FDA Executive Summary

Prepared for the August 22, 2023 Meeting of the
Circulatory System Devices Panel Meeting
to be held virtually

Premarket Application (PMA) for Pxxxxxx

ReCor Medical's Paradise Ultrasound Renal Denervation System

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FDA Executive Summary

Pxxxxxx

Premarket Application for ReCor Medical's Paradise
Ultrasound Renal Denervation System

1 Introduction

This is an Executive Summary for Pxxxxxx. The submission was reviewed by the Office of Cardiovascular Devices within the Center for Devices and Radiological Health of the Food and Drug Administration.

ReCor Medical is requesting their premarket application be approved in order to market their Paradise Ultrasound Renal Denervation (uRDN) System to reduce blood pressure (BP) in patients with uncontrolled hypertension (HTN), who may be inadequately responsive to, or who are intolerant to anti-hypertensive medications.

The PMA approval request is based upon three clinical studies, the RADIANCE-HTN SOLO and RADIANCE-HTN TRIO and the pivotal study (RADIANCE-II) evaluating the Paradise uRDN System in patients with uncontrolled HTN. All three trials were randomized, double-blind, and sham-controlled. In SOLO and RADIANCE-II, subjects were taken off HTN medications 4 weeks prior to randomization. In TRIO, subjects were placed on a standardized HTN medication regimen (triple pill) 4 weeks prior to randomization and were asked to not change medications prior to 2-months post-randomization unless they met safety escape criteria. For all three trials, the primary safety endpoint was a composite of major adverse events, and the primary effectiveness endpoint was the difference between the treatment and sham groups in baseline-adjusted reduction in daytime ambulatory systolic BP (ASBP) at 2 months post-procedure.

FDA's Executive Summary presents an overview of HTN epidemiology and treatment, available clinical data on device-based therapies, considerations regarding the clinical trial design and endpoints, and a detailed review of the uRDN System clinical data.

2 Background

The study, diagnosis, and treatment of HTN gained attention as observational studies conducted over the last several decades demonstrated associations between high BP and the long-term risks of cardiovascular disease. HTN has a high prevalence in the US. The National Health and Nutrition Examination Survey (NHANES) estimated the prevalence of age-adjusted HTN between 2017–2018 to be 45.4% among adults and was higher among men (51.0%) than women (39.7%). [1] HTN prevalence was higher among African Americans (57.1%) than Caucasians (43.6%) or Hispanic (43.7%) adults.

While the adverse effects associated with HTN were initially postulated based on clinical responses after sympathectomy treatment the 1930s and 40s, the large scale observational NIH

Framingham Heart Study launched in 1948 provided additional evidence of the negative impacts of high BP. [2] The analyses from the Framingham study, as well as other large scale observational studies, demonstrated that HTN has a continuously graded association with an increased risk of fatal and nonfatal stroke, ischemic heart disease, heart failure, and noncardiac vascular disease. [3] A 2002 meta-analysis demonstrated that a 20 mmHg increase in systolic blood pressure and 10 mmHg increase in diastolic blood pressure are associated with doubling of the lifetime risk of death from stroke, heart disease, other vascular disease. [4] [5] A 2014 observational study analyzed the data from 1.25 million adult patients ≥30 years of age to determine associations of increased BP (measured at clinic visits) with 12 acute and chronic cardiovascular diseases and lifetime risks. [6] The authors found that higher systolic and diastolic BPs were associated with an increased risk of cardiovascular disease incidence and angina, myocardial infarction, heart failure, stroke, peripheral artery disease, and abdominal aortic aneurysm.

1.1 Defining Hypertension

HTN develops due to blood flow through the arteries at higher-than-normal pressures. Left untreated, HTN can lead to heart disease, stroke, kidney failure, vision loss, and other complications. Practice guidelines continue to be developed and revised in order to provide awareness, prevention recommendations, and treatment strategies to control HTN. The 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/ NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults classified the staging and treatment of hypertension (Table 1). [5] The 2017 guidelines recommend pharmacological antihypertensive treatment based on a combination of high blood pressure and absolute risk of cardiovascular disease (CVD), defined as coronary heart disease (CHD), heart failure (HF), and stroke. Pharmacological treatment is recommended for adults with SBP between 130-139 mmHg or DBP between 80-89 mmHg if they have a history of CVD, diabetes, and chronic kidney disease, or a 10-year predicted CVD risk ≥10% or age ≥65 years. Additionally, pharmacological treatment is recommended for adults with SBP ≥140 mmHg or DBP ≥90 mmHg, in the absence of CVD with an estimated 10-year atherosclerotic cardiovascular disease (ASCVD) risk <10%.

Table 1. 2017 Guideline Classification of Blood Pressure in Adults

Category	SBP		DBP
Normal	< 120 mmHg	AND	< 80 mmHg
Elevated	120-129 mmHg	AND	< 80 mmHg
Hypertension			
Stage 1	130-139 mmHg	OR	80-89 mmHg
Stage 2	≥ 140 mmHg	OR	≥ 90 mmHg

Uncontrolled HTN is diagnosed when blood pressure remains uncontrolled either when a patient is not using treatments to control BP or HTN persists despite treatment (treatment resistant HTN). Resistant HTN is defined as above-goal elevated BP despite the use of 3 anti-hypertensive medications with complementary mechanisms of action (including a diuretic). A hypertensive emergency is defined as a SBP >180 mmHg or DBP >120 mmHg associated with pulmonary edema, cardiac ischemia, neurologic deficits, and or renal failure.

The NHANES surveys conducted between 1999 and 2018 indicate that although the prevalence of BP control (<140/90 mmHg) increased from 31.8% to 43.7% of US adults with HTN, a large proportion of HTN patients still do not achieve target BP control. [7] Patient nonadherence to antihypertensive drugs is a major factor to poorly controlled BP and can result from lack of drug initiation (~12%) or poor compliance or discontinuation (30-80%). [8] Device treatment of HTN may potentially help address BP medication compliance challenges.

1.2 Etiology

Hypertension has a complex and multifactorial etiology. In most patients, HTN is termed primary (essential) HTN and may be due to a combination of genetic, environmental, and social determinants. HTN is a complex polygenic disorder, as a variety of genes or gene combinations influence its occurrence. Environmental risk factors include lifestyle behaviors that promote blood pressure elevation, such as unhealthy diets, overweight/obesity, poor physical conditioning, and excessive alcohol consumption. Social determinants include socioeconomic factors that may affect cardiovascular health, including the circumstances in which individuals live and the systems used to diagnose, treat, and prevent illness. [9] In the US, there is a strong association between social determinants of health and HTN, especially among minority populations, in economically deprived neighborhoods, and in certain geographic areas (such as the Southeastern US). [10] [11] Genetics, renal physiology, and socioeconomic factors suggest a difference in HTN presentation and treatment in different races. [12] [13] These factors are important considerations in the study and diagnosis of the hypertensive diseases and in developing patient-centered treatment plans.

1.3 Current Treatments

The most common BP medications include thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and calcium channel blockers (CCBs). Although numerous medication classes exist, these medications are considered primary agents and preferentially used as they are associated with a reduced incidence of HTN-associated complications. Secondary line medications, such as betablockers and other vasodilator classes, may also be used; however, it remains unclear whether these agents reduce cardiovascular events, or they may have safety or tolerability concerns that reduce their primary use. Clinical determinations of treatment regimens are typically based on the etiology of HTN, patient characteristics (e.g., age, race), comorbidities (e.g., diabetes, heart failure, renal disease), and previous medical history.

For initial HTN treatment, strategies include medications and determining whether combination therapy with multiple agents should be utilized. Patient-specific factors include age, genetics, concurrent medications, drug interactions, out-of-pocket costs, and comorbidities. Factors that may affect HTN treatment adherence include medication side effects and a dislike of taking pills. Nonadherence is defined in the 2017 HTN guidelines as not following recommended medical or health advice, including failure to persist with medications.

1.4 Physiology of Renal Denervation

Based on the complex physiology associated with HTN and BP control, HTN treatment devices have focused on a variety of targets—reducing or attenuating sympathetic activity (e.g., renal

nerves, carotid body), stimulating parasympathetic activity, or modifying hemodynamics. Each paradigm or device design has its own potential benefits and risks.

Renal denervation is a percutaneous interventional approach, and it applies lessons learned from historical experience with surgical sympathectomy. The renal denervation procedure is designed to reduce renal sympathetic activity by ablating the peri-arterial adventitial afferent and efferent nerves in the renal arterial adventitia (see Figure 1) using radiofrequency or ultrasonic energy or chemical neurotoxins (e.g., ethanol, guanethidine). [14] [15] The subject device of this PMA utilizes intraarterial catheters to deliver ultrasound energy through the renal arterial wall to ablate the adjacent sympathetic nerves. By reducing sympathetic nerve signaling, renal denervation technologies aim to lower blood pressure by reducing renin secretion, stimulating renal vasodilatation, and increasing sodium excretion. However, considering the location of the renal nerves, these technologies also pose the potential risk of damage to the kidney, tissues surrounding the renal artery, or the renal artery itself.

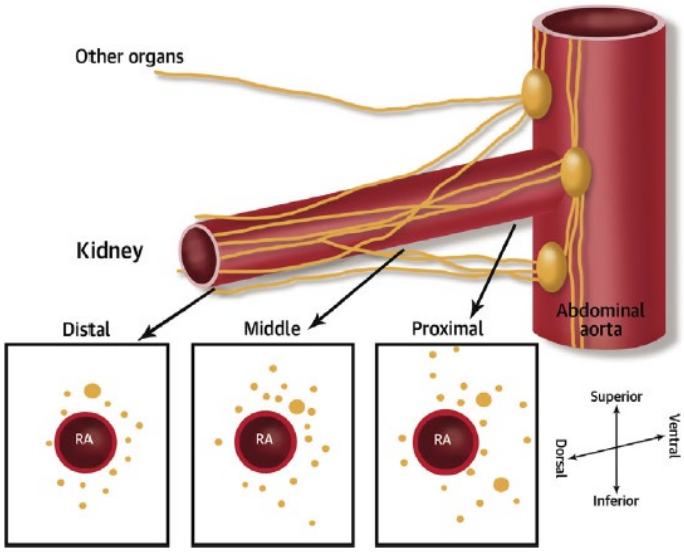


Figure 1. Graphical Illustration of Renal Artery and Circumferential Peri-Arterial Nerve Location

The durability of effective BP reduction associated with renal denervation ablation remains unclear. Results from animal and human studies are mixed. Early studies of renal sympathectomies did not always result in durable blood pressure reduction. The lack of a durable BP lowering was discussed in the executive summary for the December 2018 FDA Advisory Panel on renal denervation (Appendix 1). In Mauriello et al. studied nerve regeneration in three renal transplant patients whose kidneys were explanted compared to their native kidneys. [16] There was evidence of periadventitial nerve regeneration as early as 5 months post-transplantation with complete regeneration observed at 2 years. Nerve density reached values observed surrounding in native renal arteries and was associated with hypertension-related arteriolar lesions in transplanted kidneys. Conversely, Hansen et al. found that in 25 renal transplant patients and 10 normal subjects, transplanted kidneys showed significantly less evidence of sympathetic activation than controls, suggesting limited reinnervation. [17] A study in

swine showed that no evidence of anatomic or functional reinnervation by 180 days. [18] However, a study evaluating RDN in sheep demonstrated complete functional and anatomic reinnervation by 11 months, [19] whereas another study in sheep showed only partial but non-functioning regrowth of nerves through 30 months with sustained reductions in mean arterial pressure and heart rate. [20] The frequency, timing, and extent of potential regeneration of renal sympathetic nerves following renal denervation remain unclear.

1.5 Lessons Learned for Hypertension Device Trial Design

Following the completion of initial renal denervation studies, multi-stakeholder groups met to discuss and develop consensus recommendation for clinical trial designs to evaluate the safety and effectiveness of renal denervation for HTN.

In 2014, the American Society of Hypertension (ASH) convened a multi-stakeholder forum of representatives from academia, cardiovascular societies, industry, and regulatory agencies to identify optimal clinical trial designs to evaluate the safety and effectiveness of renal denervation therapy. [21] Discussions included initial proof-of-concept trials in HTN patients off of BP medications, consisting of small, prospective, double–blind, randomized, sham–controlled studies of the device incorporating a run-in period. Initial trials would be followed by pivotal trials in severe and/or drug-resistant hypertensive subjects.

The trial design and regulatory expectations were also discussed during the Circulatory System Device Panel Meeting on December 5, 2018 on Clinical Evaluation of Anti-Hypertensive Devices. The executive summary and the 24-hour summary are attached as Appendices 1 and 2.

In 2020, the Hypertension Academic Research Consortium (HARC) was initiated to create consensus among experts involved in developing device-based therapies for HTN (Appendix 3). [22] Like the ASH forum, the consortium defined recommendations and considerations for clinical trial design and conduct.

The recommendations from the December 5, 2018, Advisory Committee and these forums generally align and are discussed below.

Study population. The trial populations should include subjects with primary HTN and stable office SBP between a lower limit of 150 or 160 mmHg and an upper limit of 180 mmHg. Due to confounders noted in previous studies related to biases and potential placebo effects, it was deemed important to study devices in clinical trial subjects in the presence and absence of BP medication. Studies conducted in the absence of BP medications would evaluate patients who could tolerate withdrawal of medication to isolate the effects of the device by reducing confounders related to BP medication use (e.g., regimen variability, patient medication adherence/compliance). Studies conducted in the presence of BP medications would evaluate how the device may function in a real-world setting with patients on BP medication. Data from both study designs would help guide regulatory and clinical decision-making.

Effectiveness Endpoints. The guidelines and FDA Expert Panel recommended using ambulatory BP measurement (ABPM) for the primary effectiveness endpoint due to its reliability and being less prone to temporal variability. The 2017 Guidelines note that ABPM provides a superior

method to predict long-term cardiovascular outcomes compared to office BP measurement (OBPM). Although more variable, OBPM should also be collected as a secondary effectiveness endpoint, with multiple measures taken to reduce potential variability and white coat HTN.

The FDA Expert Panel and HARC recommend that average systolic ABPM reduction in RDN patients should be at least 5-7 mm Hg more than the average systolic ABPM reduction in sham patients. Verdecchia et al, (2010) conducted a metanalysis of hypertension trials to study the effect of BP reduction on cardiovascular endpoints. [23] It showed that a beneficial effect on reducing cardiovascular events was associated with a SBP reduction of at least 4.6 mmHg.

Medication Burden. Restarting BP medications, adding new BP medications, or modifying BP medication doses following the assessment of the BP reduction primary effectiveness endpoint may lead to potential challenges in interpreting trial data because of confounding due to the medication changes, Hawthorne effect, and medication compliance. An analysis of medication burden was recommended, to include accounting for the number, type, and dose of BP medications. In addition, medication adherence should be measured at multiple timepoints.

3 Device Description

The Paradise Ultrasound Renal Denervation System (Paradise uRDN System) includes the Paradise Catheter with ultrasound transducer, Paradise Generator, Paradise Cartridge, and the Paradise Connection Cable. The Paradise uRDN System is a catheter-based system that delivers ultrasound energy circumferentially to thermally ablate and disrupt renal sympathetic nerve activity with the goal of reducing systemic arterial blood pressure.

The Paradise Catheter is delivered percutaneously into the renal artery via the femoral artery under fluoroscopic guidance using commercially available compatible introducer sheaths and guiding catheters over a guidewire. The Paradise uRDN System requires the use of commercially available sterile water circulated within the balloon as a coolant during thermal ablation to prevent arterial wall injury. Figure 2 shows the components of the Paradise uRDN System.

ReCor Medical designed the Paradise uRDN System to target circumferential peri-arterial tissue ablation in the range of 1 mm to 6 mm from the arterial lumen. To achieve target tissue ablation, the transducer is set at an operating frequency range of 8.7 - 9.3 MHz; the transducer length, thickness, and resonant frequencies are matched to the operating frequency range to produce consistent acoustic output.

The Paradise Catheter has a distal balloon pressurized with sterile water to an average of 1.8 atmospheres. The pressurized balloon centers and stabilizes ultrasound transducer positioning within the artery (Figure 3) and provides a circulating conduit to cool the renal artery wall.

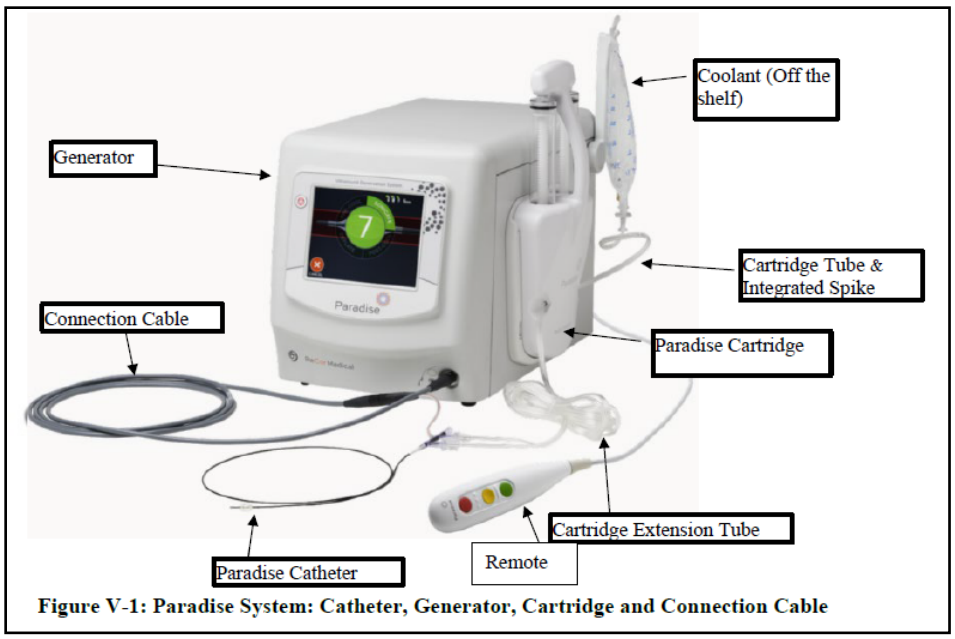


Figure 2. Paradise uRDN System

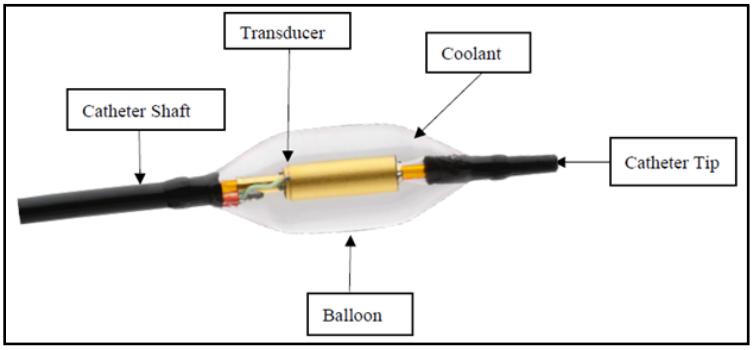


Figure 3. Ultrasound Transducer with Balloon at Distal End of Paradise Catheter

4 Proposed Indications for Use

The Sponsor's proposed indications for use are as follows:

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

FDA Comment: The Panel will be asked to discuss whether a reasonable assurance of safety and effectiveness has been established for the proposed indications for use based on the totality of the data. Additionally, the Panel will be asked to discuss and make recommendations on whether the evidence supports the intended patient population and HTN medication status.

5 Regulatory History

The Investigational Device Exemption (IDE) application for the Paradise uRDN System was approved in 2015 for the RADIANCE-HTN SOLO (SOLO) and RADIANCE-HTN TRIO (TRIO) studies. Following initial study results, the RADIANCE-II pivotal study was approved in 2018. All three clinical studies were prospective, global, multi-center, randomized, double-blind, sham-controlled studies, and each trial was powered to demonstrate a reduction in daytime ASBP at 2-months post-procedure and to demonstrate device and procedural safety. These three trials contain the key clinical data to support the PMA. The device received CE marking in 2012.

5.1 Breakthrough Device Designation

FDA's Breakthrough Devices Program is a voluntary program for selected devices that have the potential to provide more effective treatments or diagnoses of life-threatening or irreversibly debilitating diseases or conditions. This program is intended to provide patients and health care providers with timely access to important new medical devices by accelerating their development, assessment, and review. The statutory standard for PMA approval of a breakthrough device is the same as a non-breakthrough device, that is, a reasonable assurance of safety and effectiveness.

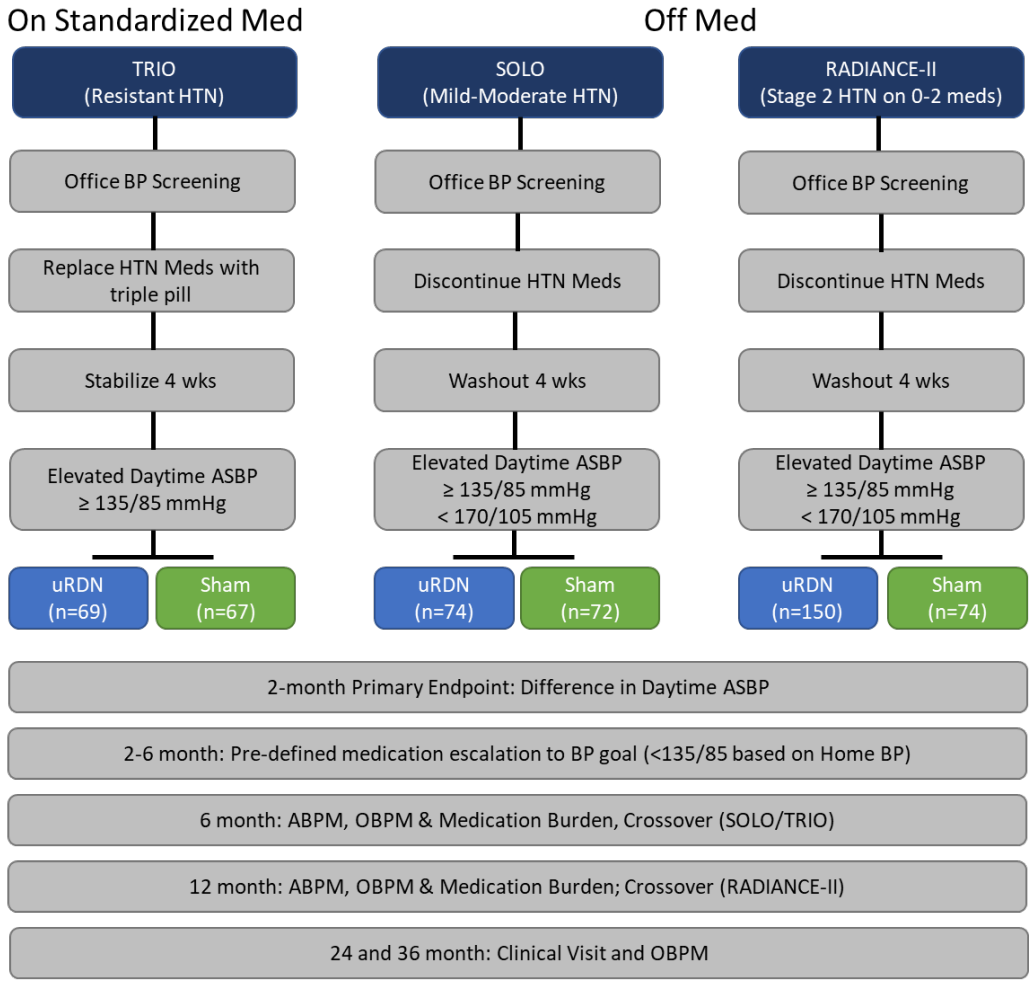
The subject device for this PMA received breakthrough device designation in December 2020. FDA determined that the Paradise uRDN System met the criteria for inclusion in the program because it was a novel technology with the potential to provide more effective treatment in subjects with resistant or uncontrolled hypertension.

FDA Comment: Although the Breakthrough Device Program offers increased communication and collaboration with FDA, it does not modify or reduce the statutory requirement for PMA approval. The totality of the data still needs to demonstrate a reasonable assurance of safety and effectiveness for its intended population.

6 Clinical Studies Overview

ReCor Medical studied the Paradise catheter in two sham-controlled studies (SOLO and TRIO) and one sham-controlled pivotal trial (RADIANCE-II). These studies have some differences in patient population and medication regimen, as shown in Figure 4.

- Enrolled patient populations:
  - SOLO (1:1 randomization): Subjects with mild to moderate hypertension, including those uncontrolled on 0, 1, or 2 antihypertensive medications or controlled on 1 or 2 antihypertensive medications.
  - TRIO (1:1 randomization): Subjects with resistant hypertension, defined as those on a minimum of 3 antihypertensive medications, including a diuretic.
  - RADIANCE-II (2:1 randomization): Subjects with Stage 2 hypertension uncontrolled on 0, 1, or 2 antihypertensive medications.



HTN: Hypertension; uRDN: Renal Denervation; BP: Blood Pressure; ASBP: ambulatory systolic BP; ABPM/OBPM: ambulatory/office BP measurement

Figure 4. Overview of the RADIANCE Studies

- Antihypertensive medication use:
  - Off-medication trials (SOLO and RADIANCE-II): Patients taken off medications 4 weeks prior to randomization through 2-month post-procedure unless they met safety escape criteria:
    - Low BP Action: OSBP <110 mmHg with associated signs of hypotension or an increase in plasma creatinine ≥30%.
    - High BP Action: 7 days home BP ≥170 (systolic) or ≥105 mmHg (diastolic) and confirmed by OBP ≥180 or ≥120 mmHg (if required by institutional practice).
  - On-standardized-medication trial (TRIO): Antihypertensive medications replaced with standardized antihypertensive (triple pill) medication 4 weeks prior to randomization with no medication changes prior to 2-months post-procedure unless patients met safety escape criteria.

- Blood pressure measurement: All studies
  - Twenty-four hour ambulatory blood pressure measurement (ABPM) at 2, 6, and 12 months
  - Home blood pressure measurements (HBPM) monthly through 6 months and at 12 months
  - Office blood pressure measurements (OBPM) at 2, 6, 12, 24, and 36 months

- Antihypertension medication escalation (as needed): All studies
  - Guideline-based antihypertensive medication escalation protocol between 2 and 6 months post-randomization, if needed, to achieve blood pressure control.
  - Beyond 6-months, all subjects were managed medically, per physician discretion.

6.1 Key Inclusion and Exclusion Criteria

Inclusion criteria for SOLO, TRIO, and RADIANCE-II studies

- Age ≥18 and ≤75 years
- History of hypertension
- Suitable renal anatomy for the renal denervation procedure based on renal CTA or MRA performed within one year of consent

Trial specific inclusion criteria: See Table 2.

Table 2. Trial-specific Inclusion Criteria

	SOLO	TRIO	RADIANCE-II
OBP	• ≥140/90 & <180/110 mmHg on 0, 1 or 2 meds; *or* • ≤140/90 on 1 or 2 meds	≥140/90 on ≥3 meds, including a diuretic	• ≥140/90 & <180/120 mmHg on 0, 1, or 2 meds; *and* • Previous or currently prescribed antihypertensive therapy
Daytime ABP	≥135/85 & <170/105 mmHg after washout	≥135/85 mmHg after stabilization	≥135/85 & <170/105 mmHg after washout
Antihypertensive Medication	0, 1, or 2	At least 3	0, 1, or 2

OBP/ABP: Office/Ambulatory blood pressure

Exclusion criteria for RADIANCE SOLO, TRIO, and RADIANCE-II studies

- A single functioning kidney
- Abnormal kidney tumors
- Renal artery with aneurysm
- Pre-existing renal stent or history of renal artery angioplasty
- Pre-existing aortic stent or history of aortic aneurysm
- Prior renal denervation procedure
- Fibromuscular disease of the renal arteries
- Presence of renal artery stenosis (RAS) of any origin ≥ 30%
- Evidence of active infection within 7 days of procedure

- Iliac/femoral artery stenosis precluding insertion of the Paradise Catheter
- Type I diabetes mellitus or uncontrolled Type II diabetes (defined as a plasma Hb1Ac ≥ 9.0%)
- History of chronic active inflammatory bowel disorders
- eGFR of <40 mL/min/1.73 m2 (by Modification of Diet in Renal Disease formula)
- Brachial circumference ≥42 cm
- Episode(s) of stable or unstable angina[1]
- Persistent or permanent atrial tachyarrhythmia
- Implantable medical device (e.g., ICD or CRT-D, neuromodulator/spinal stimulator, baroreflex stimulator)
- Chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea
- History of severe cardiovascular event (myocardial infarction, CABG, acute heart failure requiring hospitalization (NYHA III-IV) (within 3 months prior to consent in TRIO)
- History of cerebrovascular event (e.g., stroke, transient ischemic event, cerebrovascular accident) (within 3 months prior to consent in TRIO)
- Repeat (>1) hospitalization for hypertensive crisis within the prior 12 months (within 3 months prior to consent in TRIO)
- Primary pulmonary hypertension
- Contraindication or allergy to contrast medium not amenable to treatment
- Limited life expectancy of <1 year
- Pregnant, nursing or planning to become pregnant; negative pregnancy test required for all women of childbearing potential. Effective contraception required for women of childbearing potential

Trial-specific exclusion criteria

SOLO

- Renal artery anatomy on either side ineligible for treatment including:
  - Main renal artery diameter <4 mm and >8 mm
  - Main renal artery length <25 mm
  - Accessory artery diameter between 2mm and 4 mm or ≥8 mm
- Prescribed antihypertensive medication (e.g., beta blockers) for other chronic conditions (e.g., ischemic heart disease) such that discontinuation might a pose serious risk to health

TRIO

- Renal artery anatomy on either side ineligible for treatment including:
  - Main renal artery diameter <3.5 mm or >8 mm
  - Main renal treatable artery length <20 mm (may include proximal branching)
  - Accessory artery diameter between 2 mm and 3.5 mm or ≥8 mm
- Prescribed to any standard antihypertensive medication (other than beta blockers) for other chronic conditions (e.g., ischemic heart disease) such that discontinuation might pose a serious risk to health

- Secondary hypertension not including sleep apnea (documented workup within 12 months prior to consent)
- Intolerance or contraindication for any of the antihypertensive drugs prescribed as a requirement of the study

RADIANCE-II

- Renal artery anatomy on either side ineligible for treatment including:
  - Main renal artery diameter <3 mm or >8mm
  - Main renal treatable artery length <20 mm (may include proximal branching)
  - Accessory artery diameter between 2 mm and 3 mm or ≥8mm
- Uncorrected causes of secondary hypertension other than sleep apnea

6.2 Follow-up Schedule

The follow-up schedule for selected endpoints from the three studies is shown in Table 3.

Table 3. Selected Follow-up

	Screening	Baseline	Procedure	1M	2M	6M	12M	24-60M
OBPM	x	x		x	x	x	x	x
HBPM		x		x	x	x	x	
ABPM		x			x	x	x	
Renal DUS[1]		x[2]			x	x		x[5]
CTA/MRA			x		x[3]	x[3,4]	x[5]	
Urine chemistry and drug metabolite		x			x	x		
Blood chemistry		x			x	x	x	
Quality of Life	x	x			x	x	x	
Blinding assessment			x (discharge)		x	x		

OBPM/HBPM/ABPM: Office/home/ambulatory blood pressure measurement; CTA: computed tomography angiography; MRA: magnetic resonance angiography

[1] SOLO/TRIO only

[2] Recommended. A recent (within 6 months of consent) good quality renal duplex ultrasound is acceptable

[3] if required in the event of clinical suspicion of renal artery stenosis (RAS)

[4] Required for all RII subjects (Sham and uRDN)

[5] procedure was conducted on uRDN treated subjects

6.3 Statistical Analysis Populations

The analysis population for the primary effectiveness and primary safety endpoints was the intention-to-treat (ITT) cohort. Additional effectiveness analyses were conducted on the per protocol and complete ABPM populations.

- **Intention-to Treat (ITT)** cohort: subjects according to their randomization assignment.
- **Per-Protocol (PP)** cohort: subjects treated per their assigned treatment group without deviation from major enrollment criteria, for example:
  - Successful delivery of treatment (minimum of 2 emissions bilaterally)

  - Baseline daytime ABP <135/85 mmHg or failure to obtain a baseline ABP measurement
  - Renal artery anatomical exclusion criteria
  - Failure to obtain 2-month follow-up ABP measurement
  - Subjects restarting antihypertensive medication for any reason prior to the 2-month primary endpoint.

- **Complete ABPM (CA)** cohort: subjects treated per their assigned treatment group that have ABP values at both baseline and follow-up.
- **Crossover (CO)** cohort: subjects who received uRDN treatment after being randomized to the sham control group.
  - Crossover allowed:
    - After 6-months follow-up in SOLO and TRIO
    - After 12-months follow-up in RADIANCE-II

6.4 Study Endpoints

6.4.1 Primary Safety Endpoint

The pre-specified primary safety analysis was an analysis of the uRDN-treated subjects from RADIANCE-II, defined as a patient-level composite of the incidence of the following:

a. 30-day
   - All-cause mortality
   - New onset (acute) end-stage renal disease (eGFR<15 mL/min/m^2 or need for renal replacement therapy)
   - Significant embolic event resulting in end-organ damage (e.g., kidney or bowel infarct, lower extremity ulceration or gangrene, or doubling of serum creatinine)
   - Renal artery perforation requiring invasive intervention
   - Renal artery dissection requiring an invasive intervention
   - Major vascular complications (e.g., clinically significant groin hematoma, arteriovenous fistula, pseudoaneurysm) requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion (>2 units of packed red blood cells within any 24-hr period during the first 7 days post-randomization)
   - Hospitalization for hypertensive or hypotensive crisis
   - Hospitalization for major cardiovascular- or hemodynamic-related events (e.g., HF; MI; stroke)
   - New stroke
   - New MI

And

b. 6 Month: New onset renal artery stenosis (RAS), defined as a >70% stenosis, confirmed by CTA/MRA

The primary safety endpoint composite event rate was compared to a pre-specified performance goal of 9.8%, derived from a literature review of adverse events in studies observed in renal artery angioplasty and stent studies.

Additional analyses

- Pre-specified pooled analysis of all uRDN-treated subjects from SOLO, TRIO, and RADIANCE-II, including subjects that were treated at the index procedure or crossed over from the control group. The safety endpoint definitions for the pooled analysis were consistent with the RADIANCE-II definition of the primary safety MAE composite endpoint.
- An analysis of the primary safety endpoint was also performed for the SOLO and TRIO studies individually.

Primary safety events were adjudicated by the RADIANCE-II Clinical Events Committee (CEC). All safety events were reviewed by an independent data safety monitoring board (DSMB). CTA/MRA were assessed by an imaging core lab or independent radiologists.

6.4.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint was reduction in average daytime ambulatory systolic blood pressure (ASBP) from baseline to 2-months post-procedure.

- Daytime: ABP between 7:00 AM – 10:00 PM
- Nighttime: ABP between 10:30 PM – 6:30 AM
- For patients that met the protocol defined "High BP Action" changes, the last BP measurement prior to the medication change (i.e., the baseline value) was used in the analyses.

Primary effectiveness endpoint analysis

- The mean difference between randomized groups in daytime ASBP reduction at 2 months post-procedure was compared via a linear regression (ANCOVA) model adjusted for subjects' baseline daytime ASBP.
- Study success definition: A statistically significant difference in the average daytime ASBP reduction from baseline to 2-months between the uRDN treatment group and the sham control group.

Missing data

- SOLO and TRIO: For patients missing the reduction in BP value, a value of zero was used for the reduction in BP in the ITT analysis.
- RADIANCE-II: For patients missing 2-month follow-up BP values, multiple imputation was used for BP in the ITT analysis.

6.4.3 Key Secondary and Observational Endpoints

Secondary Effectiveness Endpoints

SOLO and TRIO

- Reduction in average 24-hour and night-time ASBP at 2 months post-procedure from baseline
- Reduction in average 24-hour, daytime, and night-time ambulatory diastolic blood pressure (ADBP) at 2 months post-procedure from baseline

RADIANCE-II

- Reduction in average 24-hour ASBP at 2 months post-procedure from baseline
- Reduction in average 24-hour and daytime ADPB at 2 months post-procedure from baseline
- Reduction in average home SBP and DBP at 2 months post-procedure from baseline
- Reduction in average office SBP and DBP at 2 months post-procedure from baseline

Note: Home BP is the average of BP collected at home twice daily 7 days prior to clinical visit.

Observational Endpoints

SOLO and TRIO

- Reduction in average home SBP and DBP at 2 months post-procedure from baseline
- Reduction in average office SBP and DBP at 2 months post-procedure from baseline

RADIANCE-II

- Reduction in average night-time ASBP and ADBP at 2 months post-procedure from baseline

SOLO, TRIO, and RADIANCE-II

- Reduction in average office SBP/DBP at 6, 12, 24, 36, 48, and 60 months post-procedure
- Reduction in average daytime/24-hr/night-time ASBP at 6 and 12 months post-procedure
- Reduction in average daytime/24-hr/night-time ADBP at 6 and 12 months post-procedure
- Reduction in average home SBP/DBP at 1, 3, 4, 5, 6, and 12 months post-procedure
- Incidence of ASBP (daytime/24-hr/night-time) reductions of ≥5 mmHg, ≥10 mmHg, and ≥15 mmHg at 2, 6, and 12 months post-procedure
- Proportion of subjects with BP control in the absence of changes in hypertensive medication at 2, 6, and 12-months post-procedure
  - BP control defined as daytime ABP <135/85 mmHg, night-time ABP <120/70 mmHg, 24-hr ABP <130/80 mmHg, or office BP <140/90 mmHg
- Proportion of subjects with BP control including any changes in hypertensive medication in each group at 2, 6, and 12-months post-procedure
- Change in office and ambulatory pulse pressure at 2, 6 and 12 months post-procedure
- Change in office and ambulatory heart rate at 2, 6 and 12 months post-procedure
- Antihypertensive treatment score (defined as the number, doses, and classes of antihypertensive drugs) at 6 months post-procedure
- Proportion of subjects requiring initiation of additional antihypertensive drug therapy between 2 and 6 months post-procedure
- Proportion of subjects without any antihypertensive treatment at 6 and 12 months post-procedure

Secondary effectiveness endpoints were analyzed using the same methodology as the primary effectiveness endpoint analysis. Observational endpoints were analyzed using observed data, except for nighttime ABPM measurements in RADIANCE-II, which followed the same methodology as the primary effectiveness endpoint analysis.

FDA Comment: Ambulatory BP measurement (ABPM) has been shown to have greater prognostic value compared to office BP measurement (OBPM), which may be due to the large number of measurements made for ABP that are free from potential biases (e.g., white coat effect). The Panel will be asked to discuss the clinical value of ABP and OBP in assessing BP changes and in evaluating device effectiveness.

6.4.4 Subgroup Analyses

The primary effectiveness endpoint was analyzed for the following pre-specified subgroups:

- Age
- Race
- Sex
- Geography: US vs EU/UK
- Baseline daytime ASBP (<median vs. ≥median)
- Baseline office SBP (<median vs. ≥median)
- Abdominal obesity
  - Male waist circumference (>102 cm vs. ≤102 cm)
  - Female waist circumference (>88 cm vs. ≤88 cm)
- Total number of bilateral ultrasound emissions (4, 5, 6, >6)

6.4.5 Additional Analyses

Assessment of study blinding

Subjects were unblinded to their randomization assignment at 6 months in SOLO and TRIO and at 12 months in RADIANCE-II.

Assessments performed at discharge, 2-months, and 6-months. Subjects were asked whether they believed they were assigned to the uRDN treatment group, the sham control group, or if they did not know their assignment.

- Bang Blinding Index assigns a value to each treatment arm ranging from -1 to +1. A value of 0 indicates total or successful blinding, values >0 indicate a positive correlation (a tendency of subjects to correctly identify their randomization assignment), and values <0 indicate a negative correlation (a tendency of subjects to incorrectly identify their randomization assignment).
- James Blinding Index assigns a single value for both arms ranging from 0 to 1. A 0-value indicating a total lack of blinding (subjects correctly identify the treatment assignment), 1 indicating successful blinding, and 0.5 indicating random guessing (i.e., 50% correct and 50% incorrect guesses).

7 RADIANCE Studies' Results

SOLO, TRIO, and RADIANCE-II were prospective, multi-center, randomized, double-blind, sham-controlled trials that were independently powered to assess daytime ASBP at 2-months and device and procedure safety in subjects with uncontrolled HTN. Across the three studies, a total

of 506 subjects were randomized to uRDN treatment or to sham control (sham procedure was a renal angiogram).

Patients were either taken off their medications (SOLO and RADIANCE-II) or had their BP medications replaced with a single, fixed dose, triple combination pill (TRIO) 4 weeks prior to randomization. No BP medication changes were to be made prior to 2-months post-procedure unless patients met safety escape criteria. Subjects were unblinded to their randomization assignment at 6 months in SOLO and TRIO and at 12 months in RADIANCE-II. Sham control subjects were allowed to cross over to receive uRDN after the 6-month follow-up assessment in SOLO/TRIO after the primary effectiveness endpoint was assessed, and at 12-months in RADIANCE-II. Subjects will be followed through 3 years for SOLO and 5 years for TRIO and RADIANCE-II.

7.1 Subject Accountability

- SOLO enrolled 146 subjects (74 uRDN and 72 Sham) between March 28, 2016, and December 28, 2017, and 37 Sham subjects crossed over to uRDN (Figure 5).
- TRIO enrolled 136 subjects (69 uRDN and 67 Sham) between March 11, 2016, and March 13, 2020, and 21 Sham subjects crossed over to uRDN (Figure 6).
- RADIANCE-II enrolled 224 subjects (150 uRDN and 74 Sham) between January 14, 2019, and March 25, 2022, and 19 Sham subjects crossed over to uRDN (Figure 6).

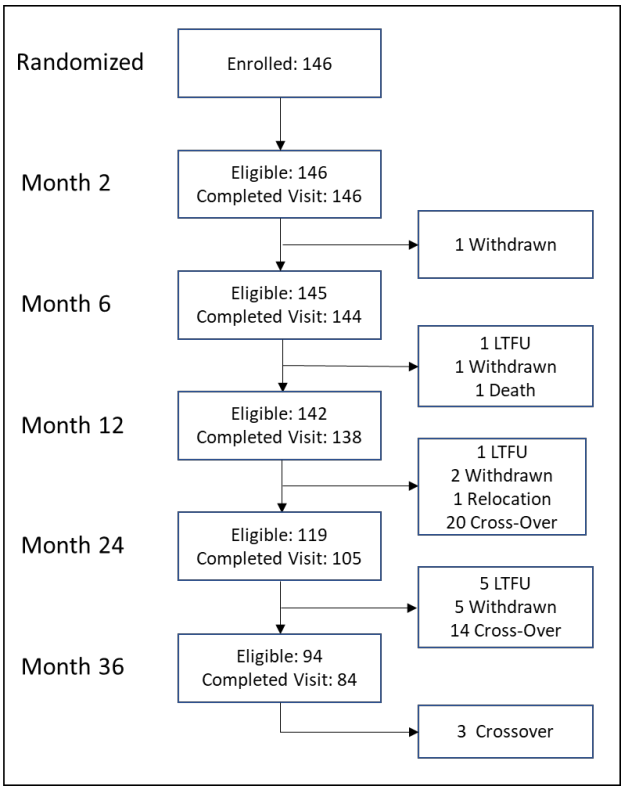


Figure 5. Accountability for SOLO

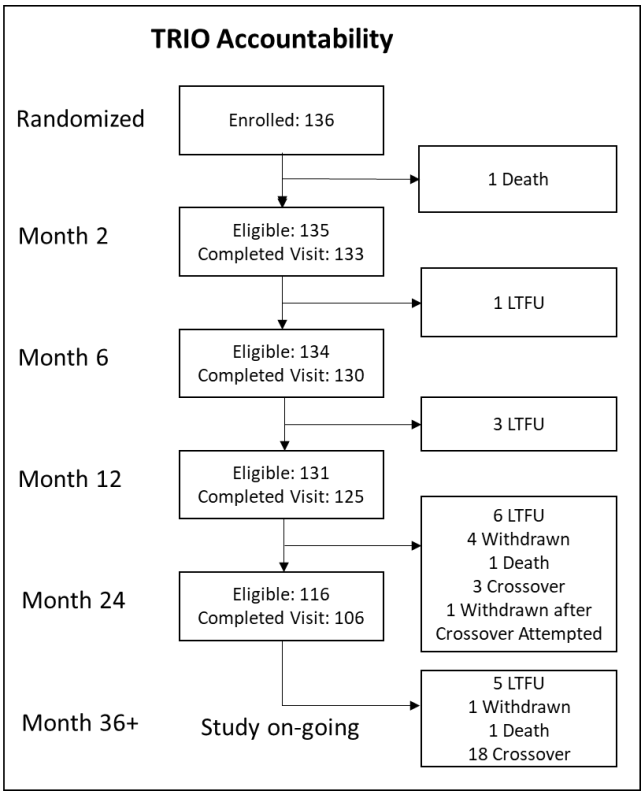
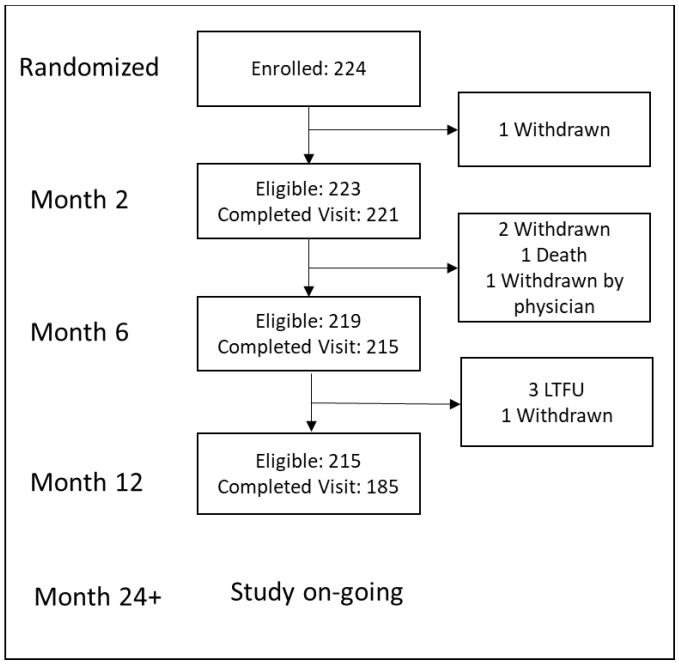


Figure 6. Accountability for TRIO



LTFU: Lost to follow-up

Figure 7. Accountability for RADIANCE-II

7.2 Baseline Characteristics

Baseline characteristics for the three studies are shown in Table 4. There were numerical differences between groups for some characteristics, which may be expected given small sample sizes. See Section 7.5.3 Subgroup Analyses.

Table 4. Baseline Demographics, uRDN vs Sham (ITT)

	SOLO		TRIO		RADIANCE-II	
Measure	**uRDN (n=74)**	**Sham (n=72)**	**uRDN (n=69)**	**Sham (n=67)**	**uRDN (n=150)**	**Sham (n=74)**
Sex						
Male	46 (62.2%)	39 (54.2%)	56 (81.2%)	53 (79.1%)	103 (68.7%)	57 (77.0%)
Female	28 (37.8%)	33 (45.8%)	13 (18.8%)	14 (20.9%)	47 (31.3%)	17 (23.0%)
Age	54.4 ± 10.2	53.8 ± 10.0	52.3 ± 7.5	52.8 ± 9.1	55.1 ± 9.9	54.9 ± 7.9
Geography						
US	35 (47.3%)	34 (47.2%)	28 (40.6%)	25 (37.3%)	100 (66.7%)	46 (62.2%)
OUS	39 (52.7%)	38 (52.8%)	41 (59.4%)	42 (62.7%)	50 (33.3%)	28 (37.8%)
Race						
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.00%)	1 (1.52%)	0 (0.0%)	0 (0.0%)
Asian	1 (1.3%)	0 (0.0%)	1 (1.5%)	1 (1.5%)	0 (0.0%)	1 (1.3%)

	SOLO		TRIO		RADIANCE-II	
Measure	**uRDN (n=74)**	**Sham (n=72)**	**uRDN (n=69)**	**Sham (n=67)**	**uRDN (n=150)**	**Sham (n=74)**
Black	12 (16.2%)	13 (18.0%)	14 (20.6%)	13 (19.7%)	21 (14.0%)	15 (20.2%)
Caucasian	60 (81.0%)	52 (72.2%)	45 (66.2%)	51 (77.3%)	114 (76.0%)	56 (75.6%)
Hispanic or Latino	1 (1.3%)	4 (5.5%)	5 (7.4%)	0 (0.0%)	15 (10.0%)	2 (2.7%)
Native Hawaiian or other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other/Mixed Race	0 (0.0%)	0 (0.0%)	3 (4.41%)	0 (0.0%)	15 (10.00%)	2 (2.7%)
BMI	29.9 ± 5.9	29.0 ± 5.0	32.8 ± 5.7	32.6 ± 5.4	30.1 ± 5.2	30.6 ± 5.2
Abdominal circumference (cm)	101.5 ± 14.2	98.5 ± 15.1	109.4 ± 15.5	109.2 ± 12.9	102.4 ± 12.3	104.3 ± 13.1
Office Systolic blood pressure (mmHg)* - Screening	142.6 ± 14.7	144.6 ± 15.9	161.9 ± 15.5	163.6 ± 16.8	155.8 ± 11.1	154.3 ± 10.6
Office Diastolic blood pressure (mmHg)* - Screening	92.3 ± 10.1	93.6 ± 8.3	105.1 ± 11.6	103.3 ± 12.7	101.3 ± 6.7	99.1 ± 5.6
History of Hypertension	74 (100%)	72 (100%)	69 (100%)	67 (100%)	150 (100%)	74 (100%)
Hospitalization for hypertensive crisis	2 (2.7%)	2 (2.7%)	15 (21.7%)	11 (16.4%)	9 (6%)	3 (4%)
Peripheral vascular disease	2 (2.7%)	0 (0.0%)	1 (1.4 %)	3 (4.5%)	0 (0.0%)	0 (0.0%)
Primary pulmonary hypertension	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cerebrovascular event(s)	0 (0.0%)	0 (0.0%)	6 (8.7%)	4 (5.9%)	0 (0.0%)	0 (0.0%)
Type II Diabetes	2 (2.7%)	5 (6.9%)	21 (30.4%)	17 (25.3%)	9 (6.0%)	6 (8.1%)
Sleep Apnea	6 (8.1%)	8 (11.1%)	19 (27.5%)	11 (16.4%)	21 (14.0%)	13 (17.5%)
Chronic kidney disease	0 (0.0%)	0 (0.0%)	3 (4.4%)	4 (6.0%)	8 (5.3%)	3 (4.0%)
Ischemic heart disease	0 (0.0%)	0 (0.0%)	2 (2.9%)	1 (1.5%)	0 (0.0%)	0 (0.0%)
Document episodes of Angina	0 (0.0%)	0 (0.0%)	4 (5.80%)	1 (1.5%)	1 (0.6%)	2 (2.7%)
Prior myocardial infarction	0 (0.0%)	0 (0.0%)	2 (2.9%)	4 (5.9%)	0 (0.0%)	0 (0.0%)
History of heart failure	0 (0.0%)	0 (0.0%)	1 (1.4 %)	3 (4.4%)	1 (0.6%)	0 (0.0%)
Bradycardia	1 (1.3%)	2 (2.7%)	1 (1.4 %)	0 (0.0%)	2 (1.3%)	3 (4.0%)
Atrial arrhythmias	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (4.4%)	0 (0.0%)	0 (0.0%)
Prior atrial ablation	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.5%)	1 (0.6%)	0 (0.0%)
Ventricular arrhythmias	0 (0.0%)	0 (0.0%)	1 (1.4 %)	2 (2.9%)	0 (0.0%)	1 (1.3%)

Data displayed as n (%)

Baseline Antihypertensive Medication

Table 5 shows the number of antihypertensive medications subjects were taking at screening. The number of baseline BP medications were balanced between the treatment groups in each study.

Table 5. Antihypertensive Medication at Screening (ITT)

Number Antihypertensive Medications	Randomized	uRDN	Sham
SOLO			
0	28/146 (19.2%)	12/74 (16.2%)	16/72 (22.2%)
1	61/146 (41.8%)	33/74 (44.6%)	28/72 (38.9%)
2	55/146 (37.7%)	28/74 (37.8%)	27/72 (37.5%)
3	2/146 (1.4%)	1/74 (1.4%)	1/72 (1.4%)
TRIO			
3	55/136 (40.4%)	27/69 (39.1%)	28/67 (41.8%)
4	44/136 (32.4%)	20/69 (29.0%)	24/67 (35.8%)
5	26/136 (19.1%)	16/69 (23.2%)	10/67 (14.9%)
6+	11/136 (8.1%)	6/69 (8.7%)	5/67 (7.5%)
RADIANCE-II			
0	77/224 (34.4%)	54/150 (36.0%)	23/74 (31.1%)
1	77/224 (34.4%)	52/150 (34.7%)	25/74 (33.8%)
2	69/224 (30.8%)	44/150 (29.3%)	25/74 (33.8%)
3	0/224 (0%)	0/150 (0%)	0/74 (0%)
4	1/224 (0.4%)	0/150 (0%)	1/74 (1.4%)

Data displayed as n/N (%)

7.3 Procedural Characteristics

Procedural characteristics for the uRDN-treated group are shown in Table 6. The majority of subjects were sedated using conscious sedation (84%-SOLO, 64%-TRIO, and 76%-RADIANCE-II) with remaining subjects receiving general anesthesia or monitored anesthesia (i.e., intravenous as opposed to inhalant) care per regional hospital practice (at non-US sites). Successful delivery of a minimum of two ultrasound emissions bilaterally (minimum of two emissions per side) was achieved in >95% of the treated subjects across the studies.

Table 6. Procedural Characteristics (ITT)

	SOLO Study	TRIO Study	RADIANCE-II
Renal Denervation Cohort	**N=74**	**N = 69**	**n=150**
Procedure time (sheath removal - sheath insertion) (min)[1]	71.9 ± 23.2	83.0	76.7 ± 25.2
Contrast volume (cc)	138.5 ± 66.6	176.9 ± 77.0	135.7 ± 67.4
Fluoroscopy exposure (minutes)	13.7 ± 6.8	19.0 ± 11.5	15.9 ± 8.6
Total Number of Emissions[2]	5.3 ± 1.1	5.8 ± 1.2	5.6 ± 1.0
Number of Subjects with Accessory and/or Proximal Side Branch Emissions	9 / 74 (12.16%)	17 / 69 (24.64%)	30 / 150 (20.00%)
Treatment successfully delivered (minimum 2 emissions bilateral)	71 / 74 (95.95%)	67 / 69 (97.10%)	148 / 150 (98.67%)
Total Emission Time (seconds)	37.4 ± 8.0	40.7 ± 8.1	38.9 ± 7.3

Data displayed as either n/N (%), Mean±SD, or Median [IQR] (Minimum, Maxiumum).
[1]Procedure time was defined as the time from arterial sheath placement to sheath removal.
[2]Includes main renal and accessory artery emissions.

Reasons for Incomplete Treatment

SOLO

- 1: unilateral treatment because of tortuosity in the ostial segment of their renal artery
- 1: no treatment due to ostial renal artery tortuosity
- 1: no treatment because the generator was non-functioning after randomization but prior to insertion of catheter.

TRIO

- 1: unilateral treatment because the balloon was too small to occlude the other artery
- 1: unilateral treatment (no further explanation in CSR)

RADIANCE-II

- 1: no treatment because their right renal artery could not be accessed.
- 1: subject was manually assigned via coin flip to sham group because the automated randomization system was down at the time. This subject was later assigned by the automated system to the treatment group but received no treatment.

7.4 Safety Results

7.4.1 Primary Safety Endpoint

Primary safety endpoint

The pre-specified primary safety analysis was an analysis of the uRDN-treated subjects from RADIANCE-II, defined as a patient-level composite of MAE events. No events met the definition, so the composite MAE rate was 0.0% (95% CI 0-1.63%), which met the performance goal of 9.8% (Table 7).

Pooled analyses of all uRDN-treated subjects from SOLO, TRIO, and RADIANCE-II

- Population: 367 uRDN randomized subjects treated at the index procedure and 77 randomized Sham subjects treated at crossover
- 46 adverse events (AEs) were submitted to the CEC for adjudication, and 6 of 46 events met the definition of a MAE
    - 5 events in TRIO (two deaths, two major vascular complications, and one hospitalization for hypertensive or hypotensive crisis)
    - 1 event in SOLO (hypotension and low pulse, which resolved within 4 hours)
    - No MAEs in RADIANCE-II
- The MAE composite rate overall was 1.1% with a 95% confidence interval of 0.3% - 2.77% (Table 8).

All CEC-assessed events were determined as being not related or unlikely related to the device, and as unlikely to have a causal relationship with the procedure.

Table 7. Primary Safety Results (ITT)

	MAE Rate	95% CI	Performance Goal	Result
RADIANCE-II	0.0%	0 - 1.63%	9.8%	Met
Pooled uRDN subjects	1.1%	0.3% - 2.77%	--	--

Table 8. Pooled Primary Safety Endpoint for uRDN-treated (Initial Procedure and Crossover)

	SOLO		TRIO		RADIANCE-II		Combined
Number of Events (% Subjects with Event)	**Initial**	**Crossover**	**Initial**	**Crossover**	**Initial**	**Crossover**	
30-day events							
All-cause mortality		0	1 (1.4%)	1 (4.8%)	0	0	2 (0.5%)
New onset (acute) end-stage renal disease (eGFR< 15 mL/min/m^2 or need for renal replacement therapy)		0	0	0	0	0	0
Significant embolic event resulting in end-organ damage (e.g., kidney/bowel infarct, lower extremity ulceration or gangrene, or doubling of serum creatinine)		0	0	0	0	0	0
Renal artery perforation requiring an invasive intervention		0	0	0	0	0	0
Renal artery dissection requiring an invasive intervention		0	0	0	0	0	0
Major vascular complications (e.g., clinically significant groin hematoma, arteriovenous fistula, pseudoaneurysm) requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion (requiring more than 2 units of packed red blood cells within any 24-hr period during the first 7 days post randomization)		0	2 (1.4%)	0	0	0	2 (0.3%)
Hospitalization for hypertensive or hypotensive crisis		0	1 (1.4%)	0	0	0	1 (0.3%)
Hospitalization for major cardiovascular- or hemodynamic- related events (e.g., HF; MI; Stroke)		0	0	0	0	0	1 (0.3%)
New onset Stroke		0	0	0	0	0	0
New onset Myocardial Infarction		0	0	0	0	0	0
6-month events		0	0	0	0	0	0

	SOLO		TRIO		RADIANCE-II		Combined
Number of Events (% Subjects with Event)	**Initial**	**Crossover**	**Initial**	**Crossover**	**Initial**	**Crossover**	
New onset renal artery stenosis of more than 70%, confirmed by CT or MR angiography	0	0	0	0	0	0	0
Overall Composite*	1 (1.4%)	0	4 (2.9%)	1 (4.8%)	0	0	**6 (1.1%)** **Exact 95% CI 0.30% - 2.77%**

Data displayed as n (%)

MAE rates for the uRDN and Sham control groups for SOLO, TRIO, and RADIANCE-II through current available follow-up are shown in Table 9.

Table 9. Pre-specified Safety Events through Follow-up, uRDN vs Sham (ITT)

	SOLO		TRIO		RADIANCE-II	
Number of Events (% Subjects with Event)	**uRDN (n=74)**	**Sham (n=72)**	**uRDN (n=69)**	**Sham (n=67)**	**uRDN (n=150)**	**Sham (n=74)**
All-cause mortality	0	1 (1.39%)	1 (1.45%)	1 (1.49%)	1 (0.67%)	1 (1.35%)
Hypertensive emergency resulting in hospitalization	1 (1.35%)	2 (2.78%)	3 (4.35%)	2 (2.99%)	1 (0.67%)	1 (1.35%)
Hospitalization for heart failure	0	0	4 (5.80%)	0	0	0
Stroke, transient ischemic attack, cerebrovascular accident	1 (1.35%)	1 (1.39%)	0	2 (2.99%)	2 (1.33%)	1 (1.35%)
Acute myocardial infarction (STEMI/non-STEMI)	0	1 (1.39%)	2 (2.90%)	1 (1.49%)	0	0
Any coronary revascularization	0	0	2 (2.90%)	1 (1.49%)	2 (1.33%)	0
End stage renal disease, the need for permanent renal replacement therapy (i.e., the need for dialysis); doubling of plasma creatinine	0	0	2 (2.90%)	0	0	0
Any renal artery complication requiring intervention (e.g., dissection; perforation)	0	0	0	0	0	0
Major access site complications requiring intervention	0	0	1 (1.45%)	1 (1.49%)	1 (0.67%)	0
Significant embolic events resulting in end organ damage	0	0	1 (1.45%)	1 (1.49%)	1 (0.67%)	1 (1.35%)
Procedure-related pain lasting for > 2 days	12 (16.22%)	4 (5.56%)	12 (17.39%)	10 (14.93%)	40 (26.67%)	13 (17.57%)

	SOLO		TRIO		RADIANCE-II	
Number of Events (% Subjects with Event)	**uRDN (n=74)**	**Sham (n=72)**	**uRDN (n=69)**	**Sham (n=67)**	**uRDN (n=150)**	**Sham (n=74)**
Acute renal injury	0	0	0	0	0	0
Significant (>50%) 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	0	0	0	0
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	0	0	0	0
Need for renal artery angioplasty or stenting	1 (1.35%)	0	0	0	0	0

Data displayed as n (%)

7.4.2 Renal Artery Stenosis

SOLO and TRIO
Per protocol assessment

- Renal duplex ultrasound (DUS) required for all randomized subjects at 2-months and 6-months and for uRDN-treated subjects at 24-months and 36-months.
- CTA/MRA required for all uRDN-treated subjects at 12 months

CTA or MRA required to assess potential RAS if renal DUS showed:

- Peak systolic velocity >180 cm/sec in either renal artery;
- Renal to aortic peak systolic velocity ratio ≥3.5 in either renal artery; or
- Absent Doppler signal in any portion of the main or accessory renal artery

Renal imaging results

Across all timepoints through 36 months, 10-13% of renal DUS studies triggered an MRA/CTA evaluation (Table 10). A vast majority of these CTA/MRA were within normal limits, defined as the absence of significant (>50%) or severe (>75%) new renal artery stenosis.

SOLO

- At 12 months, 65 of 69 eligible subjects had MRA/CTA completed. 98.5% (64 of 65) evaluable CTA/MRA studies were within normal limits at 12 months per site radiologists.
- Through 36 months, 5 MRA/CTA studies showed mild narrowing (<50% diameter stenosis narrowing), most often at the renal artery ostium and not at the site of ultrasound emissions. There was one case of renal artery stenting at 5 months post-procedure due to progression of preexisting ostial stenosis (>30% diameter stenosis), which should have excluded this subject.
- There were no cases of clinically significant new renal artery stenosis at 12, 24, and 36 months and no renal artery interventions through 36 months.

TRIO

- At 12 months, 54 of 62 subjects completed CTA/MRA. 100% (54/54) evaluable CTA/MRA studies were within normal limits.
- Through 24 months, 3 MRA/CTA studies showed mild narrowing (<25% narrowing) near ostium and not at site of emissions.
- There were no cases of clinically significant new renal artery stenosis at 12 and 24 months and no renal artery interventions through 24 months.

Table 10. Imaging Follow-up for SOLO and TRIO

	SOLO		TRIO	
	uRDN (N=74)	**Sham (N=72)**	**uRDN (N=69)**	**Sham (N=67)**
2 Month Follow-up				
Ultrasounds completed	97.3% (72/74)	90.3% (65/72)	93.9% (62/66)	91.0% (61/67)
Ultrasounds not done	2.7% (2/74)	9.7% (7/72)	6.1% (4/66)	9.0% (6/67)
Ultrasounds trigger MRA/CTA	10.8% (8/74)	8.3% (6/72)	3.0% (2/66)	9.0% (6/67)
Of triggered, MRA/CTA completed	50.0% (4/8)	50.0% (3/6)	50.0% (1/2)	66.7% (4/6)
MRA/CTA completed, but not due to Ultrasound trigger	0.0% (0/74)	0.0% (0/72)	0.0% (0/66)	0.0% (0/67)
6 Month Follow-up				
Ultrasounds completed	98.6% (72/73)	95.8% (68/71)	92.4% (61/66)	95.3% (61/64)
Ultrasounds not done	1.4% (1/73)	4.2% (3/71)	7.6% (5/66)	4.7% (3/64)
Ultrasounds trigger MRA/CTA	11.0% (8/73)	8.5% (6/71)	4.5% (3/66)	9.4% (6/64)
Of triggered, MRA/CTA completed	75.0% (6/8)	16.7% (1/6)	66.7% (2/3)	50.0% (3/6)
MRA/CTA completed, but not due to Ultrasound trigger	0.0% (0/73)	0.0% (0/71)	1.5% (1/66)	0.0% (0/64)
24 Month Follow-up				
Ultrasounds completed	91.7% (55/60)	--	88.9% (48/54)	--
Ultrasounds not done	8.3% (5/60)	--	11.1% (6/54)	--
Ultrasounds trigger MRA/CTA	13.3% (8/60)	--	11.1% (6/54)	--
Of triggered, MRA/CTA completed	50.0% (4/8)	--	50.0% (3/6)	--
MRA/CTA completed, but not due to Ultrasound trigger	1.7% (1/60)	--	1.9% (1/54)	--
36 Month Follow-up				
Ultrasounds completed	68.3% (41/60)	--	--	--
Ultrasounds not done	31.7% (19/60)	--	--	--
Ultrasounds trigger MRA/CTA	10.0% (6/60)	--	--	--
Of triggered, MRA/CTA completed	50.0% (3/6)	--	--	--
MRA/CTA completed, but not due to Ultrasound trigger	1.7% (1/60)	--	--	--

Data displayed as % (n/N)

RADIANCE-II

Per protocol assessment

CTA/MRA was required for all randomized subjects at 6-months and for uRDN-treated subjects at 12-months.

Renal imaging results

Table 11 shows completed follow-up imaging at 6 and 12 months. At 6 months, 215 subject completed their 6 months visit, and 184 of 224 subjects completed the 6-month CTA/MRA imaging. 124 subjects randomized to uRDN reached 12 months and completed CTA/MRA. Table 12 shows 6 and 12-month RADIANCE II imaging results. There were no cases of new renal artery stenosis (defined as a >70% diameter stenosis) through 12 months.

Table 11. RADIANCE-II CTA/MRA Imaging Completed at 6 and 12 Months (ITT subjects in window)

	uRDN (n=150)	**Sham (n=74)**
6 Month follow-up		
CTA/MRA	94.5% (138/146)	85.5% (59/69)
CTA	76.7% (112/146)	65.2% (45/69)
MRA	17.8% (26/146)	20.3% (14/69)
12 Month follow-up		
CTA/MRA	94.4% (117/124)	--
CTA	80.6% (100/124)	--
MRA	13.7% (17/124)	--

Data displayed as % (n/N)
Data based on available imaging forms; 6 and 12 month data are ongoing.
NOTE: Sham subjects are not required to have imaging at 12 months under the current protocol.

Table 12. Summary of 6- and 12-month CTA/MRA Imaging for RADIANCE II (by Core lab)

Visit	**Total Evaluable**	**1-30% % (n)**	**31-50% % (n)**	**51-70% % (n)**	**>70% % (n)**
6 Month follow-up	195	1.0% (2)	1.5% (3)	0.0% (0)	0.0% (0)
uRDN	137	1.5% (2)	0.7% (1)	0.0% (0)	0.0% (0)
Sham	58	0.0% (0)	3.4% (2)	0.0% (0)	0.0% (0)
12 Month follow-up	126	2.4% (3)	2.4% (3)	1.6% (2)	0.0% (0)
uRDN	112	2.7% (3)	2.7% (3)	1.8% (2)	0.0% (0)
Sham	14	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)

Data included in listing is based on data available from the core lab.
>70% chosen as cut-off to align with endpoint definition.

Pooled renal artery imaging data from SOLO, TRIO, and RADIANCE-II

- 238 original and crossover uRDN-treated subjects
- 12-month post-procedure CTA/MRAs reviewed by the Cardiovascular Research Foundation Imaging Core Lab.

- >98% of imaging studies considered of adequate quality.
- Arterial narrowing of ≤50% diameter stenosis considered to be incidental.

Table 13 shows renal artery stenosis assessment by CTA/MRA at 12 months in 238 pooled uRDN-treated subjects.

- 95.8% had no evidence of renal artery narrowing
  - 10 (4.2%) subjects had some degree of arterial narrowing
    - 8 with ≤50% diameter stenosis
    - 2 with 51-70% diameter stenosis, of which was an ostial narrowing at a non-uRDN treatment site.
  - No subjects had >70% renal artery stenosis

No subjects required renal artery intervention, and no renal artery narrowing was considered clinically significant. There were no subjects with new renal >70% artery diameter stenosis.

Table 13. Renal Artery Stenosis at 12 months based on CTA/MRA

Study	Total	No measurable stenosis % (n)	1-30% stenosis % (n)	31-50% stenosis % (n)	51-70% stenosis % (n)	71-99% stenosis % (n)	Renal artery occlusion % (n)
RADAIANCE-II	112	92.9% (104)	2.7% (3)	2.7% (3)	1.8% (2)	0.0% (0)	0.0% (0)
SOLO*	64	96.9% (62)	0.0% (0)	1.6% (1)	1.6% (1)	0.0% (0)	0.0% (0)
TRIO	53	100.0% (53)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
RADIANCE-II CO	6	83.3% (5)	0.0% (0)	16.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)
SOLO CO	25	92.0% (23)	0.0% (0)	4.0% (1)	4.0% (1)	0.0% (0)	0.0% (0)
Combined	238	95.8% (228)	1.3% (3)	2.1% (5)	0.8% (2)	0.0% (0)	0.0% (0)

Data included in listing is based on data available from the Core Lab
Not all Crossover (CO) subjects have reached 12M CO f/u.
** One SOLO subject randomized to treatment was not treated, and subsequently crossed over. Their data is included in the SOLO CO summaries.*

FDA Comment: Renal arterial imaging showed no cases of >70% renal artery diameter stenosis through 12 months. However, there was a 0.8% incidence of 51-70% diameter stenosis, a 2.1% incidence of 31-50% s diameter stenosis, and a 1.3 % incidence of 1-30% diameter stenosis. Although mild to moderate luminal narrowing is not associated with a functional reduction in renal blood flow, long-term follow-up data are limited, and renal arterial lesions may progress over time. The Panel will be asked to discuss these results in considering uRDN benefit-risk profile.

7.5 Effectiveness Results

7.5.1 Primary Effectiveness

Primary effectiveness endpoint: Reduction in average daytime ambulatory systolic blood pressure (ASBP) from baseline to 2-months post-procedure.

Analysis method: The mean difference between randomized groups (ITT) in reduction of daytime ASBP at 2 months post-procedure was compared via a linear regression (ANCOVA) model adjusted for subjects' baseline daytime ASBP.

Table 14 shows the primary effectiveness results for SOLO, TRIO, and RADIANCE-II.

Table 14. Primary Effectiveness Results for SOLO, TRIO, and RADIANCE-II (ITT)

ITT Cohort	uRDN change (mmHg)	Sham change (mmHg)	Difference between uRDN and Sham (mmHg)[1]	p-value
Off-Med Trials				
SOLO	-8.5 ± 9.3 (74)	-2.2 ± 10.0 (72)	-6.3 (-9.4, -3.1)	0.0001
RADIANCE-II	-7.9 ± 11.6 (145)	-1.8 ± 9.5 (73)	-6.3 (-9.3, -3.2)	<0.0001
On-Standardized-Med Trial				
TRIO (mean)	-9.0 ± 14.5 (69)	-4.8 ± 15.9 (67)	-4.5 (-9.6, 0.6)	0.0809
TRIO (median)[2]	-8.0 [-12.5, -5.5] (69)	-3.0 [-8.6, -0.9] (67)	-4.5* [-8.5, -0.3]	(0.0223*)

Data presented as mean ± SD (n); difference presented as mean (95% CI); p-value via a baseline adjusted ANCOVA (two-sided); all p-values are not adjusted for multiplicity.

[1] Negative value favors uRDN

[2] TRIO data followed non-normal distribution, so data are also presented as median [95% asymptotic CI] (n); p-value via a baseline adjusted ANCOVA on the ranks

** In a supportive analysis, the median difference is based on the median of all pairwise differences between uRDN and Sham (Hodges-Lehmann estimate) which is not associated with the p-value via a baseline adjusted ANCOVA on the ranks*

Off-med trials: SOLO and RADIANCE-II

SOLO ITT population

- Statistically significant difference in mean daytime ASBP reduction of 6.3 mmHg (95% CI: 9.4 - 3.1 mmHg) in favor of uRDN group (p=0.0001)
- Imputed data
  - uRDN group – 1 subject restarted medication prior to 2-months meeting escape criteria, and 1 subject did not have 2-month ABPM
  - Sham group – 3 subjects in the Sham group restarted medication prior to 2-months meeting escape criteria and 1 subject did not have 2-month ABPM.

RADIANCE-II ITT population

- Statistically significant difference in mean daytime ASBP reduction of 6.3 mmHg (95% CI: 9.3 - 3.2 mmHg) in favor of uRDN group (p<0.0001).
- Imputed data
  - uRDN group – 5 subjects did not have 2-month ABPM, and 4 subjects restarted medication prior to 2-months meeting escape criteria
  - Sham group – 1 subject did not have 2-month ABPM and 6 subjects restarted medication prior to 2-months meeting escape criteria

On-standardized-med trial: TRIO

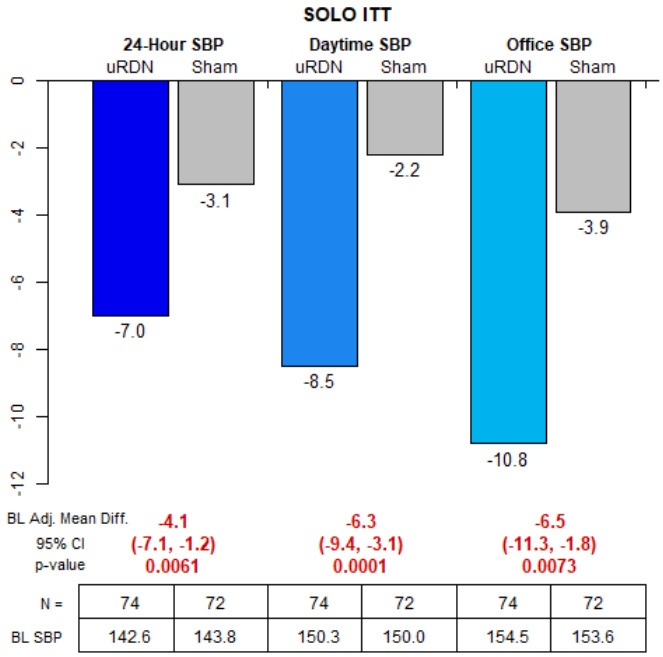
- Difference in mean daytime ASBP reduction of 4.5 mmHg (95% CI: 9.6 mmHg reduction - 0.6 mmHg increase) in favor of uRDN group (p=0.0809)
    - Because the data had a non-normal distribution due to the number of outliers, a baseline adjusted ANCOVA on the ranks was also evaluated, as pre-specified in the statistical analysis plan, and was statistically significant (p=0.0223).
    - Per the pre-specified analysis, the median difference indicated reduction of 4.5 mmHg (Hodges-Lehmann estimate) based on the median of all pairwise differences between uRDN and Sham. Note that this median is not associated with the p-value via the baseline adjusted ANCOVA on the ranks.
- Imputed data
    - uRDN group – 6 subjects did not have 2-month ABPM
    - Sham group – 4 subjects in the Sham group restarted medication prior to 2-months meeting escape criteria.
- Because of the imbalance in missing data for the primary effectiveness endpoint (6 missing for uRDN and 0 for Sham) in a study with a small sample size, the sponsor evaluated the endpoint in the per protocol (PP) and complete ABPM (CA) cohorts; the median difference between uRDN and Sham was -5.4 mmHg and -5.8 mmHg, respectively, both in favor of uRDN.

Additional analyses were conducted to evaluate the primary effectiveness endpoint the per protocol (PP) cohort and complete ABPM (CA) cohort for SOLO, TRIO, and RADIANCE-II (Appendix 4, Table 4.1).

FDA Comment: The 2018 Circulatory System Devices Advisory Committee recommended a 5-7 mmHg relative BP reduction in RDN-treated patients vs. Controls as a clinically meaningful threshold for RDN effectiveness. The Panel will be asked to discuss the clinical importance of the magnitude of uRDN effectiveness, considering the absolute BP reduction in uRDN subjects alone and the BP reduction in uRDN subjects vs. the Sham group.

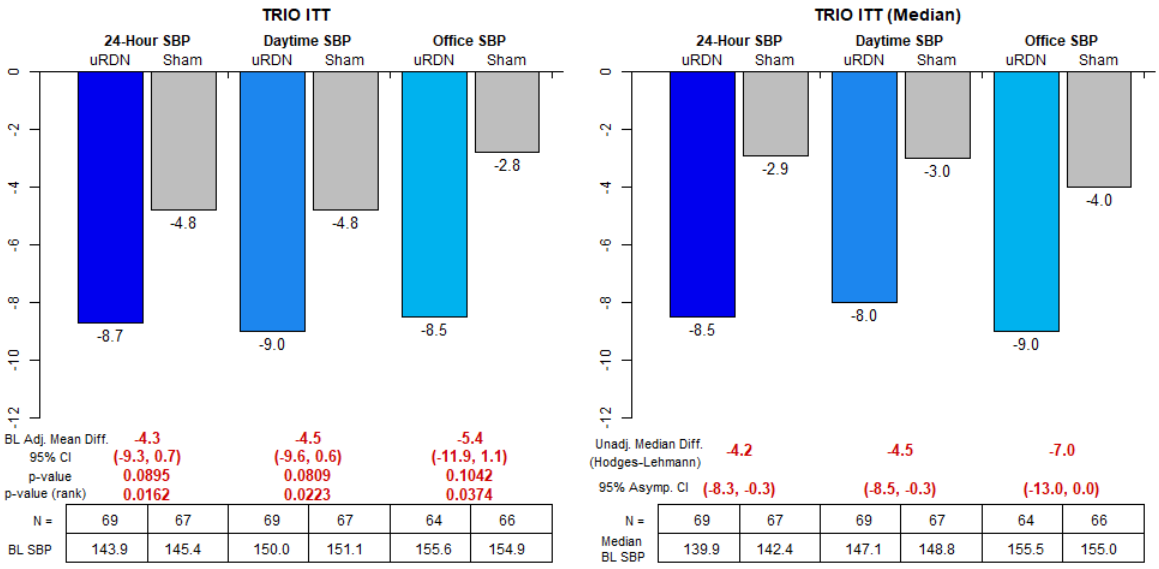
7.5.2 Secondary and Observational Effectiveness Endpoints

Figure 8, Figure 9, and Figure 10 show the secondary analyses (24-hr ASBP and office SBP) and the primary effectiveness analysis (daytime ASBP) for the ITT population for SOLO, TRIO, and RADIANCE-II, respectively. Due to higher missing ABPM in the TRIO study, Appendix 4 (Table 4.2) includes the secondary endpoints of 24-hour SBP/SBP, Nighttime SBP/DBP, and Daytime DBP at 2 months for the complete ABPM (CA) population.



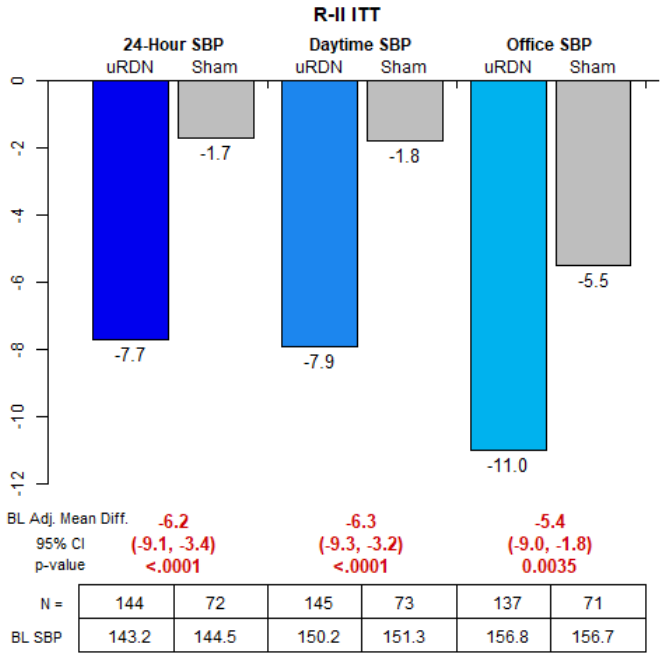
Note that all p-values are not adjusted for multiplicity

Figure 8. SBP (24-hour, Daytime, and Office) at 2 months for SOLO (ITT)



Note that all p-values are not adjusted for multiplicity and p-value (rank) uses ANCOVA on the ranks (Quade (1967) JASA).

Figure 9. SBP (24-hour, Daytime, and Office) at 2 months for TRIO (ITT)



Note that all p-values are not adjusted for multiplicity

Figure 10. SBP (24-hour, Daytime, and Office) at 2 months for RADIANCE-II (ITT)

Table 15 shows these data, differences in nighttime SBP and DBP, and home and office DBP.

Table 15. Secondary and Observational BP Effectiveness Endpoints at 2 months for ITT Population

	SOLO		TRIO		RADIANCE-II	
	Mean Difference (95% CI) (uRDN - Sham)[1]	**p-value**	**Mean Difference (95% CI) (uRDN - Sham)[1]**	**p-value**	**Mean Difference (95% CI) (uRDN - Sham)[1]**	**p-value**
Daytime Ambulatory DBP (mmHg)	-2.6 (-4.6, -0.6)	0.0118 (0.0060*)	-1.6 (-4.9, 1.7)	0.3415 (0.1835*)	-3.9 [-5.6, -2.2]	<.0001
24 Hour Ambulatory SBP (mmHg)	-4.1 (-7.1, -1.2)	0.0061	-4.3 (-9.3, 0.7)	0.0895 (0.0162*)	-6.2 [-9.1, -3.4]	<.0001
24 Hour Ambulatory DBP (mmHg)	-1.8 (-3.7, 0.2)	0.0715	-1.7 (-4.9, 1.5)	0.3054 (0.1228*)	-4.1 [-5.7, -2.4]	<.0001
Nighttime Ambulatory SBP** (mmHg)	-2.5 (-6.0, 0.9)	0.1534	-4.4 (-9.9, 1.2)	0.1213 (0.0441*)	-5.8 [-9.0, -2.6]	0.0004 (<.0001*)
Nighttime Ambulatory DBP** (mmHg)	-1.4 (-3.8, 1.0)	0.2492	-2.2 (-5.8, 1.4)	0.2242 (0.0534*)	-4.2 [-6.3, -2.2]	<.0001 (<.0001*)
Home SBP** (mmHg)	-7.1 (-10.4, -3.8)	<.0001 (<.0001*)	-4.3 (-8.6, 0.0)	0.0524	-7.6 [-10.1, -5.0]	<.0001
Home DBP** (mmHg)	-3.6 (-5.6, -1.5)	0.0009 (<.0001*)	-2.6 (-5.2, 0.0)	0.0527	-4.3 [-5.9, -2.8]	<.0001
Office SBP** (mmHg)	-6.5 (-11.3, -1.8)	0.0073 (0.0007*)	-5.4 (-11.9, 1.1)	0.1042 (0.0374*)	-5.4 [-9.0, -1.8]	0.0035
Office DBP** (mmHg)	-4.1 (-7.0, -1.3)	0.0045	-3.2 (-7.5, 1.1)	0.1375 (0.1598*)	-2.3 [-4.9, 0.2]	0.0755

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. Note that all p-values are not adjusted for multiplicity

(**) Nighttime Ambulatory SBP and DBP were not secondary endpoints in RADIANCE II but were observational endpoints. Home and Office SBP and DBP were not secondary endpoints in SOLO and TRIO but were observational endpoints.

Ambulatory systolic blood pressure curves at 2 months are shown in Figure 11 and Figure 12 for SOLO and TRIO (ITT with imputation), respectively, and Figure 13 for the RADIANCE-II (CA). The uRDN group showed a significant mean decrease in SBP through the 24-hour period as compared to Sham in all studies.

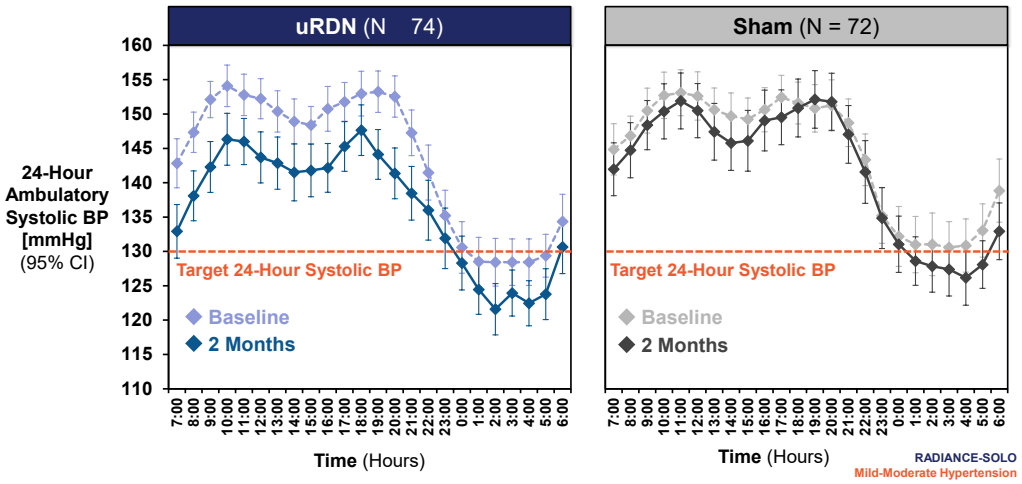


Figure 11. 24-hour ASBP curves at 2 months for SOLO (ITT)

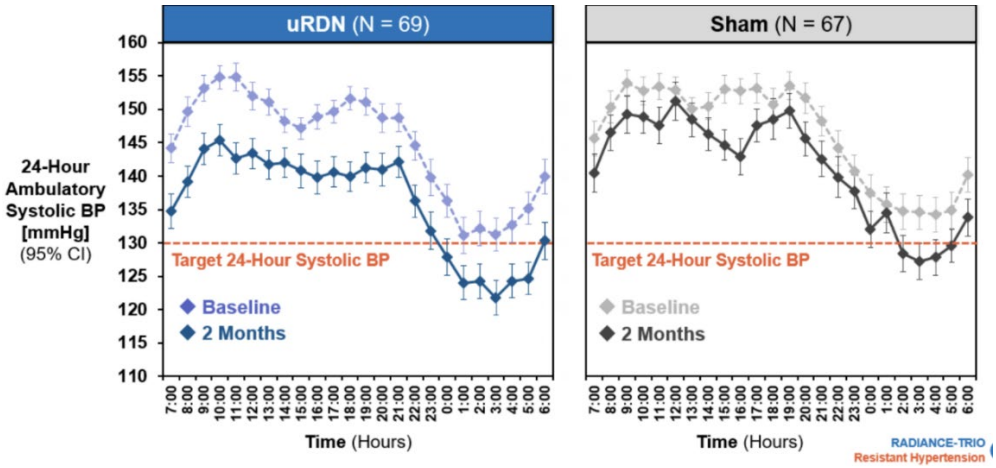


Figure 12. 24-hour ASBP curves at 2 months for TRIO (ITT)

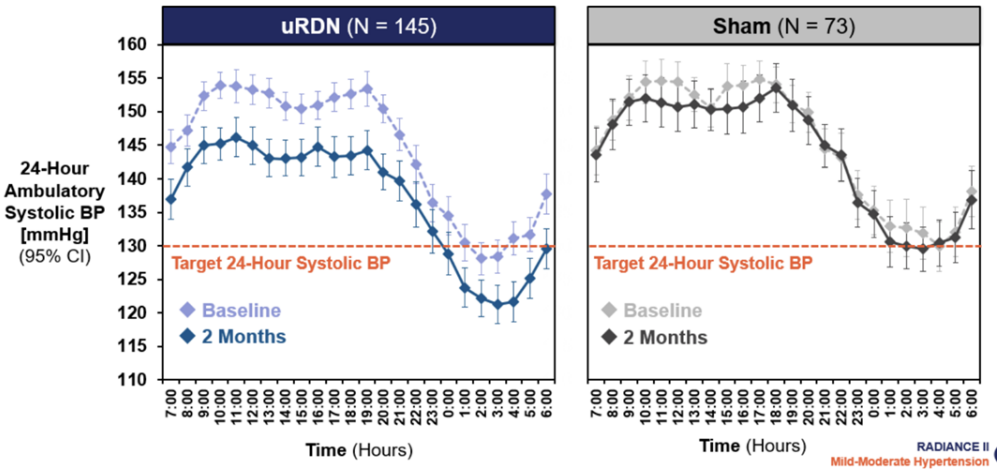


Figure 13. 24-hour ASBP curves at 2 months for RADIANCE-II (CA)

7.5.3 Subgroup Analyses

Subgroup analyses of the daytime ASBP (the primary effectiveness endpoint) are shown in Figure 14, Figure 15, and Figure 16 for SOLO, TRIO and RADIANCE-II, respectively. Subgroups included age, race, gender, geographical region, baseline daytime SBP, baseline office SBP, and abdominal obesity (stratified by male waist circumference >102 cm and ≤102 cm and female waist circumference >88 cm and ≤88 cm). RADIANCE-II subgroups also included baseline home SBP, 24-hour heart rate, and baseline eGFR. Non-black and Black races had sufficient sample size to perform subgroup analysis (see Table 4 Baseline Characteristics).

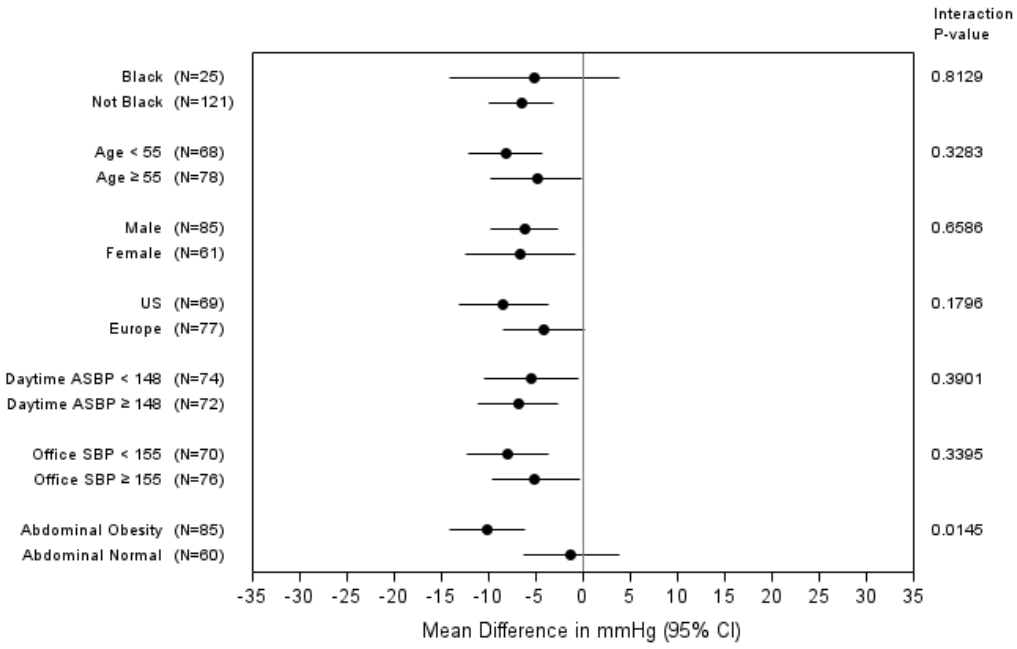


Figure 14. Subgroup Analysis for Daytime ASBP for SOLO at 2 Months

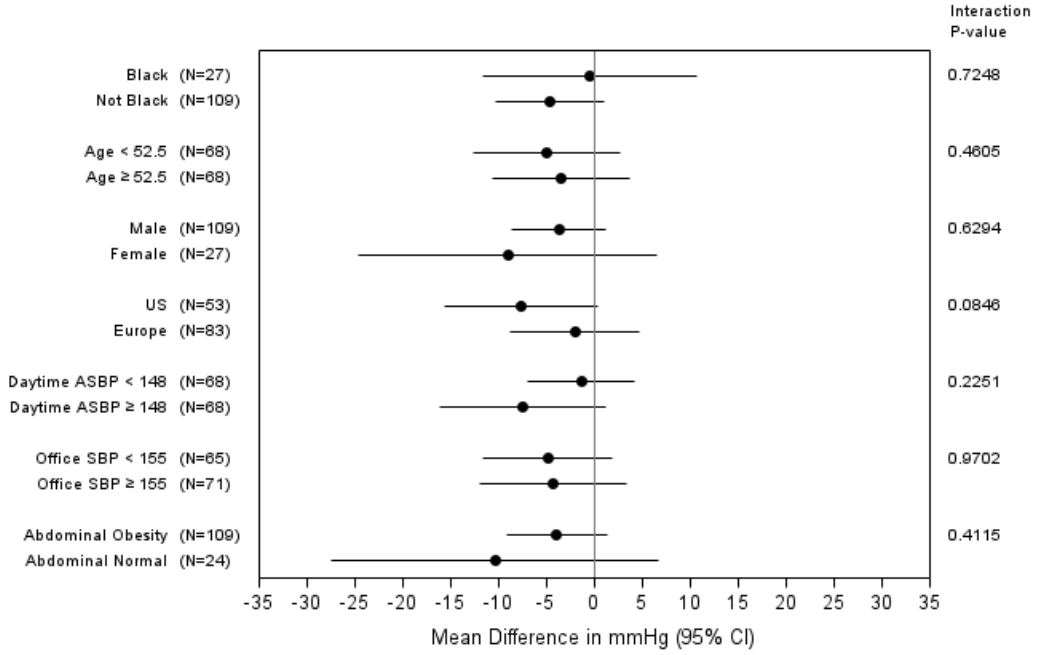


Figure 15. Subgroup Analysis for Daytime ASBP for TRIO at 2 Months

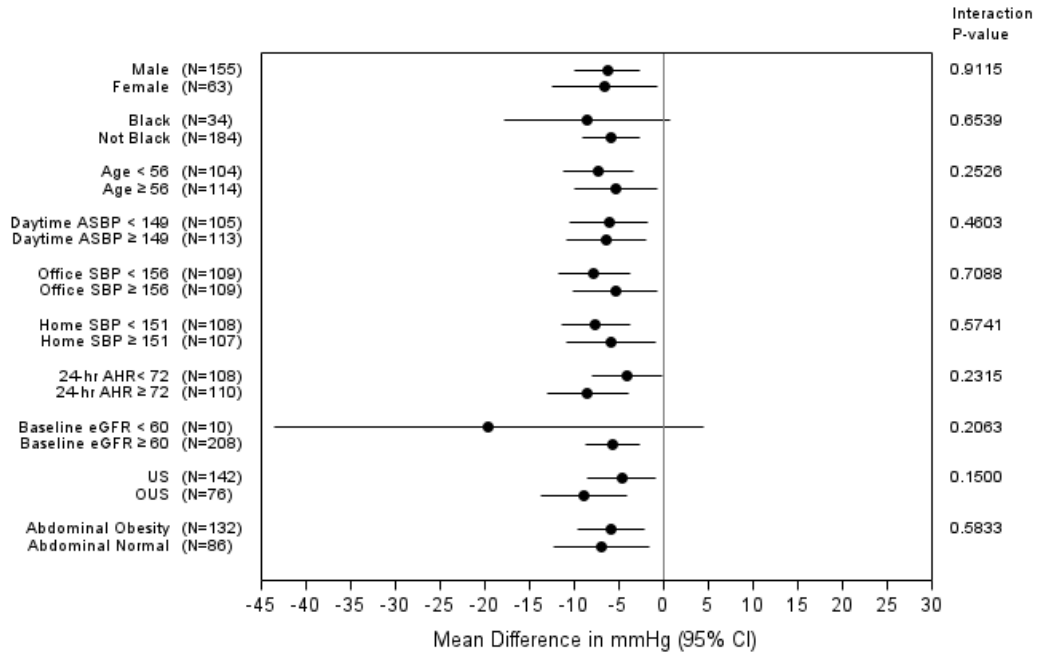


Figure 16. Subgroup Analysis for Daytime ASBP for RADIANCE-II at 2 Months

For SOLO, the abdominal obesity vs abdominal normal analysis revealed a subgroup effect based on the interaction p-value of 0.0145. For TRIO and RADIANCE-II, no significant subgroup effects were detected. However, the sample sizes of subgroups are relatively small.

For SOLO and TRIO, the US subgroup trended toward greater BP reductions than the OUS subgroup, but in RADIANCE-II, the OUS subgroup had greater BP reductions (Table 16).

Table 16. US vs OUS difference in daytime ASBP at 2 months (ITT)

	US		OUS		
	Mean Difference (95% CI) (uRDN - Sham)	**p-value btw uRDN and Sham**	**Mean Difference (95% CI) (uRDN - Sham)**	**p-value btw uRDN and Sham**	**Interaction p-value**
SOLO	-8.4 (-13.1, -3.7)	0.0006	-4.2 (-8.5, 0.1)	0.0543	0.1905 (0.1796*)
TRIO	-7.7 (-15.7, 0.3) -9.0 (-16.1, -2.3)[1]	0.0593 (0.0048*)	-2.0 (-8.8, 4.7) -1.5 (-6.1, 3.0)[1]	0.5477 (0.5388*)	0.2901 (0.0846*)
RADIANCE-II	-4.7 (-8.6, -0.9)	0.0172	-9.0 (-13.8, -4.1)	0.0005	0.1477 (0.1500*)

Data shown as mean (95% CI) and p-value via a baseline adjusted ANCOVA for SOLO and RADIANCE-II.
[1] TRIO includes median (95% asymptotic CI) which is not associated with the p-value (*) via a baseline adjusted ANCOVA on the ranks.

7.5.4 Durability of Treatment Effectiveness

To assess durability of the treatment effectiveness, ambulatory, home and office BP and medication burden were evaluated at 12-months. Office BP and medication burden were assessed beyond 12-months.

BP Change through 24 months

Ambulatory blood pressure was measured at 2, 6, and 12 months post-procedure to assess treatment effect durability, and OBP will be measured through study completion (5 years). Of note:

- SOLO and RADIANCE-II subjects had antihypertensive medications stopped through the 2-month post-procedure follow-up (unless subjects met BP escape criteria).
- TRIO subjects were treated with a standardized single, fixed-dose, triple combination pill through the 2 months post-procedure follow-up (unless subjects met BP escape criteria).

After the collection of primary effectiveness endpoint data at 2-months post-procedure, subjects in SOLO, TRIO, and RADIANCE-II were treated with a guideline-based antihypertensive medication escalation protocol between 2- and 6-months post-procedure to achieve blood pressure control (≤135/85 mmHg home BP). Prescribing physicians and subjects were blinded to their treatment assignment.

Figure 17 shows the 24-hour ASBP at baseline, 2 months, and 6 months for RADIANCE-II. There is a clear reduction in the average 24-hour ASBP in uRDN-treated subjects at 2 months, whereas no clear difference is seen for the sham-treated subjects at 2 months. Following physician-directed BP medication escalation to reach a BP goal between 2 months and 6 months,

both groups saw decreases in 24-hour ASBP, and the BP curves for both treatment groups are generally similar.

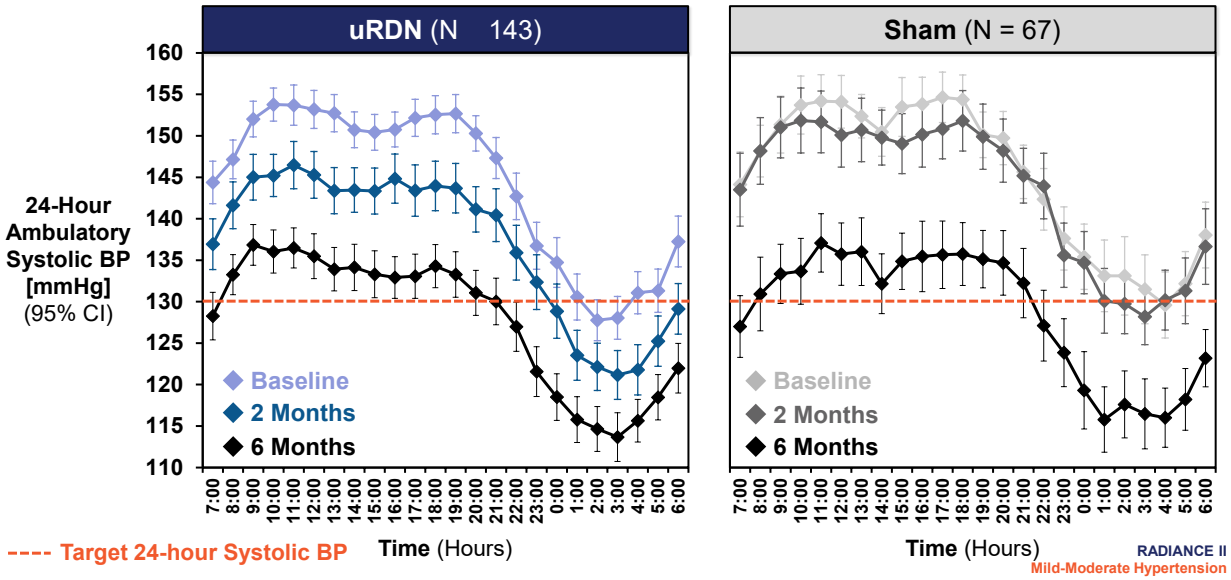


Figure 17. 24-hour ASBP at Baseline, 2 months, and 6 months for RADIANCE-II (CA)

Figure 18, Figure 19, and Figure 20 show mean differences (baseline adjusted) in 24-hour, daytime, and office SBP for the uRDN and Sham groups for SOLO, TRIO, and RADIANCE-II, respectively. In summary, the data across all studies show that 24-hour ASBP, daytime ASBP, and office SBP reductions in the uRDN and Sham groups from baseline to 2 months, with a steeper SBP decline in the uRDN subjects. From 2 to 6 months, SBP continues to decline in both treatment groups. From 6 to 12 months in SOLO AND TRIO, 24-hour and daytime SBP are generally similar between treatment groups, but office BP is higher in the Sham group.

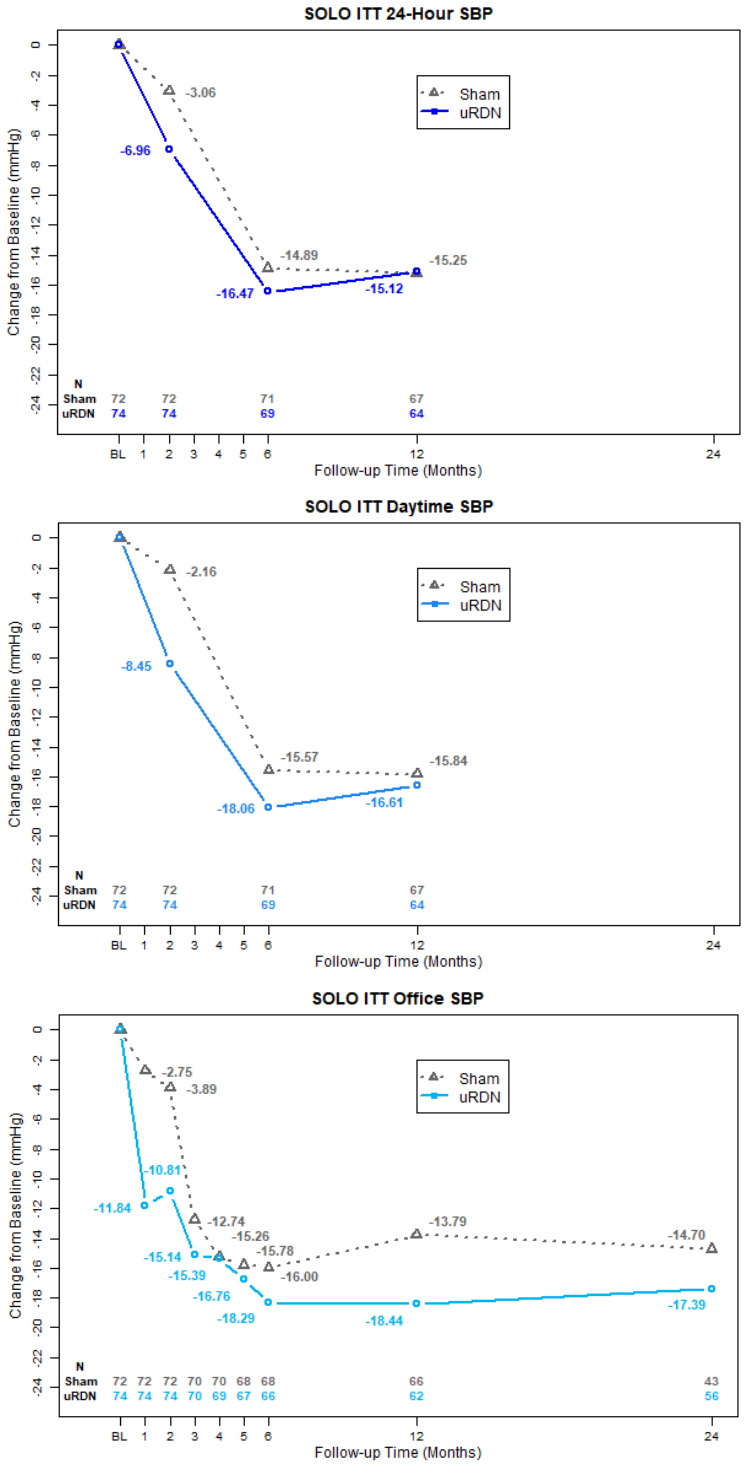


Figure 18. 24-hour, Daytime, and Office SBP over SOLO Study Follow-up (ITT)

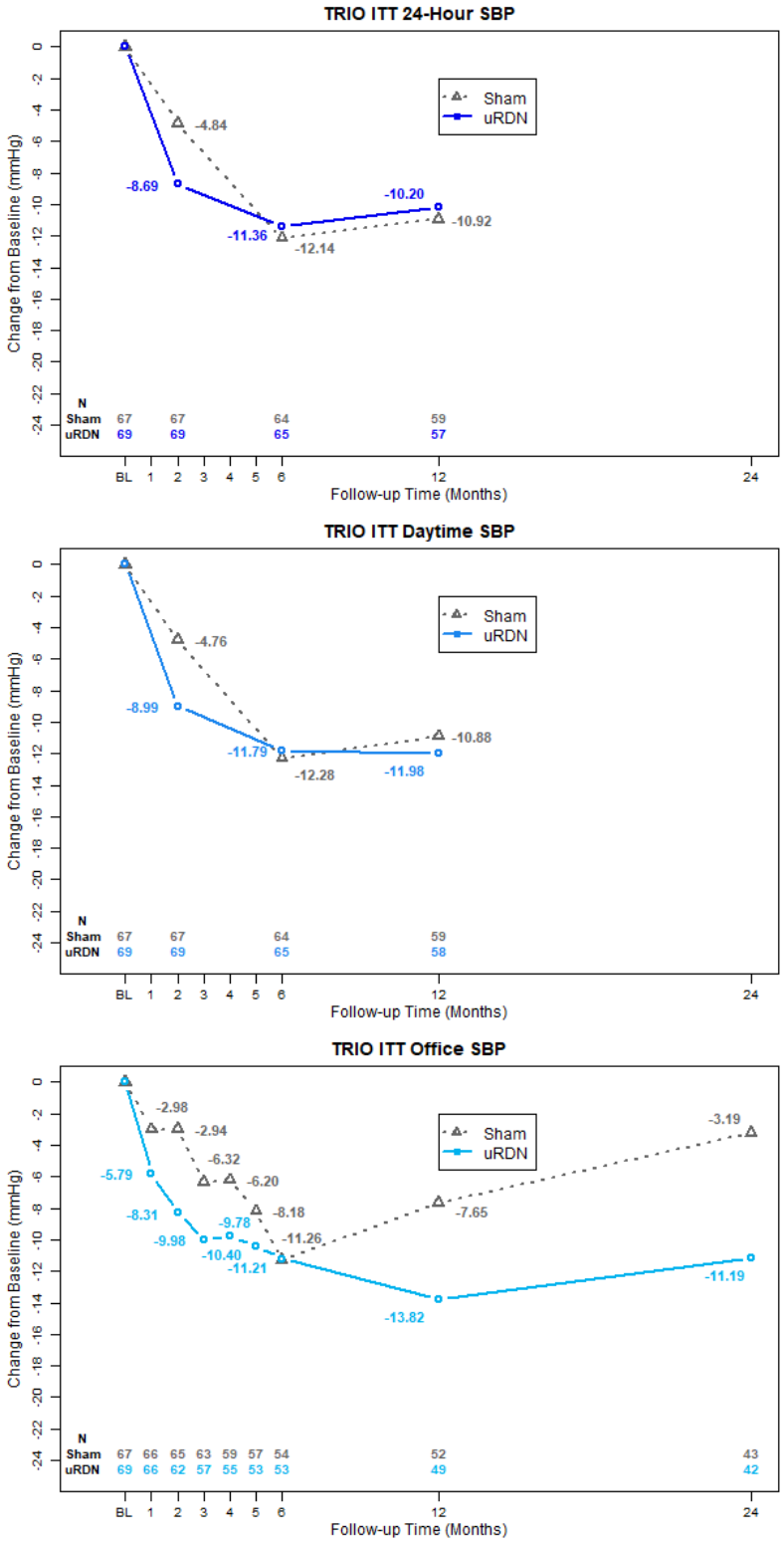


Figure 19. 24-hour, Daytime, and Office SBP over TRIO Study Follow-up (ITT)

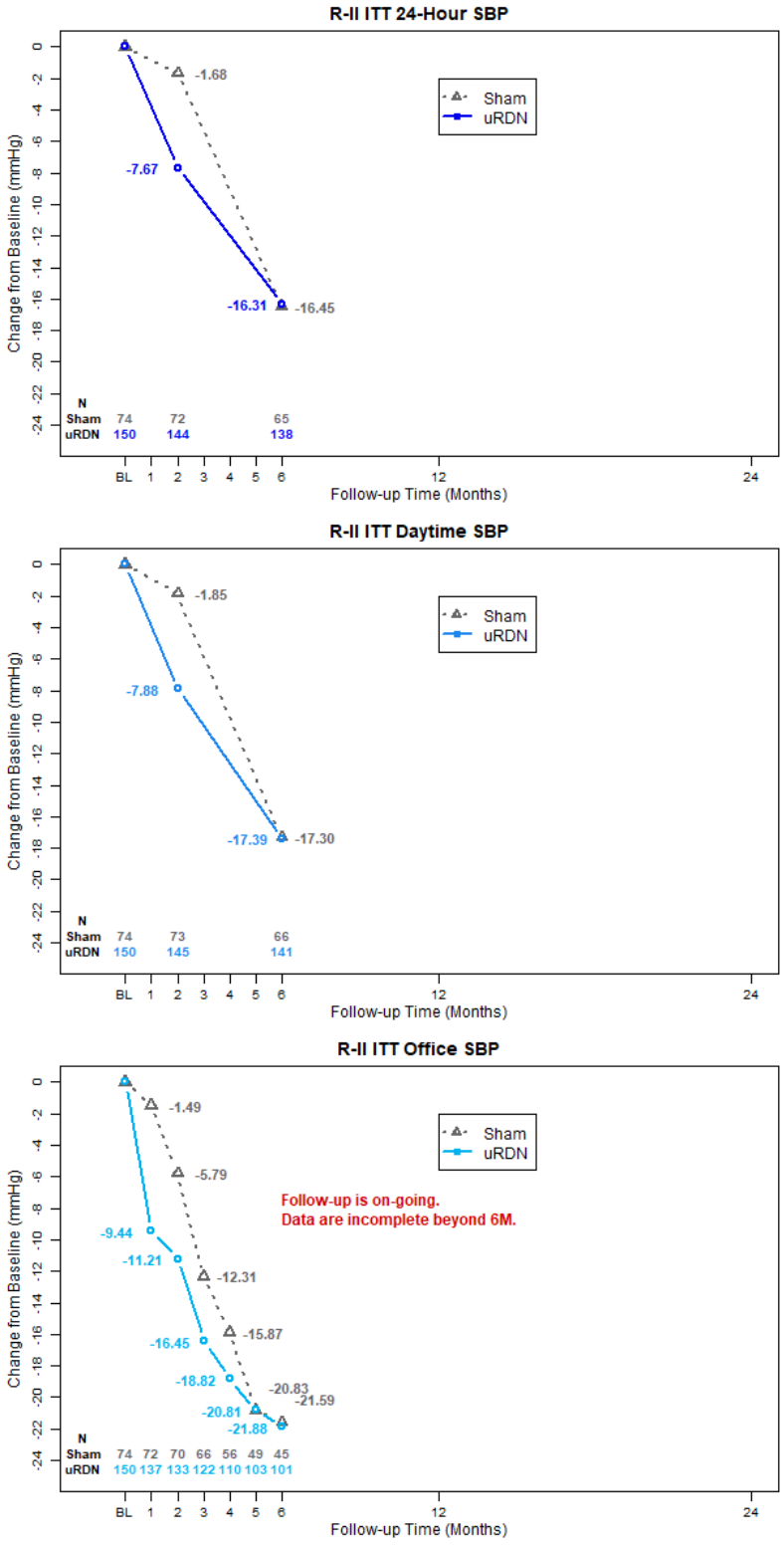


Figure 20. 24-hour, Daytime, and Office SBP over RADIANCE-II Study Follow-up (ITT)

Caveats in interpreting durability data

Longitudinal BP reduction could have been impacted by several factors:

- Unblinding at 6 months in SOLO and TRIO could have potentially led to bias for the 12 months BP measurement. RADIANCE-II subjects are unblinded at 12 months.
- Crossover after 6 months in SOLO and TRIO and after 12 months in RADIANCE II reduced the sample size and potentially biases against the Sham group as patients with controlled BP were not permitted to crossover whereas Sham patients with uncontrolled BP were permitted to crossover to uRDN.
- From 2-6 months, physicians were encouraged to use protocol-driven medication escalation to reach target blood pressure of ≤140 mmHg.

Medication Burden and Effect on ASBP

Medication burden was calculated using two methods: the Defined Daily Dose (DDD) and the antihypertensive medication load index. DDD is expressed as the sum of the average maintenance dose per day for each medication a subject is taking. Antihypertensive medication load index is calculated as described in Wan, Hart, and Hajjar, Hypertension, 2009. Briefly, for each antihypertensive medication used, the dosage actually used is expressed as a percent of the maximal dose recommended for hypertension, according to the following equation:

$$Antihypertensive\ Medication\ Load\ Index = \sum_{AH\ Meds} (class\ weight \frac{prescribed\ dose}{standard\ dose})$$

SOLO

Table 17 and Figure 21 show the number of prescribed antihypertensive medications, medication dose burden, ASBP, and OSBP at 2, 6, and 12 months.

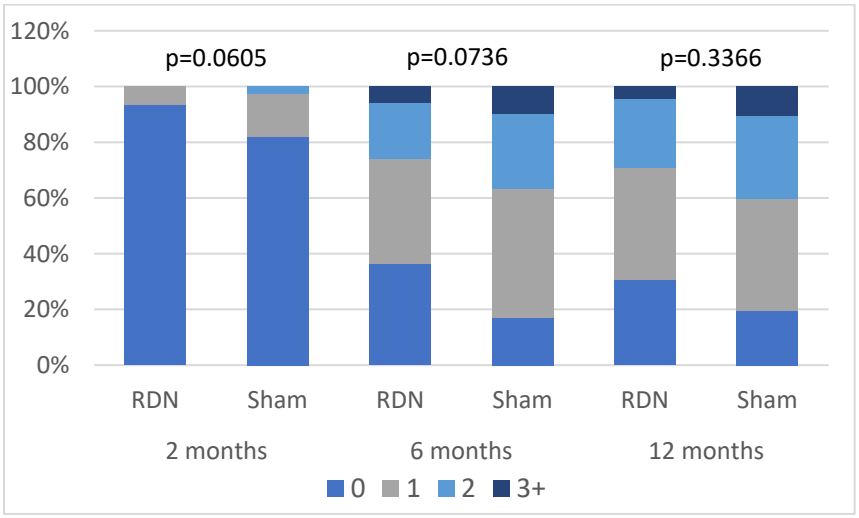
- *Medication through 2-month primary endpoint assessment*
  - Subjects were to remain off of antihypertensive medications unless BP escape criteria were met.
  - 18 subjects (5 uRDN and 13 Sham subjects) were treated with BP medications either due to meeting protocol-defined escape criteria for medication restart (2 uRDN and 3 Sham subjects), at physician discretion or patient preference.
  - 93% of uRDN and 82% of Sham subjects were off antihypertensive medications at the 2-month follow-up BP assessment.
- *Number of antihypertensive medications*
  - Compared to the Sham controls, uRDN subjects averaged fewer antihypertensive medications prescribed at 2, 6 and 12 months. Differences were significant at 2 and 6 months but not significant at 12 months.
  - At 6 and 12 months, there was a higher proportion of uRDN subjects on no medications versus Sham subjects.
- *Medication load index and difference in daytime ASBP*
  - From baseline to 2 months, the medication load index was similar between groups, and the difference in reductions in daytime ASBP in the uRDN group was significantly lower (-6.3 mmHg) as compared to the Sham group.

- At 6 months, the medication load index was significantly lower in the uRDN group, and the baseline-adjusted treatment effect for daytime ASBP in the uRDN group was numerically lower (-2.3 mmHg; p=0.24) compared to the Sham group.
- At 12 months, the medication load index was significantly lower in the uRDN group with a slightly lower (-0.4 mmHg) baseline-adjusted treatment effect for daytime ASBP in the uRDN group compared to the Sham group.

Table 17. BP change and Medication Burden for SOLO

	uRDN				Sham			
	Change in Daytime ASBP (mmHg)	**Change in office SBP** (mmHg)	**Average number of antihypertensive medications**	**Med Load Index**	**Change in Daytime SBP** (mmHg)	**Change in office SBP** (mmHg)	**Average number of antihypertensive medications**	**Med Load Index**
2 months (ITT)	-8.5 ± 9.3 (74)	-10.8 ± 13.6 (74)	0.1 ± 0.3	0.0 ± 0.1	-2.2 ±10.0 (72)	-3.9 ±17.4 (72)	0.2 ± 0.5	0.1 ± 0.3
6 months (CA)	-18.1 ± 12.2 (69)	-18.2 ± 14.2 (69)	1.0 ± 0.9	0.5 ± 0.4	-15.6 ± 13.2 (71)	-15.9 ± 17.2 (71)	1.3 ± 0.9	0.7 ± 0.5
12 months (CA)	-16.5 ± 12.9 (65)	-18.1 ± 14.9 (65)	1.0 ± 0.9	0.5 ± 0.5	-15.8 ± 13.1 (67)	-13.6 ± 17.2 (67)	1.3 ± 0.9	0.7 ±0.5

Data is presented as mean ± SD (n)



Note that all p-values are not adjusted for multiplicity

Figure 21. Number of Antihypertensive Medications at 2, 6, and 12 months for SOLO

TRIO

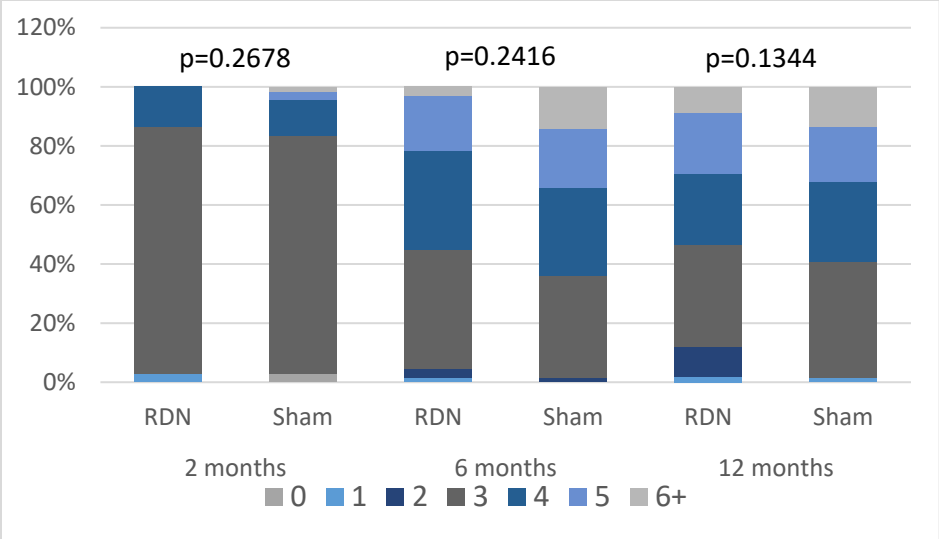
Table 18 and Figure 22 show the number of prescribed antihypertensive medications, medication dose burden, ASBP, and OSBP at 2, 6, and 12 months.

- *Medication through 2-month primary endpoint assessment*
  - Subjects were on a single, triple combination pill (with or without a β blocker) until 2 months after their procedure unless BP escape criteria were met.
  - 11 subjects (3 uRDN and 8 Sham subjects) were treated with additional BP medications either due to meeting the protocol-defined escape criteria for medication restart (4 Sham subjects), or at the physician's discretion or patient preference (3 uRDN and 4 Sham subjects).
  - At 2 months, 92% of uRDN subjects and 85% of Sham subjects were on the same number of medications compared to baseline. Dose burden and medication load index were similar between treatment groups.
- *Number of antihypertensive medications*
  - The numbers of medications were comparable between groups at 2, 6, or 12 months, although the uRDN group trended fewer antihypertensive medications.
- *Medication load index and difference in daytime ASBP*
  - The medication burden was not significantly different between treatment groups but was numerically lower for uRDN subjects at 2, 6, or 12 months.

Table 18. BP change and Medication Burden for TRIO

	uRDN				**Sham**			
	Change in Daytime ASBP (mmHg)	**Change in office SBP** (mmHg)	**Average number of antihypertensive medications**	**Med Load Index**	**Change in Daytime SBP** (mmHg)	**Change in office SBP** (mmHg)	**Average number of antihypertensive medications**	**Med Load Index**
2 months (ITT)	-9.0 ± 14.5 (69)	-8.5 ± 19.1 (64)	3.1 ± 0.5	0.0 ± 0.1	-4.8 ± 15.9 (67)	-2.8 ± 20.7 (66)	0.2 ± 0.5	1.3 ± 0.9
6 months (CA)	-11.8 ± 14.2 (65)	-10.4 ± 16.8 (63)	3.8 ± 1.0	2.3 ± 0.6	-12.3 ± 14.2 (64)	-11.2 ± 22.7 (64)	4.1 ± 1.1	2.4 ± 0.6
12 months (CA)	-12.1 ± 14.1 (59)	-12.6 ± 19.8 (59)	3.7 ± 1.5	2.3 ± 0.9	-10.9 ± 18.3 (59)	-7.8 ± 28.9 (59)	4.0 ± 1.2	2.5 ± 0.7

Data is presented as mean ± SD (n)



Note that all p-values are not adjusted for multiplicity

Figure 22. Antihypertensive Medications at 2, 6, and 12 months for TRIO

RADIANCE-II

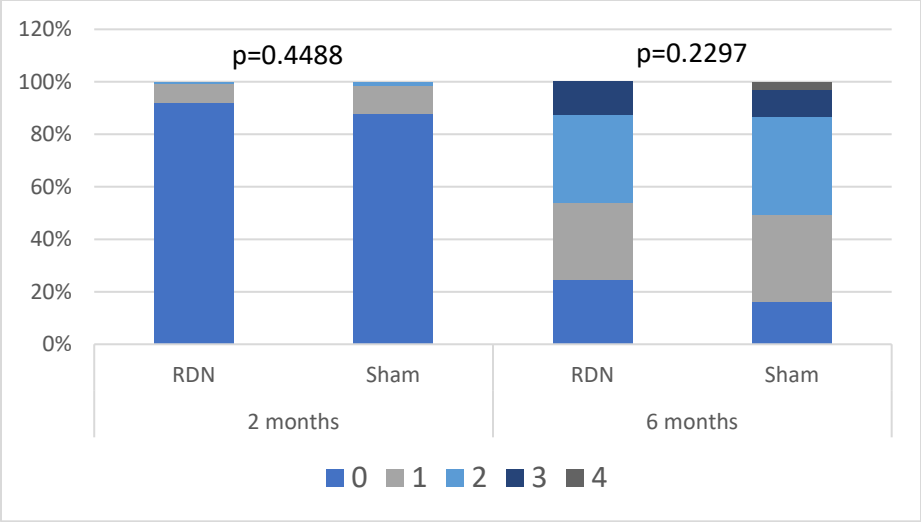
Table 19 and Figure 23 show the number of prescribed antihypertensive medications and medication dose burden at 2 and 6 months.

- *Medication through 2-month primary endpoint assessment*
  - Subjects were to remain off of antihypertensive medications unless BP escape criteria were met.
  - 22 subjects (12 uRDN and 10 Sham subjects) were treated with BP medications either due to meeting the protocol-defined escape criteria for medication restart (4 uRDN and 6 Sham subjects), physician discretion or patient preference.
- *Number of antihypertensive medications*
  - The number of antihypertensive medications was similar between the two groups at 2 and 6 months.
- *Medication load index and difference in daytime ASBP*
  - The medication burden was similar between treatment groups at 2 or 6 months.

Table 19. BP change and Medication Burden for RADIANCE-II

	uRDN				**Sham**			
	Change in Daytime ASBP (mmHg)	**Change in office SBP** (mmHg)	**Average number of antihypertensive medications**	**Med Load Index**	**Change in Daytime SBP** (mmHg)	**Change in office SBP** (mmHg)	**Average number of antihypertensive medications**	**Med Load Index**
2 months (ITT)	-7.9 ± 11.6 (145)	-11.0 ± 13.5 (137)	0.1 ± 0.3	0.1 ± 0.2	-1.8 ± 9.5 (73)	-5.5 ± 12.9 (71)	0.1 ± 0.4	0.1 ± 0.2
6 months (CA)	-17.5 ± 11.4 (143)	-20.9 ± 14.8 (143)	1.3 ± 1.0	0.7 ± 0.6	-17.4 ± 14.0 (67)	-20.2 ± 16.4 (57)	1.5 ± 1.0	0.8 ± 0.6

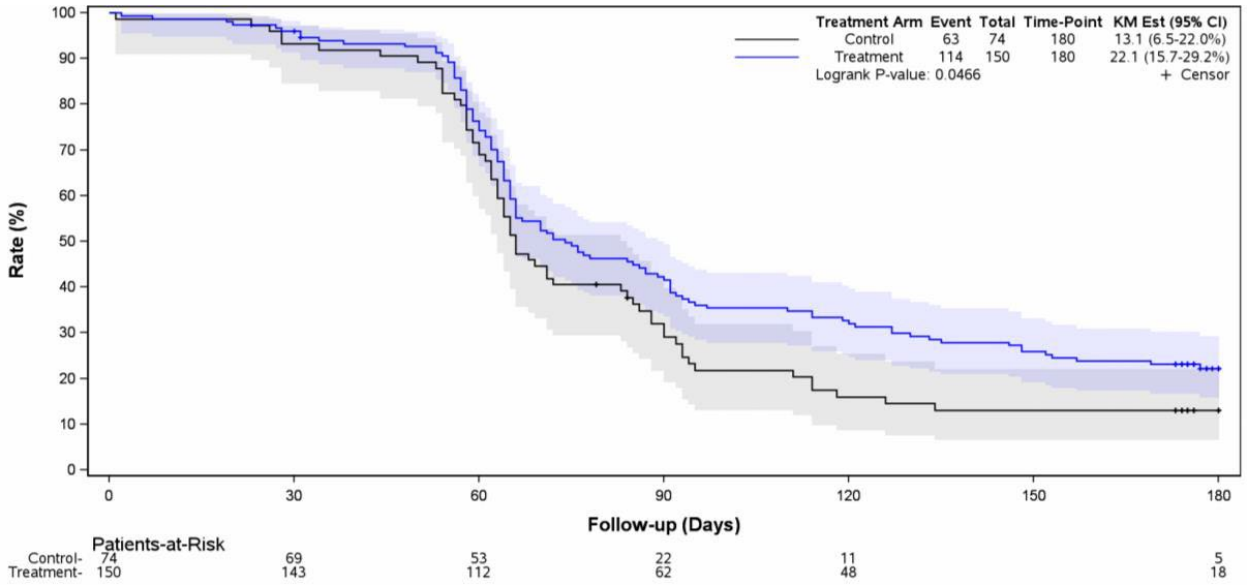
Data is presented as mean ± SD (n)



Note that all p-values are not adjusted for multiplicity

Figure 23. Antihypertensive Medications at 2, 6, and 12 months for RADIANCE-II

Figure 24 shows the time to the first prescribed antihypertensive medication as part of the pre-specified escalation protocol starting at 2 months for RADIANCE-II. Sham subjects had medications returned earlier than uRDN subjects.



Note that all p-values are not adjusted for multiplicity

Figure 24. Time to First Prescribed Antihypertensive Medication

FDA Comment: The trends for lower medication burden in the uRDN group persisted at 12 months vs. Controls. However, the SBP and medication burden differences at 12 months were narrower compared to these differences at 2 and 6 months, suggesting a reduced effect of uRDN over time. The Panel will be asked to discuss the durability of uRDN effectiveness considering

the challenges in interpreting the data (e.g., unblinding at 6 months, potential crossover after 6 months, and escalating medication treatment to reach a BP goal).

7.5.5 Additional Analyses

The following additional observational analyses were provided:

Proportion of subjects with ASBP reductions of at least 5 to 20 mmHg at 2 months

Table 20 shows the proportion of subjects who had reductions of at least 5, 10, and 15 mmHg in SOLO, TRIO, and RADIANCE-II.

- SOLO: A higher proportion of uRDN subjects vs. Sham subjects achieved ASBP reduction of ≥5, ≥10, and ≥15 mmHg.
- TRIO: A higher proportion of uRDN subjects vs. Sham subjects achieved ASBP reduction of ≥5, ≥10, and ≥15 mmHg.
- RADIANCE-II: A higher proportion of uRDN subjects vs. Sham subjects achieved ASBP reduction of ≥5, ≥10, and ≥15 mmHg.

Table 20. Daytime Ambulatory SBP Drop at 2-months

Daytime SBP Reduction	Renal Denervation	Sham Procedure	p-value
SOLO	**(n=69)**	**(n=59)**	
≥5 mmHg	49/74 (66.2%)	24/72 (33.3%)	<.0001
≥10 mmHg	32/74 (43.2%)	13/72 (18.1%)	0.0010
≥15 mmHg	19/74 (25.7%)	8/72 (11.1%)	0.0234
TRIO	**(n=69)**	**(n=67)**	
≥5 mmHg	42/69 (60.9%)	28/67 (41.8%)	0.0260
≥10 mmHg	29/69 (42.0%)	17/67 (25.4%)	0.0401
≥15 mmHg	21/69 (30.4%)	10/67 (14.9%)	0.0311
RADIANCE-II	**(n=150)**	**(n=74)**	
≥5 mmHg	64.1% (93/145)	34.2% (25/73)	<.0001
≥10 mmHg	47.6% (69/145)	16.4% (12/73)	<.0001
≥15 mmHg	25.5% (37/145)	9.6% (7/73)	0.0057
≥20 mmHg	11.7% (17/145)	6.8% (5/73)	0.2594

Note that all p-values are not adjusted for multiplicity

Proportion of subjects controlled in the absence of additional antihypertensive medications

Table 21 shows the percentage of subjects controlled in the absence of antihypertensive medications at 2 months and 6 months for SOLO and RADIANCE-II. Controlled BP was defined as:

- Daytime ABP <135/85
- Nighttime ABP <120/70
- 24-hour ABP <130/80
- OBP <140/90 mmHg.

SOLO

- At 2 months, 22% of uRDN subjects attained controlled daytime ASBP (<135/85 mmHg) in the absence of antihypertensive medications vs. 3.4% of Sham subjects. Significant differences in BP control without medications were also observed for 24-hour ABP, OBP, and home BP (p=0.001) in uRDN subjects vs. Sham subjects.
- At 6 months, the proportion of subjects controlled on no antihypertensive medication was numerically higher in the uRDN subjects vs. Sham subjects.

RADIANCE-II

- At 2 months and 6 months, uRDN subjects on no antihypertensive medication were more likely to reach BP targets than Sham subjects for all measures except home SBP at 2 months. The differences were statistically significant at 2 months but not at 6 months due to the low sample size taking no medication.

Table 21. Control of SBP in absence of antihypertensive medication per Protocol Defined Targets at 2 and 6 Months for SOLO and RADIANCE-II (CA)

	2 months			6 months		
	uRDN	**Sham**	**p-value**	**uRDN**	**Sham**	**p-value**
SOLO	**(n=69)**	**(n=59)**		**(n=25)**	**(n=12)**	
Daytime ambulatory blood pressure <135/85 mmHg	15/69 (21.7%)	2/59 (3.4%)	0.0023	9/25 (36.0%)	2/12 (16.7%)	0.2793
24-hour ambulatory blood pressure <130/80 mmHg	18/69 (26.1%)	2/59 (3.4%)	0.0004	7/25 (28.0%)	0/12 (0.0%)	0.0721
Night-time ambulatory blood pressure <120/70 mmHg	13/69 (18.8%)	5/59 (8.5%)	0.0926	6/25 (24.0%)	1/12 (8.3%)	0.3891
Office blood pressure* <140/90 mmHg	17/69 (24.6%)	5/59 (8.5%)	0.0157	7/25 (28.0%)	3/12 (25.0%)	1.0000
Home blood pressure <135/85 mmHg	11/67 (16.4%)	0/59 (0.0%)	0.0011	8/25 (32.0%)	1/11 (9.1%)	0.2225
RADIANCE-II	**(n=138)**	**(n=64)**		**(n=35)**	**(n=11)**	
Daytime ambulatory blood pressure <135/85 mmHg	25/133 (18.8%)	3/63 (4.8%)	0.0087	13/35 (37.1%)	2/11 (18.2%)	0.2962

	2 months			6 months		
	uRDN	Sham	p-value	uRDN	Sham	p-value
24-hour ambulatory blood pressure <130/80 mmHg	31/132 (23.5%)	3/63 (4.8%)	0.0013	12/35 (34.3%)	2/11 (18.2%)	0.4605
Night-time ambulatory blood pressure <120/70 mmHg	32/132 (24.2%)	5/63 (7.9%)	0.0066	12/35 (34.3%)	2/11 (18.2%)	0.4605
Office blood pressure* <140/90 mmHg	15/129 (11.6%)	0/59 (0%)	0.0033	15/35 (42.9%)	1/7 (14.3%)	0.2217
Home blood pressure <135/85 mmHg	29/125 (23.2%)	13/61 (21.3%)	0.7724	15/34 (44.1%)	1/10 (10.0%)	0.0670

Data displayed as n/N (%).
** Average of two office measures; seated position.*
Note that all p-values are not adjusted for multiplicity

TRIO

- Because TRIO subjects were on antihypertensive medications, Table 22 shows control per same definitions above in all evaluable subjects in presence of any medication at 2 and 6 months.
- The proportion of subjects who achieved BP control (daytime ABP, nighttime BP, OBP and home BP) was numerically higher in uRDN subjects vs. Sham subjects at 2 and 6 months.

Table 22. Control of SBP per Protocol Defined Targets at 2 and 6 Months for TRIO (CA)

	2 months			6 months		
	uRDN	Sham	p-value	uRDN	Sham	p-value
TRIO	**(n=69)**	**(n=67)**		**(n=65)**	**(n=64)**	
Daytime ambulatory blood pressure <135/85 mmHg	24/69 (34.8%)	14/67 (20.9%)	0.0712	26/65 (40.0%)	21/64 (32.8%)	0.3964
24-hour ambulatory blood pressure <130/80 mmHg	21/69 (30.4%)	15/67 (22.4%)	0.2876	27/65 (41.5%)	19/64 (29.7%)	0.1600
Night-time ambulatory blood pressure <120/70 mmHg	21/69 (30.4%)	12/67 (17.9%)	0.0885	21/65 (32.3%)	19/64 (29.7%)	0.7477
Office blood pressure* <140/90 mmHg	14/64 (21.9%)	14/66 (21.2%)	0.9268	20/63 (31.7%)	17/64 (26.6%)	0.5204
Home blood pressure <135/85 mmHg	16/62 (25.8%)	8/64 (12.5%)	0.0572	20/61 (32.8%)	11/61 (18.0%)	0.0613

Data displayed as n/N (%).
**Average of two office measures; seated position.*
Note that all p-values are not adjusted for multiplicity

Change in ABP by Baseline Daytime ABP at 2 months

Figure 25, Figure 26, and Figure 27 show the proportion of subjects with daytime ASBP control (<135/65 mmHg) as a function of baseline BP tertile for SOLO, TRIO, and RADIANCE-II, respectively.

- Subjects with lower baseline BPs (≤145 mmHg for SOLO and RADIANCE-II and ≤143 mmHg for TRIO) were more likely to have BP control vs. subjects with higher baseline BPs
- Subjects with higher baseline daytime ASBP trended toward a greater mean reduction in daytime ASBP.

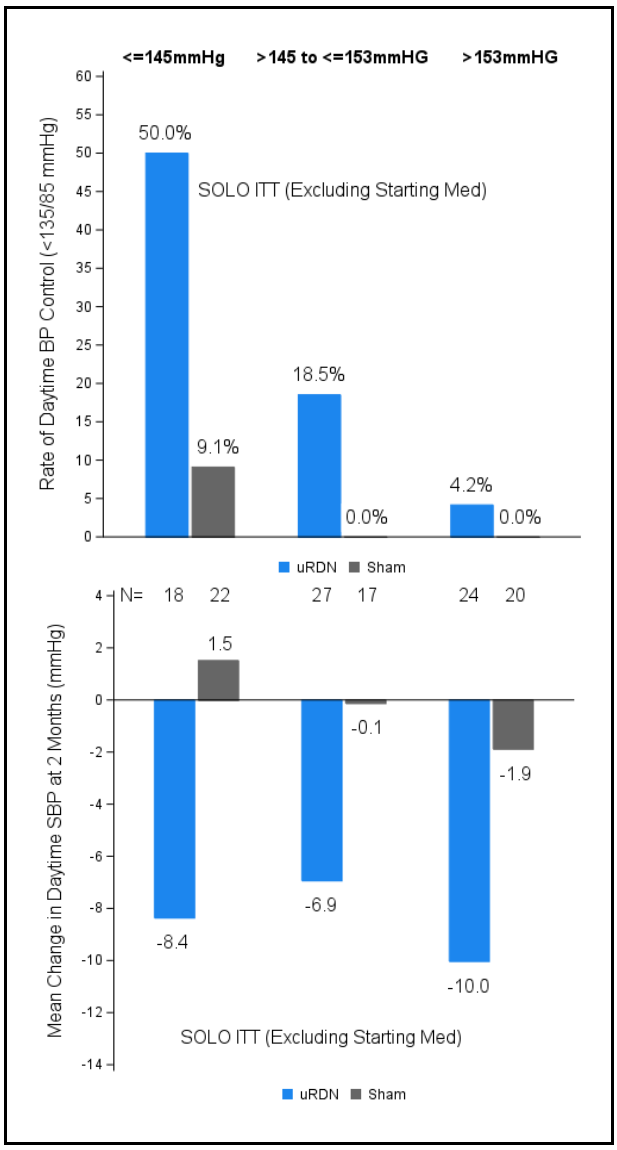


Figure 25. BP Control at 2 months by Baseline Daytime SBP Tertiles for SOLO

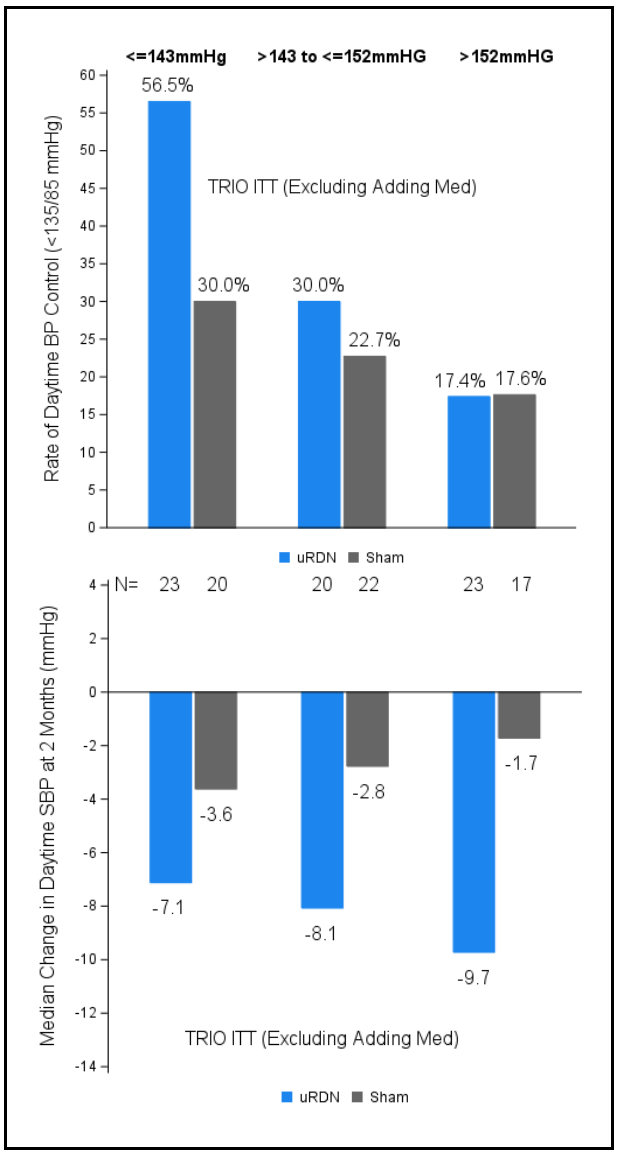


Figure 26. BP Control at 2 months by Baseline Daytime SBP Tertiles for TRIO

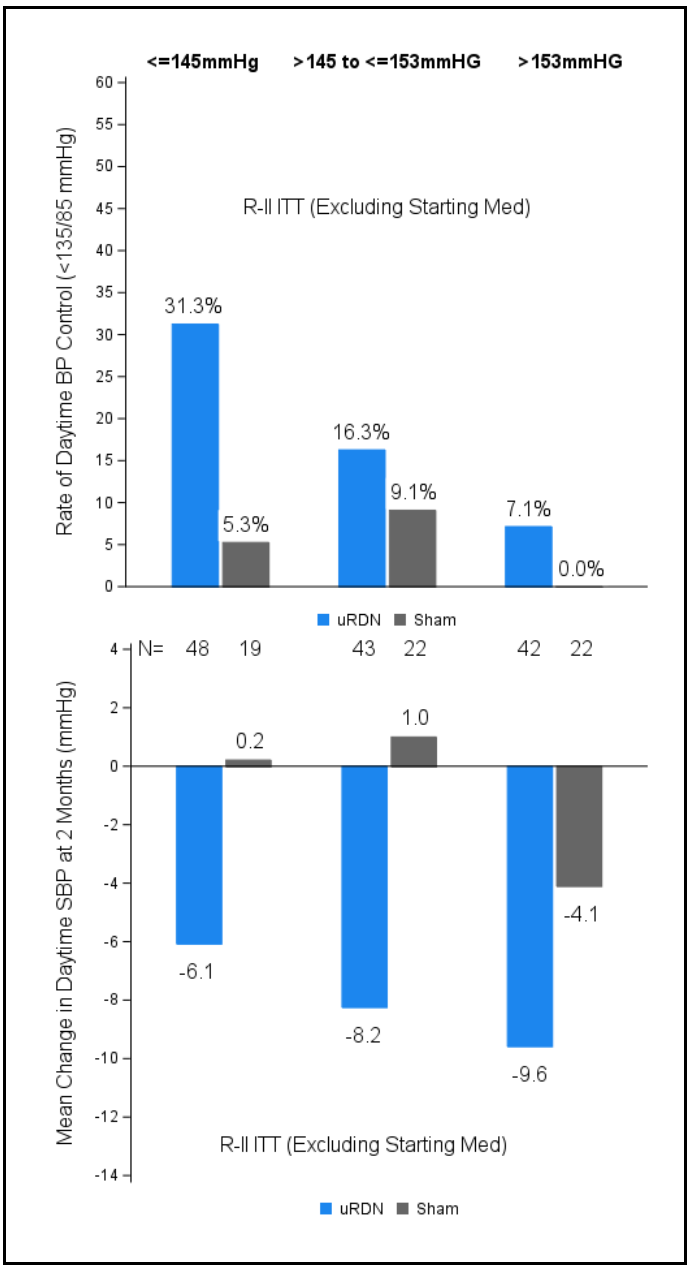


Figure 27. BP Control at 2 months by Baseline Daytime SBP Tertiles for RADIANCE-II

7.6 Blinding Assessment

Table 23 shows results from the blinding assessment performed at discharge, 2 months, and 6 months for SOLO, TRIO, and RADIANCE-II. Subjects were asked whether they believed that they were assigned to uRDN, Sham, or did not know their assignment.

Table 23. Blinding Index Results for SOLO, TRIO, and RADIANCE-II

	Bang Blinding Index		James Blinding Index
	uRDN	**Sham**	
SOLO			
Discharge	0.30 [0.161,0.442]	-0.01 [-0.173,0.144]	0.70 [0.622,0.768]
2 months	0.24 [0.077,0.410]	0.21 [0.041,0.381]	0.59 [0.513,0.673]
6-months	0.18 [-0.017,0.373]	0.38 [0.213,0.548]	0.50 [0.424,0.585]
TRIO			
Discharge	0.31 [0.172,0.446]	0.00 [-0.137,0.137]	0.74 [0.666,0.813]
2 months	0.20 [0.018,0.382]	0.15 [-0.032,0.331]	0.61 [0.531,0.697]
6-months	0.27 [0.082,0.463]	0.24 [0.039,0.445]	0.52 [0.429,0.602]
RADIANCE-II			
Discharge	0.26 [0.166,0.357]	-0.19 [-0.328, -0.051]	0.77 [0.719,0.829]
2 months	0.23 [0.091,0.368]	0.25 [0.075,0.425]	0.53 [0.464,0.593]
6-months	0.04 [-0.107,0.178]	0.50 [0.320,0.680]	0.50 [0.442,0.565]

Bang Blinding Index

- 0 indicates total or complete blinding
- >0 indicates a positive correlation (a tendency of subjects to correctly identify their randomization assignment)
- <0 indicates a negative correlation (a tendency of subjects to incorrectly identify their randomization assignment)

Results: For all studies, both groups remained generally blinded to their treatment assignment. Numerically more uRDN subjects guessed their treatment correctly at discharge, and more Sham subjects correctly guessed their treatment at 6 months, which was most evident in RADIANCE-II.

James Blinding Index – Assessment scale from 0 to 1

- 0 indicates a lack of blinding
- 1 indicates successful blinding
- 0.5 indicates completely random blinding (i.e., 50% correct and 50% incorrect guesses)
    - If the upper bound of the confidence interval (CI) of blinding index is below 0.5, the study is regarded as lacking blinding.

Results: Since upper bound of the CI was above 0.5 for all 3 studies at each time point, the James Blinding Index indicates the study was successfully blinded (i.e., complete random blinding was present).

8 Patient Preference Study

ReCor conducted a patient preference study (PPS) using a discrete choice experiment (DCE) with 258 patients to ascertain patient preferences for a uRDN procedure compared to BP medication for uncontrolled HTN. The PSS objective was to establish the maximum acceptable risk (MAR) patients would be willing to tolerate and the minimal acceptable benefit (MAB) they would require for the uRDN treatment option.

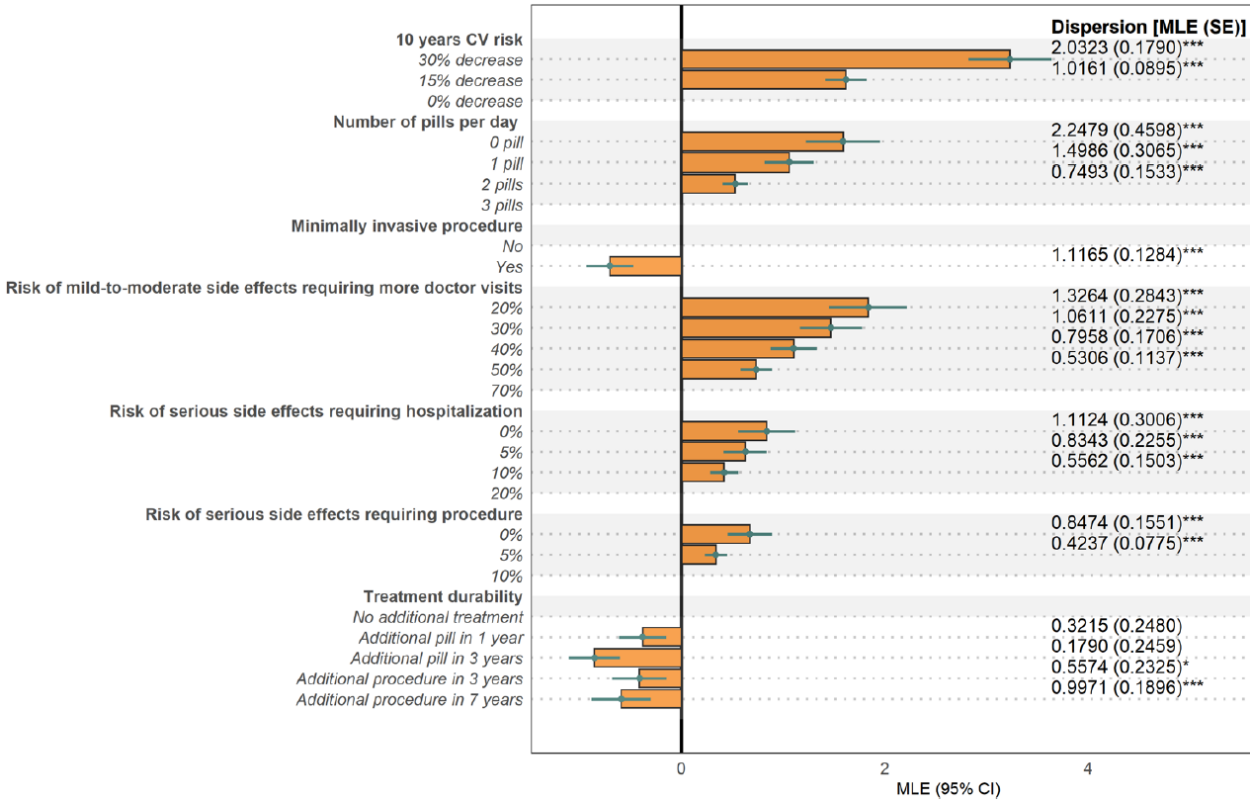
The patient preference study attributes and an example discrete choice task are in Appendix 4 (Tables 4.3-4). Select study participant characteristics are described in Table 24.

Table 24. Select Characteristics

	N=258
Age (in years)	52.5 (12.3)
Min-Max	25-74
Sex	
Male	98 (38.0%)
Female	160 (62.0%)
Ethnic/racial background*	
White	155 (60.1%)
Black or African American	68 (26.4%)
Hispanic or Latino	16 (6.2%)
Asian or Asian American	1 (0.4%)
Native Hawaiian or other Pacific Islander	7 (2.7%)
American Indian or Alaska Native	3 (1.2%)
US Geographic region	
West	29 (11.2%)
Midwest	39 (15.1%)
South	162 (62.8%)
Northeast	28 (10.9%)
Time Since High Blood Pressure Diagnosis	
1–5 years ago	120 (46.5%)
6–10 years ago	58 (22.5%)
More than 10 years ago	80 (31.0%)
Smoking Status	
Ex-smoker	22 (8.5%)
Non-smoker (smoked fewer than 100 cigarettes in lifetime)	72 (27.9%)
Current Smoker	164 (63.6)

The survey found that participant preferences were generally consistent with what would be expected. For instance, larger decreases in cardiovascular risk were preferred to lower risk, less pills were preferred to more pills, and lower risk of side effects was preferred to higher risk.

Figure 28 shows a bar graph of patient preferences where the larger the bar length on the graph, the more preferred that attribute level was, as measured in utility space.



*Utility is gained for movements to the right of the reference level line. **** p<0.001, ** p<0.01, * p<0.05.*
Abbreviations: MLE = maximum likelihood estimate; SE = standard error; CI = confidence interval

Figure 28. Patient Preference Survey DCE results

The MAR calculations in Table 25 show patient willingness to undergo a uRDN procedure. For each cell in the table, the amount that the attribute would need to be reduced for the respondent to accept switching from pills to uRDN, all else equal, is shown. For example, to be willing to undergo the renal denervation procedure, a respondent of this survey would need to be able to reduce the number of pills by at least 1.33 per day (all else equal).

Table 25. Maximal Acceptable Risk Calculations

10-year CV risk (%) [95% CI)	Number of pills per day [95% CI)	Risk of mild-to-moderate side-effects requiring more doctor visits (%) [95% CI)	Risk of serious side-effects requiring hospitalization (%) [95% CI)	Risk of serious side-effects requiring procedure (%) [95% CI)
-6.54 [-8.79; -4.28]***	-1.33 [-1.81; -0.85]***	-19.15 [-26.44; -11.87]***	-16.82 [-24.14; -9.50]***	-10.47 [-15.16; -5.79]***

Significance: *** p<0.001, ** p<0.01, * p<0.05. Abbreviations: DCE = discrete choice experiment; MXL = Mixed logit; CI = confidence interval

Note: MRS can only be calculated for continuous attributes, hence treatment durability is omitted.

Overall, the study was conducted in alignment with the CDRH PPI guidance recommendations for these types of studies. The study analysis was consistent with published literature and followed good ethical research practices. While the study was discussed at a high-level with FDA, FDA did not agree with the final study methodology. The following concerns may bias the subjects in favor of uRDN:

Caveats with interpretation

- Study levels may not have been an adequate representation of the clinical data. Since the risks presented are relative to what else is present in the DCE, this may bias upwards the risk tolerance of the respondents. This is of concern regarding the clinical accuracy of the results, since one cannot interpolate for a level that was not presented.
    - While mild-to-moderate side effects were reflective of the procedure risks, the risk did not encompass the pill risks. For example, the "mild-to-moderate side effects requiring more doctor visits" attribute lists as the lowest level of risk 20%. While that may be accurate for the lowest risk of the procedure for renal denervation, one would expect a risk of pills closer to 0% - 10%. This is not adequate because the study can only be reflective of the space modelled through the attribute levels. Since respondents were choosing risk levels that were worse than what would be clinically relevant for pills, it may be overstating the actual risk level patients would find acceptable. If patients knew a lower risk was an option, their acceptable risk level would likely be lower.
    - The treatment durability of the uRDN procedure presented to respondents was longer than has yet been demonstrated in clinical trials. Therefore, respondents were presented with information not supported by evidence that could have biased their responses favorably toward uRDN.

FDA Comment: The Panel will be asked to provide input on the interpretation of these data to support the benefit-risk of the subject device.

9 Postmarket Study

ReCor plans to continue follow-up of all enrolled SOLO, TRIO, RADIANCE-II subjects, and they have initiated a Continued Access Study/Continued Access Protocol (CAP), which is designed to include patients similar to those enrolled in RADIANCE-II in one arm, and similar to those enrolled in TRIO in a separate arm. Additionally, they plan to initiate a US arm of the Global Paradise System Registry (US-GPS) that is currently ongoing in Europe and the UK. This study will be a multi-center, non-randomized, observational study to enroll 500 US subjects at up

to 100 study centers. Patients with uncontrolled hypertension, who may be inadequately responsive to, or who are intolerant to anti-hypertensive medications, are eligible. Eligible patients will be treated per the approved device labeling and followed for 60 months post procedure. The subjects in RADIANCE-II and the CAP will be transitioned to the GPS. Office blood pressure (BP) will be collected at all in-clinic visits and telemetric home BP, and patient reported outcomes (PRO) will be collected throughout the study.

Safety Assessments	The following events will be evaluated: The 30-day post-procedure incidence of: • All-cause mortality • Major vascular complications • Hospitalization for hypertensive crisis • Hospitalization for major cardiovascular- or hemodynamic-related events (e.g., heart failure; myocardial infarction, stroke) • Renal artery injury requiring an invasive intervention The 6-month, 12-month, and annual post-procedure incidence of: • All-cause mortality • New onset renal artery stenosis >70% • Significant decline in renal function defined as ≥50% increase in serum creatinine (mg/dL) • Hospitalization for hypertensive crisis • Hospitalization for major cardiovascular- or hemodynamic-related events (e.g., heart failure; myocardial infarction, stroke)
Effectiveness assessments	Effectiveness Assessments include but are not limited to: Primary Effectiveness Assessments: • Change in average home systolic blood pressure in mmHg [baseline to 3 months post-procedure] • Change in average office systolic blood pressure in mmHg [baseline to 3 months post-procedure**]** • Change in average home diastolic blood pressure in mmHg [baseline to 3 months] • Change in average office systolic blood pressure in mmHg [baseline to 3 months] Secondary Effectiveness Assessments: • Change in average home systolic/diastolic blood pressure in mmHg [baseline to 1, 6, 12, 24, 36, 48 & 60 months] • Change in average office systolic/diastolic blood pressure in mmHg [baseline to 1, 6, 12, 24, 36, 48 & 60 months] • Change in home and office heart rate at 1, 3 6, 12, 24, 36, 48 & 60 months • Change in home and office pules pressure at 1, 3, 6, 12, 24, 36, 48 & 60 months • Change in number of antihypertensive medications taken from baseline • Change in quality-of-life score • Percentage of subjects who are controlled as measured by office blood pressure (control defined as <140/90 mmHg and < 130/80 mmHg) and home blood pressure (control defined as < 135/85 mmHg)

Subgroup Analysis	Assuming sufficient patient numbers, post-hoc analysis of effectiveness may be evaluated in specific subgroups including but not limited to: • Sex • Race (Black versus non-black) • Age • Baseline Office systolic BP • Baseline Home systolic BP • Heart Rate • Abdominal obesity • Body Mass Index • eGFR • Heart Failure (NYHA I, II, III, IV) • Isolated Systolic Hypertension • Diabetes • Number and class of antihypertension medications

FDA comment: The Panel will be asked to comment on the proposed post-approval study (PAS) elements including study design, sample size, patient population, and the need to measure ABPM.

10 Conclusions

This Executive Summary provides a review of hypertension treatment, a description of the subject device, and a review of the three RADIANCE clinical studies (RADIANCE-HTN SOLO, RADIANCE-HTN TRIO, and RADIANCE-II). Based on the information provided, the sponsor is requesting that this device be approved and indicated to reduce blood pressure in patients with uncontrolled hypertension, who may be inadequately responsive to, or who are intolerant to anti-hypertensive medications

The three clinical studies were prospective, sham-controlled RCTs to evaluate the safety and effectiveness of the Paradise System in subjects with mild-to-moderate hypertension (SOLO, RADIANCE-II) and patients with resistance to anti-hypertensive medications (TRIO). The pooled safety event rate (including composite MAEs through 30 days and new-onset RAS through 6 months) was 1.1% with a 95% confidence interval of 0.3%-2.75%, which met the pre-specified performance goal of 9.8%. Available safety data through longer time points do not raise concerns, but long-term data are limited.

The Off-Med SOLO and RADIANCE-II trials met their primary effectiveness endpoints for baseline adjusted difference of daytime ASBP at 2 months with larger reductions in uRDN versus Sham with a mean difference in reduction of 6.3 mmHg favoring uRDN ($p<0.0001$). The On-Standardized Med TRIO trial did not meet its primary effectiveness endpoint with a mean difference reduction of 4.5 mmHg favoring uRDN ($p=0.0809$). Because TRIO outcomes followed a non-normal distribution, a baseline adjusted ANCOVA on the ranks was assessed ($p=0.0223$). In a supportive analysis, the median difference in reduction (median of all pairwise differences of BP reduction) was 4.5 mmHg favoring uRDN. However, the difference in BP reduction between uRDN and Sham Control subjects was reduced once patients were unblinded

and treated with antihypertensive medications to a BP goal (<140 mmHg SBP). While the Sham group trended toward a higher medication burden at later timepoints, the clinical significance of this observation is unclear. There are limited data on the durability of BP reduction associated with uRDN.

Because of the importance of this clinical condition and FDA's desire to bring novel treatments to patients, we are seeking the Panel's input on the assessment of benefits and risks of this device. FDA is seeking Panel input before rendering a final decision on the submission as to whether the information provided demonstrates a reasonable assurance of safety and effectiveness as defined in 21 CFR 860.7(d)(l) and (e)(l). The evidence must show that when using the device properly, the evidence supports that in a significant portion of the target population, there is an absence of unreasonable risks (safety), and that there are clinically significant results in a significant portion of the target population (effectiveness).

FDA is also seeking Panel input on the device labeling and post-approval study (PAS) design (if the device is approved). Device labeling should include information relevant to the safe and effective use of the device along with associated warnings and precautions that should be considered prior to treatment. In addition, the PAS patient population should reasonably reflect the diversity of the population of patients with uncontrolled HTN.

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12 Appendices

Appendix 1. December 2018 FDA Advisory Panel on renal denervation – Executive Summary
Appendix 2. Panel 24-hour summary
Appendix 3. HARC document
Appendix 4. Supplemental Clinical Data