offers a continuous effect that does not depend on patient compliance to medication. Adherence to life-long medication therapy is well known to be poor, contributing to current hypertension control rates which are only ~50%. A device-based therapy is less reliant on patient behaviors, potentially resulting in a more consistent and reliable means of reducing blood pressure. Further, the effect of renal denervation is ‘always on’ which may minimize blood pressure variability, and ultimately reduce the risk for cardiovascular disease.

Each of the RADIANCE Studies met their prespecified primary effectiveness endpoint with similar effectiveness and safety results across sites, subgroups and a range of hypertensive patient profiles (including those with mild-to-moderate uncontrolled hypertension and resistant hypertension). At 2 months, a consistent magnitude of effect (mean 8 mmHg decrease) in daytime ambulatory systolic blood pressure was observed following treatment with uRDN and a > 5mmHg benefit compared to sham.

In the Paradise System clinical development program, the benefit observed at the primary 2-month endpoint evaluation was maintained over time. The blood pressure reduction observed at 2 months was maintained or decreased further at 36 months (SOLO) and 24 months (TRIO), in the presence of fewer or stable medications compared to screening.

The risks associated with the procedure were anticipated, and consistent with other catheter-based procedures, and generally did not result in any lasting adverse effects. There were no SAEs with long-term sequelae, nor any evidence of renal injury nor cardiovascular events attributable to the device.

Importantly, uncontrolled HTN can lead to stroke, heart failure, myocardial infarction or other cardiovascular events (Ettehad et al 2016). Medications to manage hypertension have documented risks/side effects which increase when multiple antihypertensives are required to achieve control. Increased numbers of medications required for control also increase the risks of noncompliance and interaction with other medications (Tedla and Bautista 2016). The risks of uncontrolled hypertension should be considered when considering the benefit/risk profile of uRDN wherein BP lowering can be achieved with few procedure-related risks.

In summary, the Paradise System, as demonstrated in 3 clinical studies, has been shown to be safe and effective in lowering blood pressure across a range of hypertensive patients.

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12 APPENDICES

12.1 Safety Data from Cross-Over Patients (Sham to Renal Denervation)

Twelve months after receiving the sham procedure, patients randomized to the sham group were able to cross-over and receive renal denervation in each of the clinical studies. At the time of data cutoff, SOLO, TRIO, and RADIANCE II had 37, 21, and 19 patients cross-over to renal denervation, respectively. A summary of AEs among patients who crossed over is presented in Table 48.

Table 48: RADIANCE Studies: Summary of Adverse Events in Patients Who Crossed-over from Sham to Renal Denervation 12 Months after Initial Procedure

Patients with m, n (%):	SOLO (N=37)	TRIO (N=21)	RADIANCE II (N=19)
Any AE	75, 25 (67.6)	18, 14 (66.7)	26, 8 (42.1)
Serious AE	12, 7 (18.9)	3, 3 (14.3)	2, 2 (10.5)
Any ADE	26, 16 (43.2)	10, 6 (28.6)	19, 10 (52.6)
Serious ADE	0	0	2, 2 (10.5)
Unexpected ADE	0	0	0
Unexpected serious ADE	0	0	0

ADE=adverse device event; AE=adverse event; m=number of events; n=number of patients with an event; %=percentage of patients with an event.

Overall, rates of ADEs and SADEs were low among cross-over patients (Table 49).

Table 49: RADIANCE Studies: Adverse Device and Serious Adverse Device Events Affecting ≥ 2 Patients who Crossed-over from Sham to Renal Denervation 12 Months after Initial Procedure

	SOLO (N=37)		TRIO (N=21)		RADIANCE II (N=19)	
Adverse Event, m (%):	ADE	SADE	ADE	SADE	ADE	SADE
Back pain	5 (13.5)	0	1 (4.8)	0	4 (21.1)	0
Vascular access site pain	2 (5.4)	0	2 (9.5)	0	4 (21.1)	0
Bradycardia	5 (13.5)	0	1 (4.8)	0	-	-
Groin pain	-	-	-	-	2 (10.5)	0
Vasospasm	2 (5.4)	0	1 (4.8)	0	-	-
Vasospasm, drug therapy	2 (5.4)	0	-	-	-	-

ADE=adverse device event; m=number of events; SADE=serious adverse device event; %=percentage of patients with an event.