FDA Executive Summary

Prepared for the August 23, 2023 Meeting of the
Circulatory System Devices Panel Meeting
to be held virtually

Premarket Application (PMA) for Pxxxxxx

Medtronic, Inc. Symplicity Spyral Renal Denervation System

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Pxxxxxx

Premarket Application for Medtronic's Symplicity Spyral 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.

Medtronic, Inc. is requesting their premarket application be approved in order to market their Symplicity Spyral Multi-electrode Renal Denervation (RDN) catheter and Symplicity G3 RF generator for blood pressure (BP) reduction in patients with hypertension (HTN), uncontrolled hypertension (HTN), despite the use of anti-hypertensive medications or in patients in whom blood pressure lowering therapy is poorly tolerated.

The PMA approval request is based primarily upon the results of the SPYRAL HTN-OFF and HTN-ON randomized trials with other studies and a global registry providing supplementary information. Both SPYRAL trials had a pilot phase with results pooled with a subsequent larger study using an adaptive Bayesian power prior approach.

HTN-OFF enrolled hypertensive patients whose medications could be discontinued at the start of the trial. The primary effectiveness endpoint was the mean difference in the baseline-adjusted 24-hour ambulatory systolic blood pressure (ASBP) from baseline to 3 months post-RDN or sham procedure. The study showed a statistically significant reduction of 3.9 mmHg ASBP in radiofrequency RDN (rfRDN) subjects vs Sham control subjects (posterior probability of success = 0.9996).

HTN-ON evaluated patients with uncontrolled HTN subjects with BP medications continued during the trial. The primary endpoint was the mean difference in the baseline-adjusted 24-hour ASBP at 6 months post-RDN or sham procedure. The study showed a non-significant 0.03 mmHg ASBP reduction in rfRDN subjects vs Sham control subjects (posterior probability of success = 0.508).

The primary safety endpoint was the rate of major adverse events at 30 days post-procedure and renal artery stenosis at 6 months in rfRDN-treated subjects pooled from SPYRAL HTN-OFF and HTN-ON. The safety event rate was 0.04%, which met the predefined safety endpoint performance goal of 7.1%.

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 Symplicity Spyral rfRDN 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 in 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 BP and 10 mmHg increase in diastolic BP were 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 blood pressures and diastolic BPs were associated with an increased risk of angina, myocardial infarction, heart failure, stroke, peripheral artery disease, and abdominal aortic aneurysm.

2.1 Defining Hypertension

HTN develops due to blood flow through the arteries at higher-than-normal pressures. Left untreated, HTN can lead to health problems, such as heart disease, stroke, kidney failure, vision loss, and other complications. Practice guidelines continue to be developed and revised 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 above target levels either when a patient is not using treatments to control BP or HTN persists despite treatment (treatment resistant HTN). Resistant HTN is defined as 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 >120mmHg associated with pulmonary edema, cardiac ischemia, neurologic deficits, and or renal failure.

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

2.2 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 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.

2.3 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 medication, such as other vasodilator classes and betablockers, may also be used; however, it remains unclear whether these agents reduce cardiovascular events similar to primary HTN agents, or they may have safety or tolerability concerns that reduce their primary use. 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 medication classes 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.

2.4 Physiology of Renal Denervation

Based on the complex physiology associated with HTN and BP control, HTN treatment devices have focused on a variety of treatment 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 afferent and efferent nerve fibers in the retroperitoneal space (see Figure 1) using radiofrequency or ultrasonic energy or chemical neurotoxins (e.g., ethanol, guanethidine). [14] [15] The subject device of the current PMA utilizes intraarterial catheters to deliver radiofrequency 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, stimulate renal vasodilatation, and increase 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.

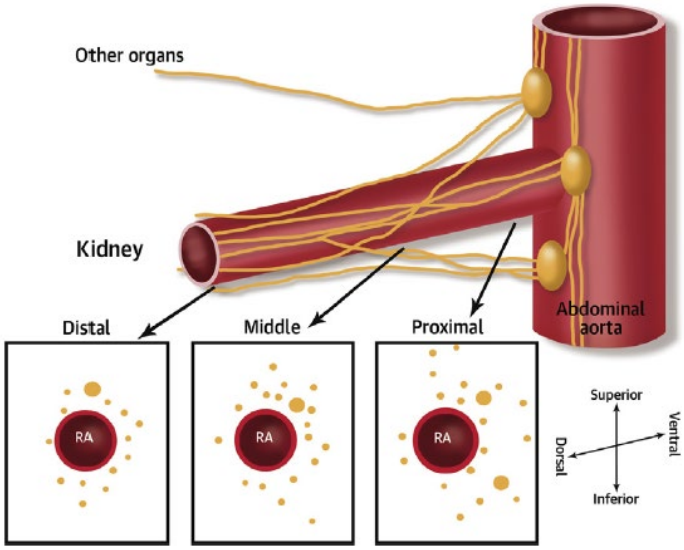


Figure 1. Graphical Illustration of Renal Artery and Circumferential Peri-Arterial Nerve Location

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 December 2018 FDA Advisory Panel on renal denervation (Appendix 1). In addition, 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 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. The frequency, timing, and extent of potential regeneration of renal sympathetic nerves following renal denervation remains unclear.

2.5 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 [20]. Recommendations 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). [21] 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 medication. "OFF" BP medication studies would evaluate patients who could tolerate withdrawal of BP medications to isolate the effects of the device by reducing confounders related to medication use (e.g., regimen variability, patient medication adherence/compliance). "ON" BP medication studies would evaluate how the device may function in a real-world setting with patients on BP medications. Data from both study designs could 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 (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 recommended 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 different hypertension trials to study and the effect of BP reduction on cardiovascular endpoints. [22] The study showed that a beneficial effect on reducing cardiovascular events was associated with an office SBP reduction of at least 4.6 mmHg.

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

3 Device Description

The Symplicity Spyral Renal Denervation System (Symplicity Spyral rfRDN System) is comprised of two main components: a single-use, disposable catheter (Symplicity Spyral multi-electrode renal denervation catheter, also referred to Symplicity Spyral catheter) and a reusable RF generator (Symplicity G3 Renal Denervation RF generator, also referred to as Symplicity G3 RF generator). An optional remote control and power cord are included with the generator.

The catheter connects to the generator using the integrated cable attached to the catheter handle. The catheter requires a 0.36 mm (0.014 in) guidewire for delivery. The catheter has an effective length of 117 cm and is compatible with a 6 Fr guide catheter. It is designed to treat vessels with diameters ranging from 3 mm to 8 mm. Figure 2 and Figure 3 how the catheter, which has 4 gold radiopaque electrodes at the spiral (helical) distal end. The electrodes are deployed into a spiral (helical) shape by partially retracting the guidewire proximal to the spiral section of the catheter. The catheter's treatment length (the distance between the most distal and proximal electrodes) is a function of the vessel diameter. A radiopaque marker is located 1 mm proximal to the catheter tip and assists positioning of the catheter using fluoroscopic guidance.

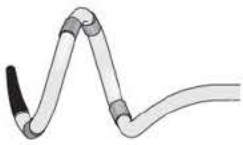


Figure 2. Helical Self-Expanding Electrode Array Assembly

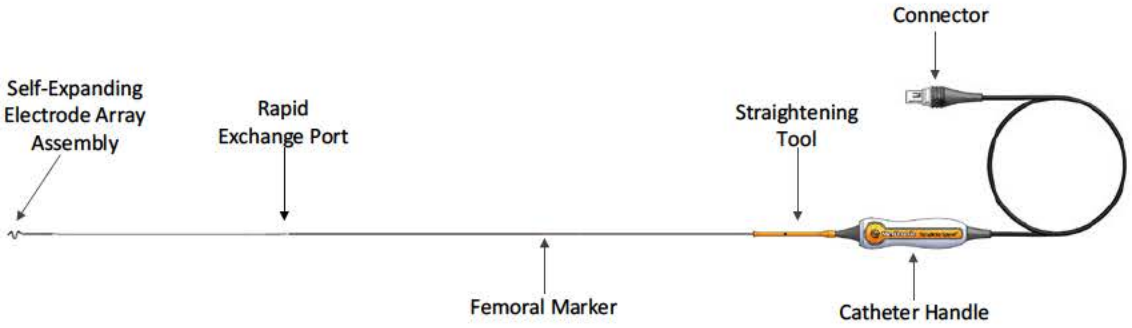


Figure 3. Symplicity Spyral Catheter

4 Proposed Indications for Use

The Sponsor's proposed indications for use of the rfRDN System is as follows:

> The Symplicity Spyral multi-electrode renal denervation catheter and the Symplicity G3™ RF Generator are indicated for the reduction of blood pressure in patients with uncontrolled hypertension despite the use of anti-hypertensive medications or in patients in whom blood pressure lowering therapy is poorly tolerated.

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

Medtronic studied an earlier version of their rfRDN device, the Symplicity Flex Renal Denervation System, outside the United States as well as under an Investigational Device Exemption (IDE) application. The first-in-man feasibility study (HTN-1) was an open-label, single-arm study of 153 subjects with systolic blood pressure (SBP) ≥160 mmHg on at least 3 BP medications (including a diuretic) at optimum doses. [23] At 6 months post-RDN treatment, 92% of patients had an office BP (OBP) reduction of ≥10 mmHg, with reductions in SBP and diastolic (DBP) of 25/11 mmHg, respectively ($p<0.0001$). Based on these results, Medtronic initiated HTN-2, a multi-center, prospective, open-label, randomized (1:1) study of rfRDN versus medical management in 106 patients with uncontrolled HTN. At 6 months, the mean OBP reduction in the rfRDN group was 32/12 mmHg vs. 1/0 mmHg in the medical management group ($p<0.0001$). [23] [24]

Medtronic then initiated the HTN-3 study, a multi-center, US randomized, sham-controlled (2:1) trial in 535 subjects (364 rfRDN, 171 Sham). In HTN-3 the primary safety endpoint was met, the primary and secondary effectiveness endpoints (reduction in office systolic BP (OSBP) and 24-hour ambulatory systolic BP (ASBP), respectively) were not met. [25] [26] At 6 months, the mean OSBP reduction in the rfRDN group was 14.1 ± 23.9 mmHg vs. 11.7 ± 25.9 mmHg in the Sham group (difference 2.39 mmHg, $p=0.26$). The mean 24-hour ASBP reduction was 6.8 ± 15.1 mmHg in the rfRDN group vs. 4.8 ± 17.3 mmHg in the Sham group (difference 1.96 mmHg favoring rfRDN, $p=0.98$). At 6 months, 101 of the Sham subjects crossed over to rfRDN. Medtronic postulated that failure to meet the effectiveness endpoints may have been due to incomplete ablation (a device design issue) and impact of BP medication changes during the trial. Drug testing was not conducted to measure compliance with antihypertensive medications.

Following HTN-3, Medtronic designed their rfRDN device with a spiral configuration of multiple RF electrodes intended to deliver more effective circumferential RDN. Additionally, the treatment method was modified to include more ablation to the distal and branch renal arteries to facilitate more effective denervation of the renal nerves.

Medtronic first evaluated the Symplicity Spyral rfRDN catheter under IDE (approved in 2013) in a multi-center, randomized, feasibility study in 70 subjects with symptomatic drug refractory paroxysmal atrial fibrillation and uncontrolled HTN. This study is complete. See Appendix 5 for additional information.

The IDE application for the Symplicity Spyral rfRDN System was approved in 2015 for the SPYRAL HTN-OFF and SPYRAL HTN-ON Pilot studies in patients with uncontrolled HTN. Following initial Pilot study results, the Expansion Cohorts for SPYRAL HTN-OFF and SPYRAL HTN-ON were approved in 2018. The Pilot and Expansion SPYRAL HTN-OFF and SPYRAL HTN-ON studies were prospective, global, multi-center, randomized, single-blind, sham-controlled trials designed to demonstrate safety and effectiveness of the rfRDN device. In 2021, Medtronic initiated the single arm continued access SPYRAL AFFIRM study in 700 subjects with uncontrolled HTN; this study is on-going.

In 2019, FDA approved the IDE for DYSTAL, a single-arm feasibility study to assess rfRDN treatment limited to distal renal arteries in 56 patients with uncontrolled HTN who were withdrawn from antihypertensive medications. This study is complete, and the results are discussed in Section 9.2.

In 2012, Medtronic initiated the Global SYMPLICITY Registry (GSR) as a prospective, multi-center, single arm, observational, and open-label registry to collect long-term safety and effectiveness of renal denervation in 5000 patients with uncontrolled HTN. The subjects are followed for a minimum of 1 year and a maximum of 5 years. The registry includes both versions of the rfRDN device (the Symplicity Flex and Spyral Systems, both CE Marked). The GSR is discussed further in Section 9.3.

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 March 2020. FDA determined that the Symplicity Spyral 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 HTN.

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 SPYRAL HTN-OFF and HTN-ON Clinical Studies Overview

HTN-OFF and HTN-ON were prospective, multi-center, sham-controlled, single-blinded randomized studies in the US, Canada, Japan, Europe, and Australia in patients with uncontrolled hypertension, defined as:

- OSBP ≥150 mmHg and <180 mmHg;
- ODBP ≥90 mmHg; and
- An average 24-hour ASBP ≥140 mmHg to <170 mmHg.

Patients were randomized to either rfRDN or a sham procedure and remained blinded through 6 months in the Expansion Cohorts or 12 months in the Pilot cohorts. A standardized procedure was used to target all accessible renal arterial vessels for rfRDN treatment, including branch vessels and accessory arteries with a diameter of 3-8 mm.

The safety and effectiveness of the Symplicity Spyral catheter was evaluated in two Pilot studies followed by two Expansion studies using an adaptive Bayesian power prior approach.

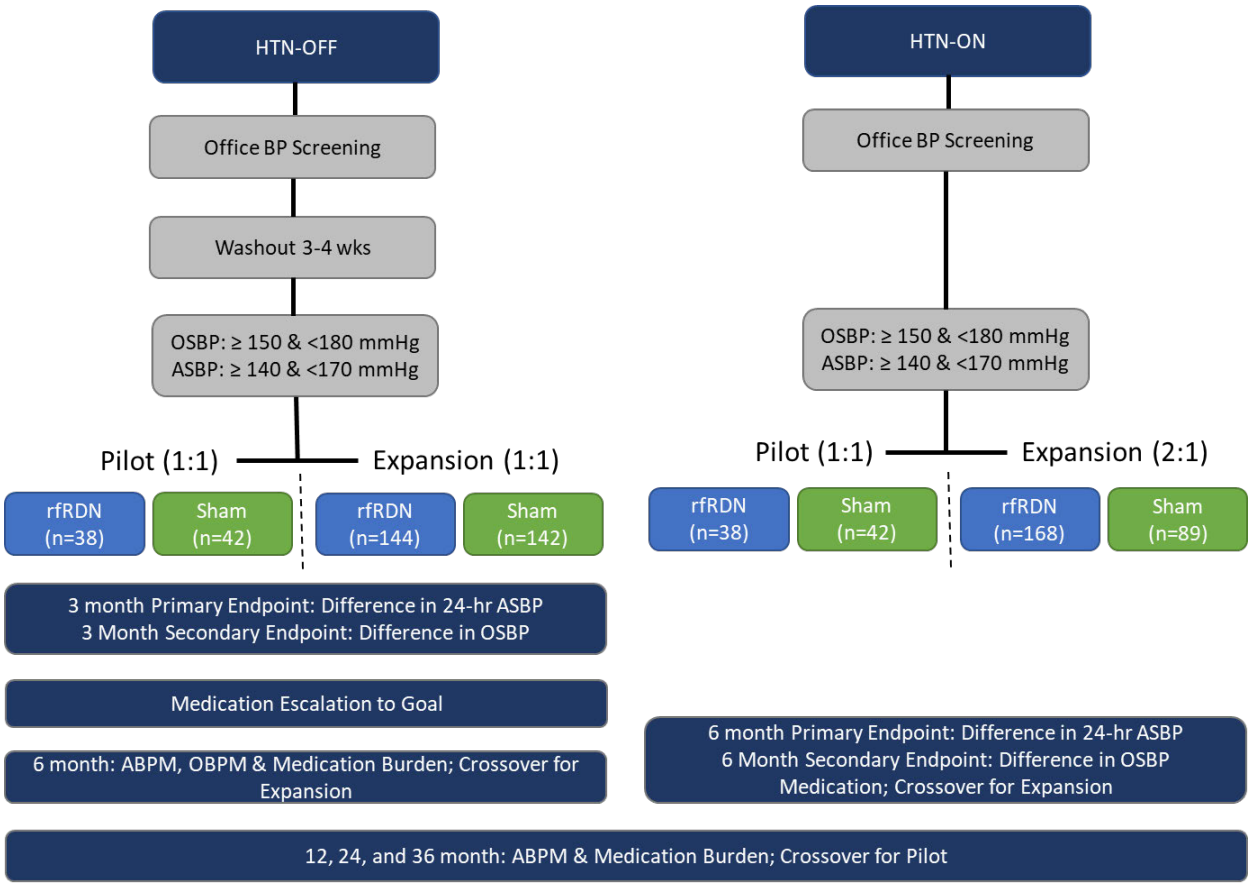
- HTN-OFF: Pilot Cohort followed by Expansion Cohort
- HTN-ON: Pilot Cohort followed by Expansion Cohort

The study cohorts and definition used in this executive summary are described in Table 2.

Table 2. Study Cohorts and Number of Subjects for HTN-OFF and HTN-ON

	HTN-OFF	**HTN-ON**
Pilot Cohort: Subjects enrolled in the pilot study	80	80
Expansion Cohort: Subjects enrolled following pilot study	251	257
Additional subjects enrolled following positive interim analysis	35	--
Primary (Bayesian) Cohort: Expansion + discounted Pilot	331 Based on Bayesian analysis	337 Based on Bayesian analysis
Full Cohort: All enrolled subjects	366	337

Figure 4 shows an overview of the SPYRAL HTN-OFF and SPYRAL HTN-ON trials. Twenty-four-hour ABP and OBP measurements were performed at 3 months, 6 months, 12 months, 24 and 36 months. Subjects will be followed through 3 years.



HTN: hypertension; BP: blood pressure; rfRDN: radiofrequency renal denervation; OSBP/ASBP: Office/ambulatory systolic BP
Note that the first 26 subjects in the HTN-ON Expansion cohort were randomized based on 1:1 fashion.

Figure 4. Overview of the SPYRAL Studies

Enrolled patient populations

- HTN-OFF: Evaluated subjects with uncontrolled HTN who could tolerate being off BP medications for several months (unless they met pre-specified escape criteria).
- HTN-ON: Evaluated subjects with uncontrolled HTN who remained on a stable medication regimen for 6 months post-procedure (unless they met prespecified escape criteria).

Antihypertensive medication use

- HTN-OFF: Patients taken off medications 3-4 weeks prior to randomization (or drug naïve patients) through 3-month post-procedure unless they met safety escape criteria: (OSBP ≥180 mmHg or safety concern). Subjects were treated with a guideline-based antihypertensive medication escalation protocol between 3 and 6 months post-randomization, if needed, to reach a goal of OSBP <140 mmHg.
- HTN-ON: Antihypertensive medications stable through 6 months, unless safety escape criteria met:

- OSBP ≥180 mmHg; or
- OSBP <115 mmHg and is associated with symptoms of hypotension.

Blinding for HTN-OFF and HTN-ON

- All studies blinded with sham procedure.
  - HTN-OFF and HTN-ON Pilot trials blinded for 12 months.
  - HTN-OFF and HTN-ON Expansion trials blinded for 6 months

6.1 Inclusion and Exclusion Criteria

Inclusion criteria for HTN-OFF and HTN-ON in Table 3

Table 3. Key Inclusion Criteria

	HTN-OFF	HTN-ON
Age	Individual is ≥20 and ≤80 years old at time of enrollment (consent).	
OBP	OSBP ≥150 mmHg and <180 mmHg ODBP ≥90 mmHg	
ABP[1]	24-hour SBP ≥140 mmHg and <170 mmHg	
Medication	Willing to discontinue antihypertensive medications at Screening Visit 1 through the three-month post-procedure visit	• On 1-3 antihypertensive medications at ≥50% maximal dose • Stable medication regimen for ≥6 weeks

[1] *ABP is considered valid if the number of successful daytime readings captured is ≥21 and the number of successful nighttime readings captured ≥12*
OBP: Office BP; ABP: Ambulatory BP; SBP: systolic BP; DBP: diastolic BP

Exclusion criteria for SPYRAL HTN-OFF and HTN-ON

- One or more of the following conditions:
  - Stable or unstable angina or MI within 3 months
  - Heart failure, stroke, TIA, or atrial fibrillation at any time (patients treated with catheter or surgical treatment for atrial fibrillation and in sinus rhythm not excluded)
- Prior renal denervation
- Renal artery anatomy ineligible for treatment (e.g., ineligible anatomy, calcification)
- Estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73m2, using the 4 variable MDRD calculation (in mL/min per 1.73 m2 = 175 x SerumCr-1.154 x age-0.203 x 1.212 (if patient is black) x 0.742 (if female))
  - eGFR calculation specific to Japanese patients used for subjects enrolled in Japan.
- Type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus with HbA1c >8.0%
- Use of SGLT2 inhibitors or GLP-1 agonists prescribed <90 days from Screening Visit 1 or plans not to remain on these drugs for the duration of the trial
- ≥1 episode(s) of orthostatic hypotension not related to medication changes within the past year or reduction of SBP of ≥20 mmHg or DBP of ≥10 mmHg within 3 minutes of

standing coupled with symptoms during the screening process
- Untreated secondary cause of hypertension (either known or suspected) or taking drugs that increase sympathetic tone and could contribute to hypertension
- Polycystic kidney disease, unilateral kidney, atrophic kidney, or history of renal transplant

6.2 Follow-up Schedule

The follow-up schedule for selected endpoints from the three studies is shown Table 4.

Table 4. Selected Follow-up Activities

	Screening	Baseline	Procedure	1M	3M	6M	12M	24-36M
OBPM	x	x		x	x	x	x	x
ABPM		x			x	x	x	
Duplex Ultrasound						x	x[1]	
CTA/MRA			x					
Drug testing		x			x	x	x	x
Blood chemistry		x		x	x	x	x	x
Quality of Life		x			x	x	x	x
Blinding assessment			discharge		x	x		

OBPM/ABPM: Office/ambulatory blood pressure measurement
[1] *Required for select number of subjects or if RAS is suspected*

Renal imaging notes
- Duplex ultrasound (DUS) required as first line imaging modality at 6 and 12 months (and at 24M and 36M as applicable).
- Repeat DUS, magnetic resonance angiography (MRA), computed tomography angiography (CTA), or angiogram used if DUS nondiagnostic.
- Renal angiography performed (and study sent to the angiographic core lab) if repeat DUS/CTA/MRA nondiagnostic or stenosis >60-70% suspected or found
- 6M DUS not required for subjects crossing over from Sham to rfRDN
- If initial or subsequent imaging non-diagnostic, the investigator chose the repeat imaging modality (DUS or MRA) expected to yield the required information.

6.3 Statistical Analysis Population

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.

- **Intent-to-Treat (ITT)** cohort: Subjects analyzed according to their randomized assignment.
  - BP in subjects meeting BP medication escape criteria (OSBP ≥180 mmHg or <115 mmHg associated with symptoms of hypotension or safety concerns requiring

medication changes recorded using last observation carried forward (LOCF) for BP measurements.

- **Per Protocol (PP)**: Randomized subjects with BP medication compliance based on blood/urine testing at follow-up compared with prescribed antihypertensive medications at baseline, excluding those that did not meet selected inclusion/exclusion criteria, did not meet BP escape criteria, and did not receive their randomized treatment assignment.
- **As Treated (AT)**: Randomized subjects according to the actual treatment received.
  - BP in subjects meeting BP medication escape criteria (OSBP ≥180 mmHg or <115 mmHg associated with symptoms of hypotension or safety concern requiring medication changes) recorded using last observation carried forward (LOCF) for BP measurements.
- **Crossover (CO)**: Subjects who received rfRDN treatment after being randomized to the Sham control group. Crossover was allowed after 6-months follow-up or 12 months follow-up.

6.4 Study Endpoints

6.4.1 Primary Safety Endpoint

The pre-specified primary safety analysis is a pooled analysis of first 253 evaluable rfRDN-treated subjects from the SPYRAL HTN-OFF and SPYRAL HTN-ON trials, defined as a patient-level composite of the incidence of the following major adverse events (MAEs):

- 1-month post-randomization adjudicated by the clinical events committee
  - All-cause mortality
  - End stage renal disease (ESRD)
  - Significant embolic events resulting in end-organ damage
  - Renal artery perforation requiring intervention
  - Renal artery dissection requiring intervention
  - Vascular complications (e.g., complications that require surgical repair, interventional procedures, thrombin injection or blood transfusion)
  - Hospitalization for hypertensive crisis not related to non-adherence with BP medications or the study protocol

And

- Renal artery stenosis (RAS) at 6 months, as defined as >70% diameter stenosis by angiography confirmed by the angiographic core lab

The imaging protocol is described in Section 7.3. Briefly, renal artery narrowing would have been first identified by protocol-driven Doppler Ultrasound (DUS) or other imaging modalities. Only stenosis confirmed by renal angiography was considered for the primary endpoint.

Events for the composite MAE were adjudicated by the Clinical Events Committee (CEC).

A performance goal of 7.1% for the primary safety endpoint was derived from a literature review of event rates for renal interventions, such as renal stenting. The primary safety null and alternative hypotheses are:

$$H_0: \pi \geq 7.1\%$$

$$H_a: \pi < 7.1\%$$

where π is the MAE rate for patients undergoing renal denervation. Under the assumption that the true rate is 3.5%, and using a one-sided 0.05 level of significance, an evaluable sample size of 253 renal denervation patients yields 80% power to reject the null hypothesis in favor of the alternative. The exact binomial test was used for the sample size calculation for the primary safety endpoint hypothesis.

6.4.2 Primary Effectiveness Endpoint

The primary effectiveness endpoints for HTN-OFF and HTN-ON are the following evaluated on the ITT population of the Primary Cohort using a Bayesian power prior approach (see Section 6.4.4):

- HTN-OFF: Change in SBP from baseline to 3-months post-procedure (prior to restarting BP medications) measured by 24-hour ABPM
- HTN-ON: Change in 24-hour SBP from baseline to 6-months post-procedure measured by 24-hour ABPM

See Section 6.4.4 for more detail on that statistical plan.

6.4.3 Secondary Endpoints

Powered Secondary Effectiveness Endpoint for HTN-OFF

- Change in office SBP from baseline to 3 months post-procedure compared between treatment groups using a Bayesian linear regression model

Secondary Effectiveness Endpoints for HTN-OFF and HTN-ON

- Change in SBP from baseline (screening visit 2) to 3, 6, 12, 24, and 36 months post-procedure measured by 24-hour ABPM
- Change in office SBP from baseline (screening visit 2) to 1, 3, 6, 12, 24, and 36 months post-procedure
- Rate of achieving target OBP (SBP <140 mmHg) at 1, 3, 6, 12, 24, and 36 months post-procedure
- Change in office DBP from baseline (screening visit 2) to 1, 3, 6, 12, 24, and 36 months post-procedure
- Change in DBP from baseline (screening visit 2) to 3, 6, 12, 24 and 36 months post-procedure measured by 24-hour ABPM
- Quality of life (QOL) assessed by EQ5D and SF36 (HTN-OFF only)

Secondary Safety Endpoints for HTN-OFF and HTN-ON

- Acute procedural events at 1-month post-procedure (rfRDN vs. Sham subjects) at 1 month post-procedure:
    - Significant embolic event resulting in end-organ damage
    - Renal artery perforation or dissection requiring intervention
    - Vascular complications
    - End-stage renal disease
    - ≥40% decline in eGFR
    - New MI or stroke
    - Renal artery re-intervention
    - Major bleeding per the TIMI definition (intracranial hemorrhage, ≥5g/dl decrease in hemoglobin concentration, ≥15% absolute decrease in hematocrit, or death due to bleeding within 7 days of the procedure)
    - Increase in serum creatinine >50% from Screening Visit 2
    - Renal artery stenosis (>70% diameter stenosis) confirmed by angiography and determined by the angiographic core laboratory
    - Hospitalization for hypertensive crisis not related to non-adherence with BP medications or study protocol
- Chronic safety endpoints at 3, 6, 12, 24, and 36 months post-procedure (rfRDN vs. Sham subjects)
    - All-cause mortality
    - End-stage renal disease
    - Significant embolic event resulting in end-organ damage
    - ≥40% decline in eGFR
    - New MI or stroke
    - Renal artery re-intervention
    - Major bleeding per the TIMI definition
    - Increase in serum creatinine >50% vs. screening visit 2
    - Renal artery stenosis (>70% diameter stenosis confirmed by angiography and determined by the angiographic core laboratory (at 6 and 12 months only, or if renal artery imaging was performed outside of the protocol-specified windows)
    - Hospitalization for hypertensive crisis not related to non-adherence with BP medications or the study protocol
- RAS through 12-month based on CTA/MRA imaging. Sub-study on at least 150 patients who underwent rfRDN (in either HTN-OFF or HTN-ON studies) to assess extent of renal artery damage, including diameter stenosis <70%.

6.4.4 Adaptive Bayesian Design

HTN-OFF and HTN-ON designed as adaptive Bayesian trials with informative priors (data from the HTN-OFF and HTN-ON Pilot studies, respectively).

HTN-OFF Adaptive Design and Interim Analysis

- Expansion cohort interim analyses could be performed at 210, 240, and 300 evaluable subjects to determine if the enrollment could be stopped.

- HTN-OFF enrollment was stopped after the first interim analysis.

HTN-ON Adaptive Design and Interim Analysis

- Expansion cohort interim analyses could be performed at 110, 149, and 221 evaluable subjects to determine if the enrollment could be stopped.
- HTN-ON enrollment continued to full enrollment (257 subjects).

Bayesian Power Prior Methodology for HTN-OFF and HTN-ON

A Bayesian power prior discount function approach was employed to develop the informative prior distribution for the unknown parameters, using Pilot cohort outcomes (BP measurements). See Appendix 4 and Böhm, et al. (2020) [27], for more detail on the methodology. Briefly, the method determines the amount of prior information (Pilot cohort outcomes) to be borrowed based on the similarity of the Pilot cohort outcomes to the Expansion cohort outcomes.

- Under the adaptive procedure, if the available Expansion cohort outcomes diverge from the prior Pilot cohort outcomes at an interim analysis, a larger discount is applied to the Pilot cohort outcomes, resulting in continued enrollment to maintain the study power to meet the endpoint.
- Alternatively, if the Pilot cohort outcomes and the available Expansion cohort outcomes are similar, a smaller discount is applied to the Pilot cohort outcomes, and fewer prospective patients would be needed to maintain the study power.
- The power prior discount parameter (α) ranges from 0 to 1.
    - Discount parameter equal to 1.0 means the outcomes are very similar, and all outcomes from both the Pilot and Expansion cohorts are used.
    - On the other hand, a discount parameter equal to 0.1 means that the outcomes are very different and less information of Pilot cohort can be used with the Expansion cohort.
    - See Figure 5 from Böhm, et al. (2020). The posterior is the final estimate based on the current outcomes and a discounted prior based on similarity.

This analysis method was prespecified for the primary effectiveness endpoint for HTN-OFF and HTN-ON and the powered secondary effectiveness endpoint for HTN-OFF. In this executive summary, the analyzed cohort is referred to as the Primary (Bayesian) cohort for HTN-OFF and HTN-ON studies.

As the dynamic borrowing method is novel, FDA also asked for sensitivity analyses to be performed using the more common frequentist approach (using all subjects) for each cohort.

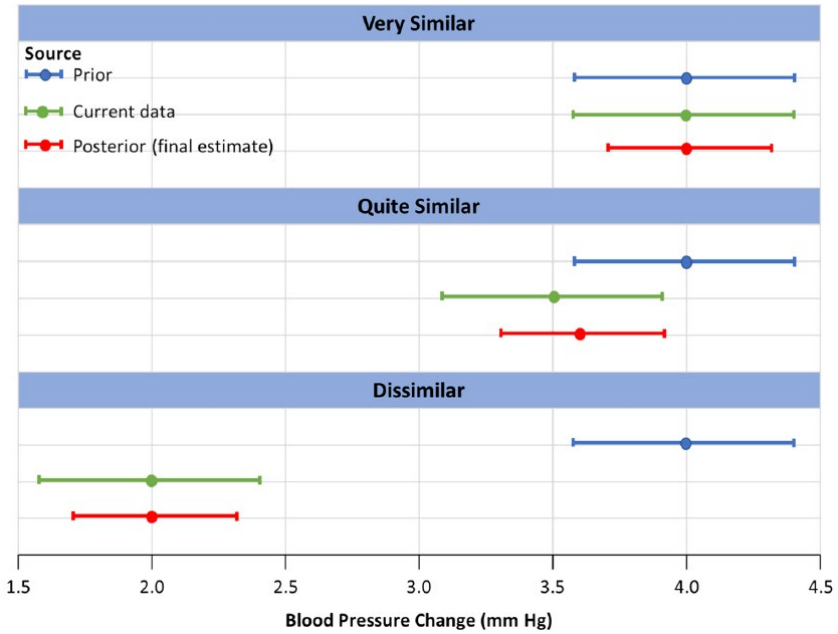


Figure 5. Diagrammatic Illustration of Bayesian Discount Prior Methodology [27]

6.4.5 Subgroup analyses

The primary effectiveness endpoint was analyzed for the following subgroups:

- Age, gender, and ethnicity/race
- Geography (US and non-US)
- Diabetes mellitus
- eGFR < 60 vs. ≥ 60 (mL/min/1.73 m2)
- Obstructive sleep apnea
- Number, duration, and location of ablations
- Medication adherence at 3 months (HTN-OFF) and 6 months (HTN-ON) post-procedure
- Tertiles of baseline ASBP, OSBP, and heart rate

6.4.6 Blinding Assessment

A blinding assessment for the subjects and BP assessors was performed at post-procedure discharge, 3 months, and 6 months.

- The James Blinding Index was completed, and the index ranges from 0 to 1.
  - 0: all patients correctly guessed their study-group assignments
  - 1: all patients incorrectly guessed their study-group assignments
  - Index values >0.5 indicating successful blinding.
- After the 6-month follow-up, subjects were unblinded and Sham subjects were allowed to cross over.

6.4.7 Medication Burden Index Analysis

Medication burden index calculated at 6, 12, 24 and 36-months.

- At 6 months, rfRDN and control groups compared.
- At 12, 24 and 36 months, rfRDN plus crossover subjects compared to non-crossover controls.

Two of the pre-specified medication burden index methods used by the Sponsor are as follows:

- Medication Index 1: A composite index based on the doses of prescribed BP medications (sum of the ratio of the current daily dosage divided by the maximum JNC7 recommended daily dosage for each medication), according to the following equation:

$$MedIndex1 = \sum_{AH\ Meds} (class\ weight \frac{prescribed\ dose}{standard\ dose})$$

- Medication Index 2: A composite index based on the number and doses of BP medications, according to the following equation:

$$MedIndex2 = \#\ of\ AH\ Meds \times \sum_{AH\ Meds} (class\ weight \frac{prescribed\ dose}{standard\ dose})$$

FDA Comment: HARC authors (Appendix 3) noted that medication indices should account for both number and dose of prescribed medications, and reference Medication Index 1 (Med Index 1) [28], which has been used in prior studies [29]. Medication Index 2 (Med Index 2) is novel. Med Index 1 has been independently validated and is linear, which allows for a straightforward clinical interpretation (0.25 = ¼ of a full dose), whereas Med Index 2 is non-linear and small changes can lead to larger differences in the results, as shown in the example table below.

Patient	Original Dose	Med Index 1	Med Index 2	Change in Dose #2	New Med Index 1	New Med Index 2
1	½ dose of 1 med	0.5	0.5	½ dose of new med	1	2
2	½ dose of 2 meds	1	2	½ dose of new med	1.5	4.5
3	½ dose of 3 meds	1.5	4.5	½ dose of new med	2	8

Because of its use on in prior studies, FDA recommended use of Med Index 1 as the primary analysis of medication burden; Medtronic chose Med Index 2 as the primary analysis. The Panel will be asked to discuss the strengths and limitations of the two medication burden analysis methods and their clinical implications.

6.4.8 Additional Analyses

These following two analyses were added into the protocol later during the clinical study and after data for the Pilot cohorts and interim data were available.

Win-ratio Analysis (HTN-ON Study Only)

The Win-ratio compares subjects pairwise on multiple endpoints ranked in order of importance. Each subject pair (one rfRDN and one Sham) is compared to determine a winner or a tie. The Win-ratio endpoints are intended to be clinically meaningful and the hierarchy reflects their clinical importance.

The Win-ratio for the HTN-ON study analysis included the two endpoint comparisons below between rfRDN and Sham subject pairs. The medication index was only compared if the SBP comparison resulted in a tie. The hierarchical comparisons included:

- Comparing the 24-hr SBP change at 6 months with threshold difference of >5 mmHg;
- Comparing the change in Medication Index 2 from baseline.

Percentage Time in Target Range (TTR)

TTR is a recently developed measure of BP control effectiveness and is defined as the percentage of time BP was in the therapeutic range within the TTR time interval.

- Therapeutic range: OSBP ≤140 mmHg or 24-hour ASBP ≤130 mmHg, using the maximum SBP value
- TTR% is calculated by linearly interpolating the BP between measurement times.
- TTR% calculated at 3 (HTN-OFF only), 6, 12, 24, and 36 months using baseline BP measurement.

7 SPYRAL HTN Study Results

7.1 SPYRAL HTN-OFF Results

The HTN-OFF Pilot Cohort initiated enrollment June 25, 2015, and the Expansion Cohort completed enrollment February 3, 2020. Subjects will be followed through 3 years.

7.1.1 Subject Accountability

Figure 6 shows subject accountability through 12 months for the HTN-OFF Full Cohorts, including the crossover group which received treatment at 6 months post procedure.

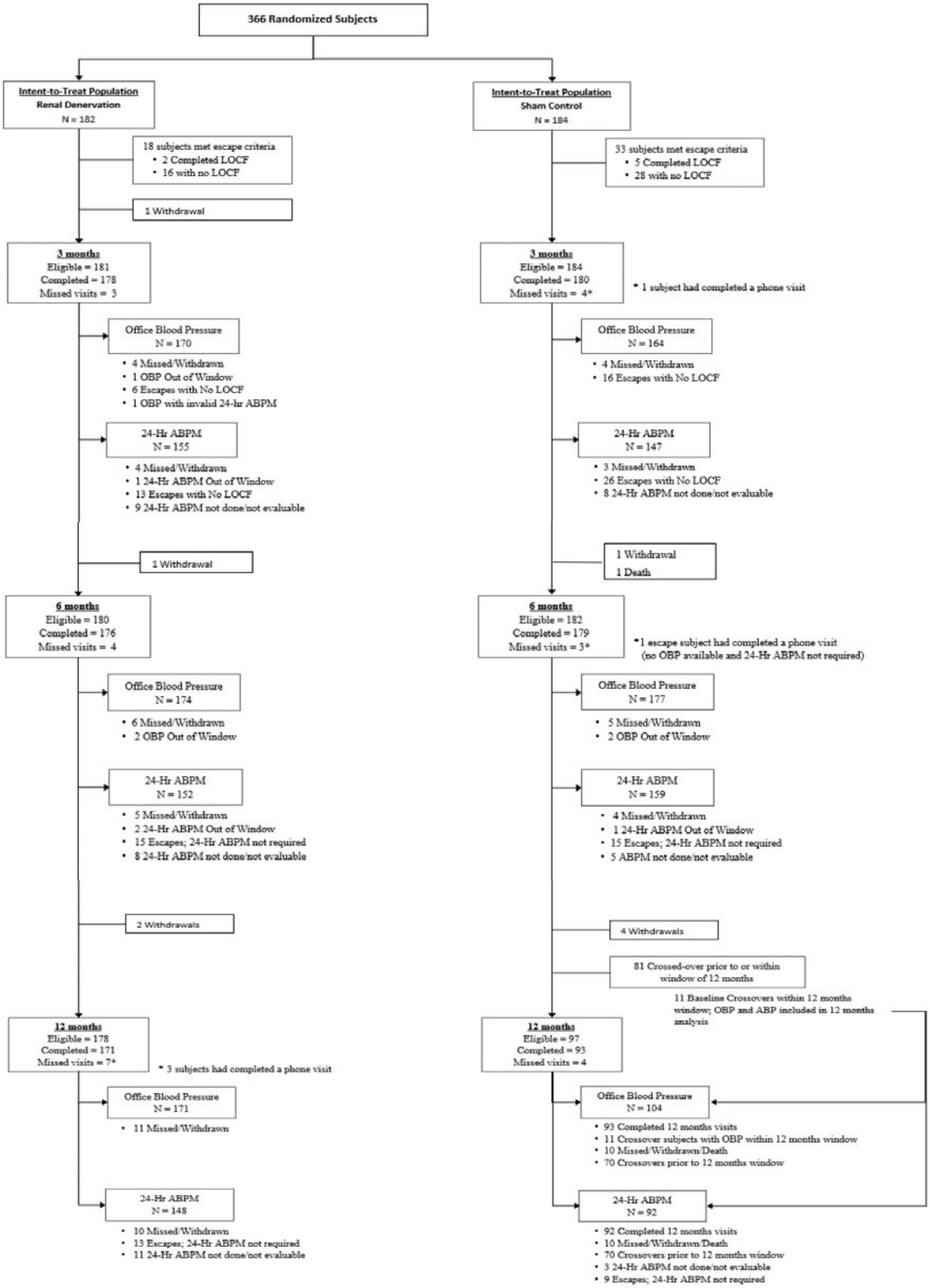


Figure 6. Subject Accountability through 12 Months for HTN-OFF Full Cohort

7.1.2 Baseline Characteristics

Baseline HTN-OFF subject characteristics are shown in Table 5, and baseline BPs are shown in Table 6. Baseline characteristics were well-balanced between the rfRDN and Sham groups and between Pilot and Expansion Cohorts.

Table 5. HTN-OFF Select Baseline Characteristics

	Pilot Cohort		**Expansion Cohort**		**Full Cohort (Pilot + Expansion + Add'l Subjects)**	
Subject Baseline Characteristic	**rfRDN (N=38 Subjects)**	**Sham (N=42 Subjects)**	**rfRDN (N= 128 Subjects)**	**Sham (N= 123 Subjects)**	**rfRDN (N=182 Subjects)**	**Sham (N=184 Subjects)**
Age (yrs)	55.8 ± 10.1	52.8 ± 11.5	51.4 ± 10.9	52.5 ± 10.0	52.5 ± 10.8	52.7 ± 10.1
Male	68.4% (26/38)	73.8% (31/42)	63.3% (81/128)	66.7% (82/123)	64.3% (117/182)	69.6% (128/184)
Length of hypertension diagnosis >5 yrs	60.5%	42.9%	53.9%	58.5%	56.1%	56.0%
Geography						
US	34.2% (13/38)	34.2% (13/38)	55.5% (71/128)	52.8% (65/123)	50% (91/182)	46.2% (85/184)
OUS	64.8% (25/38)	64.8% (25/38)	44.5% (57/128)	47.2% (58/123)	50% (91/182)	53.8% (99/184)
Race						
White	26.3% (10/38)	23.8% (10/42)	28.9% (37/128)	32.5% (40/123)	30.8% (56/182)	32.6% (60/184)
Black or African American	13.2% (5/38)	11.9% (5/42)	24.2% (31/128)	21.1% (26/123)	20.3% (37/182)	17.4% (32/184)
Asian	2.6% (1/38)	2.4% (1/42)	3.9% (5/128)	0.8% (1/123)	3.8% (7/182)	1.1% (2/184)
Japanese from Japan	5.3% (2/38)	4.8% (2/42)	0.8% (1/128)	0.0% (0/123)	1.6% (3/182)	1.1% (2/184)
Not reportable per local laws or regulations	52.6% (20/38)	57.1% (24/42)	41.4% (53/128)	44.7% (55/123)	42.9% (78/182)	47.3% (87/184)
Other	0.0% (0/38)	0.0% (0/42)	0.8% (1/128)	0.8% (1/123)	0.5% (1/182)	0.5% (1/184)
Hispanic/Latino/Spanish origin						
Yes	2.6% (1/38)	2.4% (1/42)	3.1% (4/128)	1.6% (2/123)	2.7% (5/182)	2.2% (4/184)
No	44.7% (17/38)	40.5 (17/42)	54.7% (70/128)	53.7% (66/123)	53.8% (98/182)	50.5% (93/184)
Not reportable per local law or reg	52.6% (20/38)	57.1% (24/42)	41.4% (53/128)	44.7% (55/123)	42.9% (78/182)	47.3% (87/184)
Unknown	0.0% (0/38)	0.0% (0/42)	0.8% (1/128)	0.0% (0/123)	0.5% (1/182)	0.0% (0/184)
BMI	29.8 ± 5.1	30.2 ± 5.1	31.5 ± 6.1	31.1 ± 5.6	31.2 ± 6.0	31.0 ± 5.5

	Pilot Cohort		Expansion Cohort		Full Cohort (Pilot + Expansion + Add'l Subjects)	
Subject Baseline Characteristic	**rfRDN (N=38 Subjects)**	**Sham (N=42 Subjects)**	**rfRDN (N= 128 Subjects)**	**Sham (N= 123 Subjects)**	**rfRDN (N=182 Subjects)**	**Sham (N=184 Subjects)**
Diabetes Mellitus Type 2	2.6% (1/38)	7.1% (3/42)	3.9% (5/128)	4.9% (6/123)	4.4% (8/182)	6.0% (11/184)
Current Smoker	10.5% (4/38)	23.8% (10/42)	18.8% (24/128)	13.8% (17/123)	17.0% (31/182)	15.8% (29/184)
Obstructive sleep apnea	7.9% (3/38)	7.1% (3/42)	8.6% (11/128)	7.3% (9/123)	8.2% (15/182)	7.1% (13/184)
History of coronary artery disease*	0.0% (0/38)	4.8% (2/42)	0.0% (0/128)	4.9% (6/123)	0.0% (0/182)	4.3% (8/184)
History of stroke / transient ischemic attack*	5.3% (2/38)	0.0% (0/42)	0.0% (0/128)	0.0% (0/123)	1.1% (2/182)	0.0% (0/184)
Peripheral Artery Disease	2.6% (1/38)	0.0% (0/42)	0.0% (0/128)	0.0% (0/123)	0.5% (1/182)	0.0% (0/184)

Data displayed as % (n/N)
* *Occurring > 3 months before randomization*

Table 6. Baseline Blood Pressure – HTN-OFF Full Cohort

	Pilot Cohort		Expansion Cohort		Full Cohort (Pilot + Expansion + Add'l Subjects)	
Subject Baseline Blood Pressure (mmHg)	**rfRDN (N=38 Subjects)**	**Sham (N=42 Subjects)**	**rfRDN (N=128 Subjects)**	**Sham (N= 123 Subjects)**	**rfRDN (N=182 Subjects)**	**Sham (N=184 Subjects)**
Office measurements						
Systolic blood pressure	162.0 ± 7.6	161.4 ± 6.4	162.9 ± 7.9	163.4 ± 7.8	162.8 ± 7.8	163.2 ± 7.7
Diastolic blood pressure	99.9 ± 6.8	101.5 ± 7.5	101.6 ± 7.0	102.2 ± 7.0	101.1 ± 7.1	102.2 ± 7.3
24-hour measurements (ABPM)						
Mean systolic blood pressure	153.4 ± 9.0	151.6 ± 7.4	150.8 ± 7.7	150.8 ± 7.5	151.2 ± 7.9	151.3 ± 7.6
Mean diastolic blood pressure	99.1 ± 7.7	98.7 ± 8.2	97.6 ± 7.7	99.2 ± 7.2	97.6 ± 7.9	99.3 ± 7.5

Data displayed as mean ± SD

7.1.3 Procedural Characteristics

Table 7 shows HTN-OFF procedural characteristics for pooled Pilot and Expansion subjects along with Crossovers. As expected, mean procedure time and contrast volume for rfRDN subjects were greater vs. Sham. Pain medication requirements were significantly greater in the rfRDN group.

Table 7. Procedural Characteristics – HTN-OFF Full Cohort

	rfRDN (N=182 subjects)	Sham (N=184 subjects)	Crossover (N=125 subjects)
Procedure Time[1] (min)	99.3 ± 36.2	52.9 ± 16.6	80.2 ± 26.1
Denervation Time[2] (min)	59.7 ± 24.3	--	53.1 ± 19.1
Amount of Contrast used (cc)	207.8 ± 96.1	74.1 ± 37.4	171.2 ± 75.5
Intra-procedural medication			
Pain meds	29.7% (54/182)	17.4% (32/184)	24.8% (31/125)
Sedatives/Anxiolytics	100.0% (182/182)	98.4% (181/184)	96.8% (121/125)
Atropine	2.2% (4/182)	0.0% (0/184)	3.2% (4/125)
Hospital Stay (days)	1.0 ± 0.1	1.0 ± 0.2	1.0 ± 0.2
Device success[3]	100.0% (181/181)	--	100.0% (125/125)
Procedure success[4]	100.0% (181/181)	--	100.0% (125/125)
Total number of ablations Main Artery Level (treatments to main artery)	8.8 ± 4.8 (Right Main) 7.5 ± 3.9 (Left Main) 8.1 ± 4.4 (Main Total) 13.2 ± 9.5 (Right Branch) 12.1 ± 8.6 (Left Branch) 12.7 ± 9.1 (Branch Total)	--	8.4 ± 3.9 (Right Main) 7.2 ± 3.8 (Left Main) 7.8 ± 3.9 (Main Total) 14.0 ± 9.7 (Right Branch) 11.8 ± 9.5 (Left Branch) 12.9 ± 9.6 (Branch Total)
Total number of ablations Kidney Level (treatments to all arteries)	9.8 ± 6.4 (Right Main) 8.4 ± 5.4 (Left Main) 18.2 ± 9.7 (Main Total) 14.8 ± 9.2 (Right Branch) 13.6 ± 8.2 (Left Branch) 28.4 ±15.1 (Branch Total)	--	9.2 ± 5.2 (Right Main) 8.6 ± 5.9 (Left Main) 17.8 ± 8.8 (Main Total) 15.4 ± 9.2 (Right Branch) 14.1 ± 9.1 (Left Branch) 29.4 ± 15.5 (Branch Total)

Data displayed as mean ± SD or % (n/N)
[1]Arterial closure – arterial access obtained
[2]Final Guide Catheter Removal – Initial Symplicity Spyral Catheter Insertion
[3]Successful delivery of any RF
[4]Successful delivery of any RF in the absence of in hospital MAE

7.1.4 Effectiveness Results

7.1.4.1 Powered Primary and Secondary Effectiveness

Primary Effectiveness Endpoint: The primary effectiveness endpoint was the baseline-adjusted change in SBP measured by 24-hour ABPM from baseline to 3-months post-procedure, compared between rfRDN and Sham groups in the Primary Cohort.

Powered Secondary Effectiveness Endpoint: Baseline adjusted change in OSBP from baseline to 3-months post-procedure, compared between rfRDN and Sham groups.

Pre-specified Analysis Method: The difference between randomized groups (rfRDN and Sham) using the Bayesian power prior methodology.

- Primary (Bayesian) cohort = HTN-OFF Expansion plus discounted Pilot

Table 8 shows the HTN-OFF Primary Cohort Bayesian analysis for the primary and secondary effectiveness endpoints. The α-discount parameters were close to 1 for the rfRDN and Sham groups, so a high proportion of Pilot Cohort outcome information was used.

- Primary Effectiveness Endpoint: In the rfRDN group, there was a 3.9 mmHg greater reduction in 24-hour ASBP at 3 months vs. the Sham group.
- Powered Secondary Effectiveness Endpoint: In the rfRDN group, there was a 6.5 mmHg greater reduction in OSBP at 3 months vs. the Sham group.

For both primary and secondary effectiveness endpoints, rfRDN met the statistical requirement for superiority with posterior probability of superiority >0.999.

Table 8. Powered Primary and Secondary Effectiveness Results at 3 Months – HTN-OFF Primary (Bayesian) Cohort

	α-discount parameter	**Prior N[b]**	**N**	**Bayesian Posterior mean of treatment effect[a]** $\mu = \mu_{RDN} - \mu_C$ **(95% BCI)**	**Posterior Probability of Success** $Pr\{\mu < 0 \mid Data\}$[b] **(> 0.975 to meet statistical criteria)**
Primary Endpoint: 24-hour SBP					
rfRDN	0.864	30	105	-3.9 mmHg (-6.2 to -1.6)	0.9996
Sham	0.967	34	99		
Secondary Endpoint: Office SBP					
rfRDN	0.980	36	119	-6.5 mmHg (-9.6 to -3.5)	1.000
Sham	0.998	41	109		

[a] *Computed using 10^5 draws from the Posterior Distribution of μ*
[b] *Effective prior sample size after discounting*

Additional Analyses

Table 9 shows frequentist analyses for the HTN-OFF Pilot, Expansion, and Full Cohorts. The Pilot Cohort results were generally similar to the Expansion Cohort results.

Table 9. Frequentist ANCOVA Analyses for ASBP and OSBP at 3 Months for HTN-OFF Cohorts (ITT)

ITT Population	rfRDN	Sham	ANCOVA Difference (95% CI)	ANCOVA p-value
24Hr SBP Change				
HTN-OFF Pilot Cohort	-5.5 ± 10.3 (N=35)	-0.1 ± 10.0 (N=35)	-4.9 (-9.6, -0.3)	0.0370
HTN-OFF Expansion	-4.4± 10.5 (N=105)	-0.8 ± 8.1 (N=99)	-3.6 (-6.2, -1.0)	0.0065
HTN-OFF Full Cohort	-4.5 ± 10.8 (N=153)	-0.6 ± 8.7 (N=147)	-3.9 (-6.1, -1.7)	<0.001
Office SBP Change				
HTN-OFF Pilot (3 month)	-10.0 ± 15.4 (N=37)	-2.3 ± 12.1 (N=41)	-7.1 (-13.2, -1.1)	0.0212
HTN-OFF Expansion (3 month)	-9.2 ± 14.4 (N=119)	-2.6 ± 13.2 (N=109)	-6.6 (-10.2, -3.0)	0.0003
HTN-OFF Full Cohort	-9.4 ± 14.8 (N=170)	-2.3 ± 12.7 (N=164)	-7.1 (-10.0, 4.2)	<0.001

Data displayed as mean ± SD (N)
Difference and p-values are ANCOVA adjusted for the baseline BP values
Note that all p-values are not adjusted with multiplicity

FDA Comment: In HTN-OFF, the difference in 24-hour SBP using the pre-specified Bayesian power prior analysis was -3.9 mmHg at 3 months in favor of rfRDN, which is less than the 5 mmHg clinically meaningful effect size recommended by the 2018 Advisory Panel Committee. The difference in 24-hour SBP was greater in the Pilot cohort compared to the Expansion Cohort. The difference in office SBP was -6.5 mmHg in favor of rfRDN with similar results noted in the Pilot and Expansion cohorts.

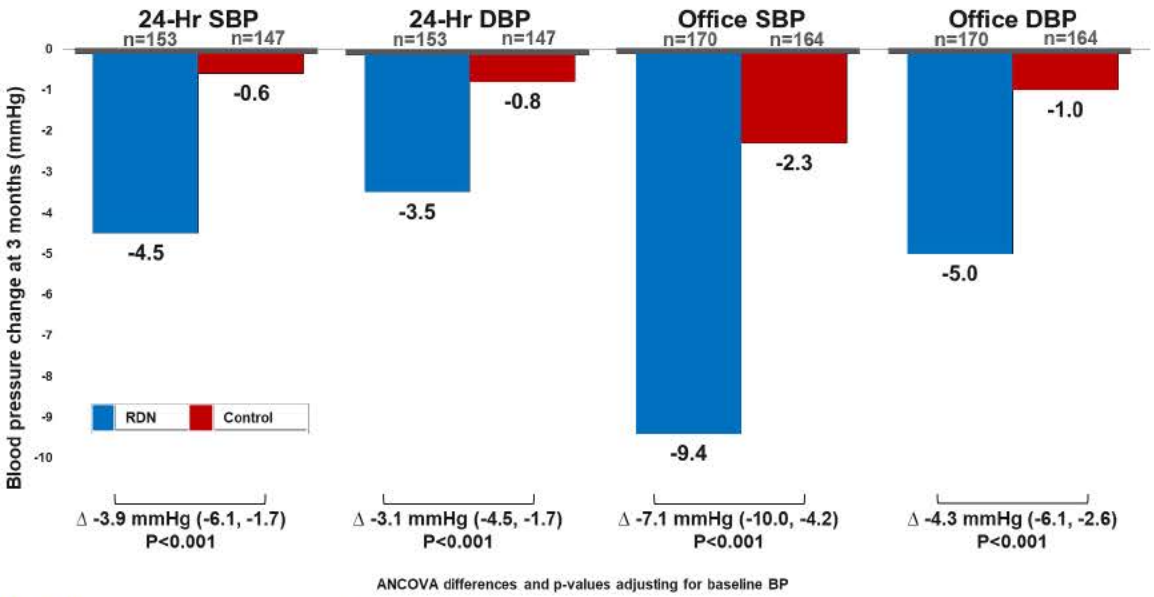
The HTN-OFF primary effectiveness results contrast with the 6 month HTN-ON outcomes, in which the mean difference in 24-hour SBP was only 0.03 mmHg in favor of the rfRDN group (see Section 7.2.4.1).

7.1.4.2 Selected Secondary Effectiveness Endpoints

All secondary endpoints were conducted using data on the HTN-OFF Full Cohort.

Change in 24-hour and Office SBP and DBP

The changes in 24-hour ambulatory SBP and DBP and office SBP and DBP at 3 months are shown in Figure 7 for all evaluable subjects using a frequentist ANCOVA method.



Note that all p-values are not adjusted with multiplicity.
SBP changes are unadjusted absolute drops from baseline. Differences and p-values are determined from ANCOVA models adjusting for the baseline value

Figure 7. Changes in 24-hour and Office SBP and DBP through 3 Months – HTN-OFF Full Cohort (ITT)

OSBP Reductions of >5-20 mmHg at 3 and 6 months

Table 10 shows the percentage of subjects with BP reductions in OSBP greater than 5, 10, 15, and 20 mmHg at 3 and 6 months for HTN-OFF.

- At 3 months, a significantly higher proportion of rfRDN subjects had OSBP reduction at all levels of BP reduction and achieved target OSBP <140 mmHg vs. Sham subjects.
- At 6 months (BP medications could be restarted at 3 months), the magnitude of BP reduction was similar between the rfRDN and Sham groups. The rfRDN had a lower number of medications compared to Sham (1.25 ± 0.92 vs 1.64 ± 1.02, $p < 0.001$) at 6 months.

Table 10. OSBP Reduction at 3 and 6 Months – HTN-OFF Full Cohort

	rfRDN	Sham	p-value
HTN-OFF (Full cohort)	**(n=182)**	**(n=184)**	
Reduction in OSBP @ 3 Months			
≥ 5 mmHg	65.3% (111/170)	40.9% (67/164)	< 0.001
≥ 10 mmHg	48.2% (82/170)	25.0% (41/164)	< 0.001
≥ 15 mmHg	35.3% (60/170)	17.7% (29/164)	< 0.001
≥ 20 mmHg	24.1% (41/170)	5.5% (9/164)	< 0.001
Achieving target SBP[1]	15.9% (27/170)	7.3% (12/164)	0.017
Reduction in OSBP @ 6 Months			

	rfRDN	Sham	p-value
≥ 5 mmHg	88.5% (154/174)	87.6% (155/177)	0.870
≥ 10 mmHg	79.3% (138/174)	79.1% (140/177)	1.000
≥ 15 mmHg	69.5% (121/174)	70.1% (124/177)	1.000
≥ 20 mmHg	55.2% (96/174)	57.1% (101/177)	0.748
Achieving target SBP[1]	50.6% (88/174)	45.8% (81/177)	0.394

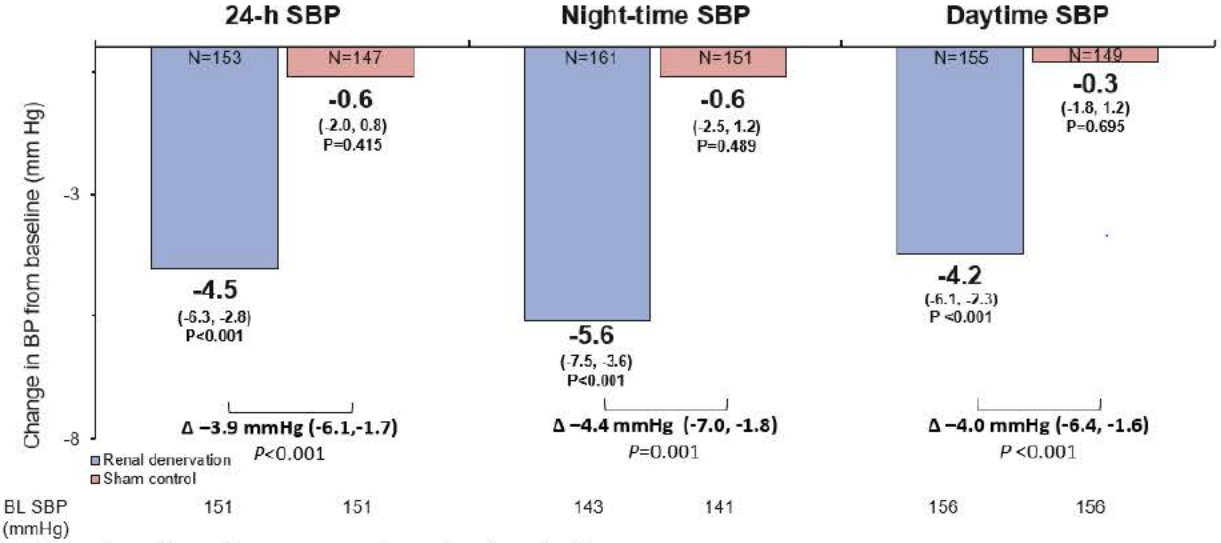
Data displayed as % (n/N)
[1] Target OSBP is <140 mmHg
Note that all p-values are not adjusted with multiplicity

Daytime and Nighttime ASBP

Figure 8 shows the changes in the 24-hour, daytime and nighttime ASBP for the HTN-OFF Full Cohort.

- Daytime was defined as any ABPM readings between 7 am and 10 pm.
- Nighttime was defined as any ABPM readings between 10 pm to 7 am.

The reduction in SBP at 3 months in rfRDN vs. Sham was significantly greater for all three measures and similar across the measures.



Note that all p-values are not adjusted with multiplicity
SBP changes are unadjusted absolute drops from baseline. Differences and p-values are determined from ANCOVA models adjusting for the baseline value

Figure 8. 24-hour, Night-time, and Daytime ASBP Change at 3 Months – HTN-OFF Full Cohort

Figure 9 shows the hourly change in ASBP at baseline and 3 months for rfRDN and Sham groups. On average, the rfRDN group has lower SBP through the day with larger reductions in night-time SBP.

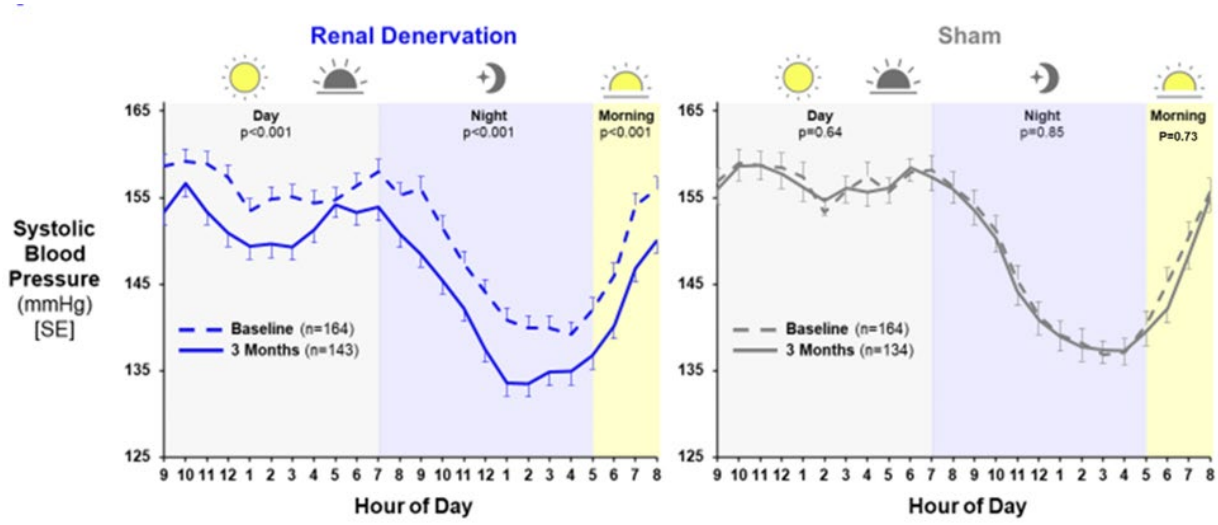


Figure 9. Hourly Change in ASBP - HTN-OFF

7.1.4.3 Durability of Treatment and Medication Burden

To assess durability of the treatment effectiveness, ambulatory and office BP and medication burden were evaluated.

In the HTN-OFF protocol, medications were to be withheld (unless escape criteria were met) through 3-month post-procedure and could be restarted after 3 months.

Table 11 shows the changes in 24-hour and Office SBP and medication burden (defined by Med Index 1 and Med Index 2) per drug testing from baseline to 3, 6, and 12-months .

- At 3-months (BP medications withheld):
  - The 24-hour SBP reduction was 3.9 mmHg greater in the rfRDN group vs. Sham.
  - The Med Index 1 was 0.11 in rfRDN subjects vs. 0.20 in Sham subjects.
- At 6-months (BP medications could be restarted at 3 months):
  - Sham subjects had a 2.3 mmHg greater reduction in 24-hour SBP vs. rfRDN subjects.
  - The Med Index 1 was 0.74 in rfRDN subjects vs. 1.02 in Sham subjects (corresponding to approximately 25% of 1 full dose of an additional BP medication in Sham vs. rfRDN subjects).
- At 12-months:
  - Sham subjects had a 4.9 mmHg greater reduction in 24-hour SBP compared to rfRDN subjects.
  - The Med Index 1 was 0.87 in rfRDN subjects vs. 1.04 in Sham subjects (corresponding to approximately 0.17 or one-sixth 1 additional BP medication in Sham vs. rfRDN subjects).
- Similar trends were observed for office SBP.

Table 11. Reduction in 24-hour and Office SBP and Medication Index 1 and 2 per drug testing from Baseline to 12 Months – HTN-OFF Full Cohort

	rfRDN				Sham			
	Change in 24-hour SBP (mmHg)	**Change in office SBP** (mmHg)	**Med Index 1**	**Med Index 2**	**Change in 24-hour SBP** (mmHg)	**Change in office SBP** (mmHg)	**Med Index 1**	**Med Index 2**
Baseline	--	--	0.05 ± 0.19 (180)	0.07 ± 0.30 (180)	--	--	0.08 ± 0.26 (184)	0.11 ± 0.51 (184)
3 months	-4.5 ± 10.8[a] (153)	-9.4 ± 14.8[a] (170)	0.11 ± 0.43 (164)	0.23 ± 1.08 (164)	-0.6 ± 8.7 (147)	-2.3 ±12.7 (164)	0.04 ± 0.23 (148)	0.05 ± 0.27 (148)
6 months	-15.3 ± 13.7 (150)	-20.8 ± 13.9 (174)	0.74 ± 0.80[a] (157)	1.51 ± 2.15[a] (157)	-17.1 ± 12.3 (159)	-21.9 ± 14.3 (177)	0.97 ± 0.87 (163)	2.22 ± 3.31 (163)
12 months	-14.3 ± 11.9 (146)	-21.3 ± 14.2 (171)	0.80 ± 0.84[a] (157)	1.60 ± 2.17[a] (157)	-19.2 ± 12.1[b] (92)	-22.4 ± 13.6 (104)	1.02 ± 0.91 (94)	2.36 ± 2.96 (94)

Data displayed as mean ± SD (n)

[a] *rfRDN significantly lower than Sham (p<0.001)*

[b] *Sham significantly lower than RDN (p=.003)*

Limitations in Interpreting Durability Data

Longitudinal BP reduction could have been impacted by several factors:

- Unblinding at 6 months could potentially lead to bias for the 12 month BP measurement.
- Crossover after 6 months reduced the sample size for the Sham group.
- After 3 months, additional medication was added. The Med Index analysis suggests that restarting medications at a higher level in the Sham group may have played a role in the greater BP reduction in the Sham vs. rfRDN group after 3 months.

7.1.4.4 Additional Analyses

Time in Target Range (TTR)

- Target SBP: OSBP ≤140 mmHg or 24-hour SBP ≤130 mmHg
- TTR methodology:
  - Determine the maximum BP value for each subject within the TTR time interval by linearly interpolating the BP between times of measurement and calculating the percentage of time the BP is in therapeutic range.
  - TTR was calculated from baseline to 3, 6, 12, and 24 months
- Note that antihypertensive medications followed a guideline-driven escalation protocol to achieve BP goals between 3 and 6 months.

Table 12 shows the TTR of OSBP (≤140 mmHg) and 24-hour ASBP (≤130 mmHg). Over the course of follow-up to 24 months, subjects were in the target range more commonly for OSBP than the 24-hour ASBP target in both treatment groups. For OSBP and 24-hour ASBP, rfRDN subjects were in the SBP target range for a higher proportion of follow-up time vs. Sham subjects.

Table 12. Percent Time in Target Range – HTN-OFF Full Cohort

	rfRDN TTR% (n)	Sham TTR% (n)	p-value
OFFICE SBP TTR (≤140 mmHg)[1]			
TTR 0-3 months	11.7 ± 23.7 (180)	4.7 ± 14.0 (180)	0.002
TTR 0-6 months	18.5 ± 25.8 (182)	12.7 ± 18.7 (184)	0.091
TTR 0-12 months	31.7 ± 30.2 (182)	23.1 ± 26.4 (184)	0.003
TTR 0-24 months	38.7 ± 33.3 (182)	25.6 ± 29.5 (184)	<0.001
24hr SBP TTR (≤130 mmHg)[1]			
TTR 0-3 months	2.0 ± 8.3 (153)	0.1 ± 0.8 (146)	0.007
TTR 0-6 months	7.8 ± 15.2 (165)	6.3 ± 11.2 (168)	0.713
TTR 0-12 months	17.6 ± 23.8 (166)	13.6 ± 20.3 (175)	0.193
TTR 0-24 months	22.1 ± 27.9 (167)	15.7 ± 23.2 (176)	0.019

Data displayed as mean ± SD (n)
[1] Analyses use all non-missing BP data from BL, 2W, 4W, 8W, 3M, 6M, 12M, 24M within time ranges P-values from non-parametric Kruskal-Wallis test
Note that all p-values are not adjusted with multiplicity

FDA Comment:
The following should be considered in interpreting the TTR analysis:

- TTR has not yet been validated for clinical outcomes.
- The number of BP assessments in the study and use of interpolation may be too few to accurately determine TTR. Literature use TTR measurements which are spaced at 1 month or 3 months apart.[30]
- The study measured BP every 6 months after the initial 6 months, and the clinical significance of assessing TTR with BP measurements every 6 months is uncertain.
- Imputed BP data may bias against the Sham group due to more missing data which used the last observation carried forward.

The panel will be asked to discuss the strengths and limitations of the TTR analysis methodology and its clinical significance as part of the totality of evidence for rfRDN effectiveness.

7.1.5 Subgroup Analyses

Subgroup Analyses by Baseline Characteristics

Figure 11 and Figure 11 show the subgroup analyses for the changes of 24-hour SBP at 3 months for the HTN-OFF Full Cohort. The sample size is small for many subgroups, and some interaction p-values are low (<0.15), but there are no clear trends. The 24-hour SBP reduction trends favoring the rfRDN group was observed for nearly all subgroups.

Geography Subgroup Analysis at 3 Months

- The difference in 24-hour SBP reduction in favor of the rfRDN group was 2.7 mmHg in US subjects (n=141) and 4.7 mmHg in OUS subjects (n=169).
- The difference in OSBP reduction in favor of the rfRDN group was 8.2 mmHg for US subjects (n=163) and 6.1 mmHg for OUS subjects (n=171).
- The 24-hour SBP and OSB outcome differences between US and OUS subjects were similar.

	N	Adjusted treatment difference (95% CI)	Interaction p-value
Age			
< 65 years	270	-3.6 (-5.9, -1.3)	0.41
≥ 65 years	30	-6.8 (-14.1, 0.6)	
Sex			
Female	95	-2.3 (-6.4, 1.8)	0.33
Male	205	-4.7 (-7.3, -2.1)	
BMI			
Tertile 1 (BMI < 28.2)	104	-3.9 (-7.5, -0.2)	0.94
Tertile 2 (28.2 ≤ BMI < 32.3)	102	-4.4 (-8.0, -0.8)	
Tertile 3 (BMI ≥ 32.3)	94	-3.3 (-7.8, 1.1)	
Diabetes			
Yes	7	-6.0 (-32.3, 20.3)	0.80
No	293	-3.8 (-6.0, -1.6)	
Smoking			
Current	49	-5.3 (-11.2, 0.6)	0.39
Former	84	-1.6 (-6.0, 2.8)	
Never	167	-4.7 (-7.6, -1.9)	
Obstructive sleep apnea			
Yes	23	-5.9 (-17.5, 5.7)	0.63
No	277	-3.8 (-6.0, -1.5)	
AH Med Compliance at Baseline and 3M			
Yes	258	-3.8 (-6.1, -1.5)	0.96
No	31	-3.8 (-13.1, 5.5)	
Geography			
US	141	-2.7 (-5.8, 0.5)	0.40
OUS	159	-4.7 (-7.7, -1.6)	

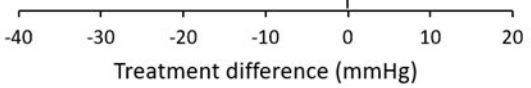


Figure 10. 24-hour SBP Subgroup Analyses at 3 Months – HTN-OFF Full Cohort

	N	Adjusted treatment difference (95% CI)	Interaction p-value
Orthostatic hypertension			
Yes	109	-6.5 (-10.5, -2.5)	0.07
No	185	-2.5 (-5.2, 0.1)	
Orthostatic Tachycardia			
Yes	119	-6.1 (-9.8, -2.4)	0.14
No	175	-2.8 (-5.6, -0.1)	
Race			
US African-American	49	-1.7 (-6.1, 2.7)	0.66
US Non-African-American	92	-3.2 (-7.6, 1.2)	
Renal function			
eGFR < 60	12	0.2 (-18.7, 19.0)	0.48
eGFR ≥ 60	288	-4.1 (-6.3, -1.8)	
Baseline ARR			
Tertile 1 (<5.39)	88	-6.17 [-10.26, -2.07]	0.13
Tertile 2 (5.39 to 12.16)	96	-4.51 [-8.23, -0.78]	
Tertile 3 (≥12.16)	87	-0.60 [-4.71, 3.51]	
Baseline Aldosterone			
Tertile 1 (<6)	98	-4.67 [-8.69, -0.66]	0.92
Tertile 2 (6 to 10)	98	-4.07 [-8.00, -0.13]	
Tertile 3 (≥10)	89	-3.57 [-7.62, 0.48]	
Plasma Renin Activity			
< 0.65	138	-1.51 [-4.79, 1.76]	0.09
≥ 0.65	137	-5.49 [-8.72, -2.26]	
24h Pulse Pressure (mmHg)			
< 60	253	-4.2 (-6.6, -1.7)	0.40
≥ 60	47	-1.7 (-7.4, 4.1)	

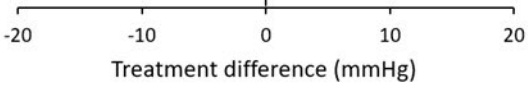


Figure 11. 24-hour SBP Subgroup Analyses at 3 Months – HTN-OFF Full Cohort

Change in ASBP as a Function of Baseline Characteristics

Figure 12 shows the difference in 24-hour SBP reductions as a function of baseline 24-hour SBP, office SBP, 24-hour HR, and office HR (stratified by tertiles). ASBP reduction favoring the rfRDN group was observed across most BP and HR tertiles. Some interaction p-values are low (<0.15), but there are no clear trends.

	N	Adjusted treatment difference (95% CI)	Interaction p-value
Baseline 24-Hour SBP (mmHg)			
Tertile 1 (<146.9)	107	-3.8 (-7.5, -0.1)	0.12
Tertile 2 (146.9 to 154)	100	-1.2 (-4.9, 2.6)	
Tertile 3 (≥154)	93	-7.0 (-11.1, -2.8)	
< Median (150)	157	-3.7 (-6.6, -0.8)	0.87
≥ Median (150)	143	-4.1 (-7.5, -0.7)	
Baseline Office SBP (mmHg)			
Tertile 1 (<158.7)	104	-3.9 (-7.9, 0.0)	0.89
Tertile 2 (158.7 to 166.7)	105	-3.3 (-7.0, 0.4)	
Tertile 3 (≥166.7)	91	-4.6 (-8.5, -0.8)	
< Median (162)	154	-3.8 (-7.0, -0.6)	0.92
≥ Median (162)	146	-4.1 (-7.1, -1.1)	
Baseline 24-Hour Heart Rate (bpm)			
Tertile 1 (<69.7)	99	-1.2 (-4.7, 2.3)	0.26
Tertile 2 (69.7 to 78.9)	103	-4.9 (-8.8, -1.0)	
Tertile 3 (≥78.9)	98	-5.4 (-9.6, -1.2)	
< Median (74.5)	151	-2.5 (-5.4, 0.4)	0.23
≥ Median (74.5)	149	-5.2 (-8.6, -1.9)	
Baseline Office Heart Rate (bpm)			
Tertile 1 (<69)	99	-0.7 (-4.3, 2.9)	0.13
Tertile 2 (69 to 78)	105	-5.7 (-9.0, -2.4)	
Tertile 3 (≥78)	96	-5.2 (-9.8, -0.7)	
< Median (73.7)	153	-1.8 (-4.7, 1.1)	0.047
≥ Median (73.7)	147	-6.2 (-9.5, -2.9)	

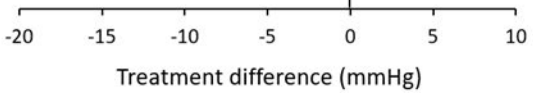


Figure 12. 24-hour SBP Reduction at 3 Months as a Function Tertiles of Baseline 24-hour SBP, Office SBP, 24-hour HR, and Office HR – HTN-OFF Full Cohort

7.2 SPYRAL HTN-ON Results

The HTN-ON Pilot Cohort initiated enrollment July 22, 2015, and the Expansion Cohort completed enrollment March 9, 2022. Subjects will be followed through 3 years.

7.2.1 Subject Accountability

Figure 13 shows subject accountability through 12 months for the HTN-ON Full Cohort.

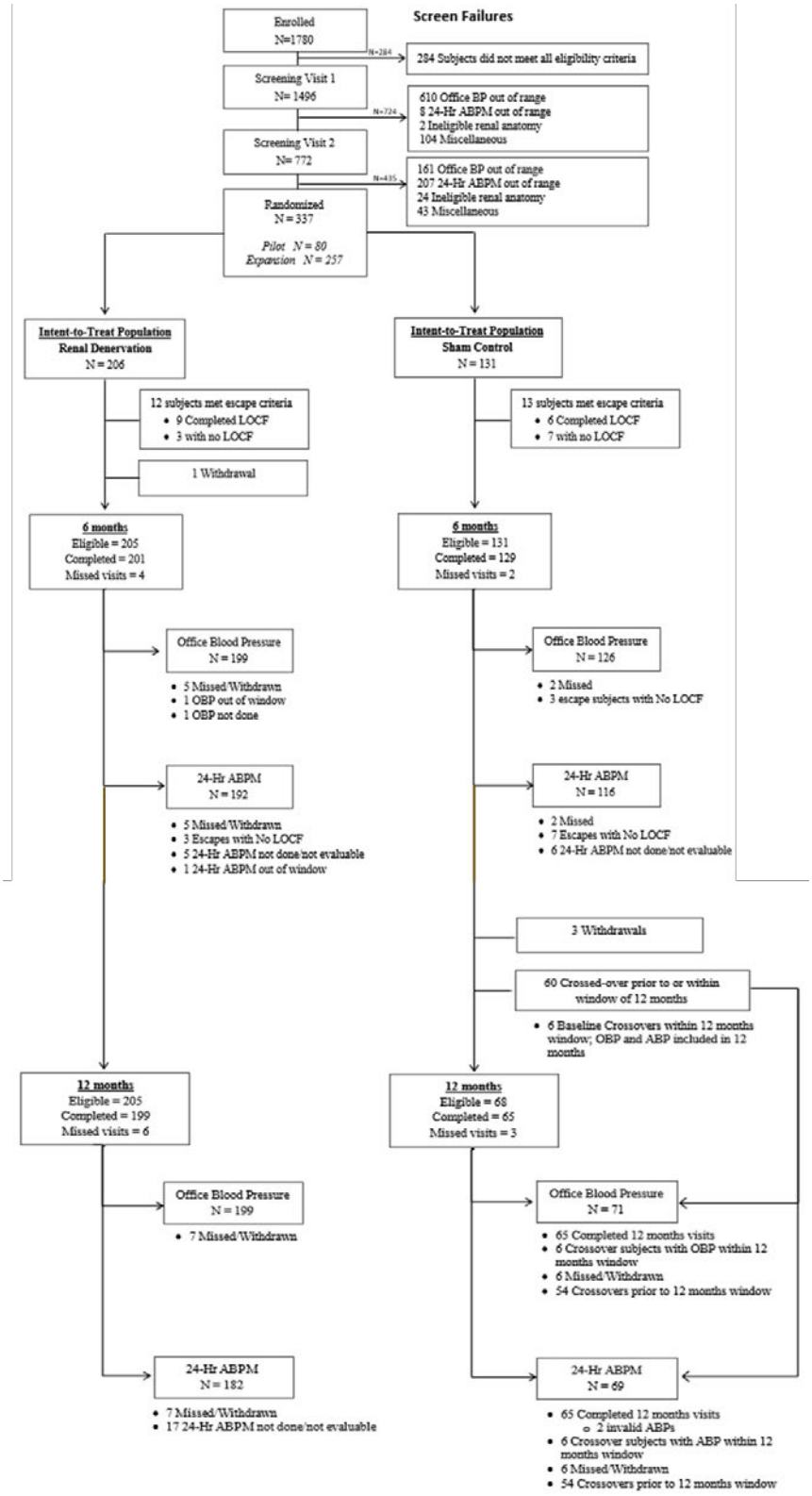


Figure 13. Subject Accountability through 12 months – HTN-ON Full Cohort

7.2.2 Baseline and Procedural Characteristics

Baseline HTN-ON subject characteristics are shown in Table 13, and baseline BPs are shown in Table 14. Baseline characteristics were well-balanced between the rfRDN and Sham groups and between Pilot and Expansion Cohorts. There was a slightly higher proportion of US subjects in the Expansion Cohort compared with Pilot Cohort.

Table 13. HTN-ON Select Baseline Characteristics

	Pilot Cohort		Expansion Cohort		Full Cohort (Pilot + Expansion)	
Subject Baseline Characteristic	**rfRDN (N=38 Subjects)**	**Control (N=42 Subjects)**	**rfRDN (N=168 Subjects)**	**Control (N=89 Subjects)**	**rfRDN (N=206 Subjects)**	**Control (N=131 Subjects)**
Age (yrs)	53.9 ± 8.7	53.0 ± 10.7	55.5 ± 9.0	55.4 ± 8.7	55.2 ± 9.0	54.6 ± 9.4
Male	86.8% (33/38)	81.0% (34/42)	79.8% (134/168)	77.5% (69/89)	81.1% (167/206)	78.6% (103/131)
Length of hypertension diagnosis >5 yrs	60.5% (23/38)	81.0% (34/42)	72.1% (121/168)	82.0% (73/89)	69.9% (144/206)	81.7% (107/131)
Geography						
US	39.5% (15/38)	42.9% (18/42)	45.2% (76/168)	52.8% (47/89)	44.2% (91/206)	49.6% (65/131)
OUS	60.5% (23/38)	57.1% (24/42)	54.8% (92/168)	47.2% (42/89)	55.8% (115/206)	50.4% (66/131)
Race						
White	34.2% (13/38)	35.7% (15/42)	34.5% (58/168)	37.1% (33/89)	34.5% (71/206)	36.6% (48/131)
Black or African American	10.5% (4/38)	11.9% (5/42)	18.5% (31/168)	22.5% (20/89)	17.0% (35/206)	19.1% (25/131)
Asian	0.0% (0/38)	2.4% (1/42)	1.2% (2/168)	3.4% (3/89)	1.0% (2/206)	3.1% (4/131)
Japanese from Japan	7.9% (3/38)	2.4% (1/42)	7.1% (12/168)	5.6% (5/89)	7.3% (15/206)	4.6% (6/131)
Not reportable per local laws or regulations	47.4% (18/38)	47.6% (20/42)	36.9% (62/168)	29.2% (26/89)	38.8% (80/206)	35.1% (46/131)
Other	0.0% (0/38)	0.0% (0/42)	0.0% (0/168)	1.1% (1/89)	0.0% (0/206)	0.8% (1/131)
Hispanic/Latino/Spanish origin						
Yes	0% (0/38)	0% (0/42)	1.8% (3/168)	4.5% (4/89)	1.5% (3/206)	3.1% (4/131)
No	52.6% (20/38)	52.4% (22/42)	60.7% (102/168)	65.2% (58/89)	59.2% (122/206)	61.1% (80/131)
Not reportable per local law or reg	47.4% (18/38)	47.6% (20/42)	36.9% (62/168)	30.3% (27/89)	38.8% (80/206)	35.9% (47.131)
Unknown	0.0% (0/38)	0.0% (0/42)	0.6% (1/168)	0.0% (0/89)	0.5% (1/206)	0.0% (0/131)

	Pilot Cohort		Expansion Cohort		Full Cohort (Pilot + Expansion)	
Subject Baseline Characteristic	**rfRDN (N=38 Subjects)**	**Control (N=42 Subjects)**	**rfRDN (N=168 Subjects)**	**Control (N=89 Subjects)**	**rfRDN (N=206 Subjects)**	**Control (N=131 Subjects)**
BMI	31.4 ± 6.4	32.5 ± 4.6	31.4 ± 6.0	32.0 ± 5.4	31.4 ± 6.0	32.1 ± 5.2
Diabetes Mellitus Type 2	13.2% (5/38)	19.0% (8/42)	10.1% (17/168)	16.9% (15/89)	10.7% (22/206)	17.6% (23/131)
Current Smoker	21.1% (8/38)	26.2% (11/42)	14.3% (24/168)	11.2% (10/89)	15.5% (32/206)	16.0% (21/131)
Obstructive sleep apnea	5.3% (2/38)	23.8% (10/42)	12.5% (21/168)	14.6% (13/89)	11.2% (23/206)	17.6% (23/131)
History of coronary artery disease*	2.6% (1/38)	2.4% (1/42)	6.0% (10/168)	9.0% (8/89)	5.3% (11/206)	6.9% (9/131)
History of stroke / transient ischemic attack*	0.0% (0/38)	2.4% (1/42)	0.6% (1/168)	1.1% (1/89)	0.5% (1/206)	1.5% (2/131)
Peripheral Arterial Disease	0.0% (0/38)	0.0% (0/42)	0.0% (0/168)	0.0% (0/89)	0.0% (0/206)	0.0% (0/131)

Data displayed as mean ± SD or % (n/N)

* *Occurring > 3 months before randomization*

Table 14. Baseline Blood Pressures – HTN-ON

Subject Baseline Blood Pressure (mmHg)	**Pilot Cohort**		**Expansion Cohort**		**Full Cohort**	
	rfRDN (N=38 Subjects)	**Control (N=42 Subjects)**	**rfRDN (N=168 Subjects)**	**Control (N=89 Subjects)**	**rfRDN (N=206 Subjects)**	**Control (N=131 Subjects)**
Office measurements						
Systolic blood pressure	164.4 ± 7.0	163.5 ± 7.5	162.6 ± 7.8	162.9 ± 8.2	163.0 ± 7.7	163.1 ± 7.9
Diastolic blood pressure	99.5 ± 6.9	102.7 ± 8.0	101.5 ± 6.9	100.9 ± 6.9	101.2 ± 7.0	101.5 ± 7.3
24-hour measurements (ABPM)						
Mean systolic blood pressure	152.1 ± 7.0	151.3 ± 6.8	149.0 ± 6.8	148.3 ± 6.9	149.6 ± 7.0	149.3 ± 7.0
Mean diastolic blood pressure	97.2 ± 6.9	97.9 ± 8.4	96.5 ± 7.7	94.6 ± 7.2	96.6 ± 7.6	95.7 ± 7.7

Data displayed as mean ± SD

7.2.3 Procedural Characteristics

Table 15 shows HTN-ON procedural characteristics for pooled Pilot and Expansion subjects. As expected, mean procedure time and contrast volume for rfRDN subjects were greater vs. Sham.

Table 15. Procedural Characteristics – HTN-ON Full Cohort

	rfRDN (N=206 subjects)	**Sham (N=131 subjects)**
Procedure Time[1] (min)	91.3 ± 31.2	51.2 ± 19.5
Denervation Time[2] (min)	54.4 ± 19.2	--
Amount of Contrast used (cc)	204.2 ± 81.4	69.9 ± 35.8
Intra-procedural medication		
Pain meds	21.8% (45/206)	17.6% (23/131)
Sedatives/Anxiolytics	98.5% (203/206)	98.5% (129/131)
Atropine	2.9% (6/206)	0.0% (0/131)
Hospital Stay (days)	1.0 ± 0.2	1.0 ± 0.2
Device success[3]	100.0% (205/205)	--
Procedure success[4]	99.5% (204/205)	--
Number of ablations Main Artery Level	9.1 ± 4.1 (Right Main) 7.9 ± 4.1 (Left Main) 8.5 ± 4.2 (Main Total) 12.9 ± 10.2 (Right Branch) 11.7 ± 8.7 (Left Branch) 12.3 ± 9.5 (Branch Total)	--
Number of ablations Kidney Level	10.5 ± 6.2 (Right Main) 8.9 ± 6.3 (Left Main) 19.4 ± 9.5 (Main Total) 14.8 ± 9.7 (Right Branch) 13.3 ± 8.3 (Left Branch) 28.0 ±14.6 (Branch Total)	--

Data displayed as mean ± SD or % (n/N)
[1]Arterial closure – arterial access obtained
[2]Final Guide Catheter Removal – Initial Symplicity Spyral Catheter Insertion
[3]Successful delivery of any RF
[4]Successful delivery of any RF in the absence of in hospital MAE

7.2.4 Effectiveness Results

7.2.4.1 Primary and Secondary Effectiveness

Primary Effectiveness Endpoint (Powered): Baseline adjusted change in SBP measured by 24-hour ABPM from baseline to 6-months post-procedure, compared between rfRDN and Sham groups

Secondary Effectiveness Endpoint (Non-powered): Baseline adjusted change in OSBP from baseline to 6-months post-procedure, compared between rfRDN and Sham groups

Pre-specified Analysis Method: The difference between randomized groups (rfRDN and Sham) using the Bayesian power prior methodology

- Primary (Bayesian) cohort = HTN-ON Expansion plus discounted Pilot

Table 16 shows the HTN-ON Primary Cohort Bayesian analysis for the primary and secondary effectiveness endpoints. Due to differences in the results for the HTN-ON Pilot and HTN-ON Expansion Cohorts, much of the Pilot data was discounted (α-discount parameter = 0.194 for rfRDN and 0.0002 for Sham) for the 24-hour SBP primary effectiveness endpoint, meaning that little Pilot Cohort outcome information was used along with the Expansion Cohort to calculate the treatment effect and posterior probability of success. In contrast, for the OSBP secondary effectiveness endpoint, the results for the HTN-ON Pilot and HTN-ON Expansion Cohorts were generally more similar such that a higher proportion of Pilot Cohort outcome information was used. Potential confounders for the differences in the Pilot and Expansion studies are discussed in Section 7.2.6 Potential Confounder Considerations for HTN-ON.

- For the Primary Effectiveness Endpoint of 24-hour ASBP at 6 Months:
  - In the rfRDN group there was a 0.03 mmHg greater reduction in 24-hour ASBP at 6 months vs. the Sham group.
  - rfRDN did not meet the statistical requirement for superiority (posterior probability of superiority = 0.51).

- For the Secondary Effectiveness Endpoint of OSBP at 6 Months:
  - In the rfRDN group there was a 4.1 mmHg greater reduction in OSBP at 6 months vs. the Sham group.
  - A high posterior probability of superiority for rfRDN (0.99) was obtained

Table 16. Primary and Secondary Effectiveness Results at 6 Months – HTN-ON Primary (Bayesian) Cohort

	α-discount parameter	Prior N[b]	N	Bayesian Posterior mean of treatment effect[a] $\mu = \mu_{RDN} - \mu_C$ (95% BCI)	Posterior Probability of Success $Pr\{\mu < 0 \mid Data\}$ (> 0.975 to meet statistical criteria)[b]
Primary Endpoint: 24-hour ASBP					
rfRDN	0.194	6.999	156	-0.02996 mmHg (-2.8232, 2.7682)	0.5084
Sham	0.0002	0.007	80		
Secondary Endpoint: Office SBP					
rfRDN	>0.999	38	161	-4.095 mmHg (-7.441, 0.748)	0.992
Sham	0.156	6.2	13.4		

[a] *Computed using 10^5 draws from the Posterior Distribution of μ*
[b] *Effective prior sample size after discounting*

FDA Comment: In HTN-ON, the mean difference in 24-hour SBP using the Bayesian power prior analysis was only 0.03 mmHg (in favor of the rfRDN group) at 6 months. In contrast, the mean difference in OSBP using the Bayesian power prior analysis was 4.1 mmHg (in favor of the rfRDN group) at 6 months. The Panel will be asked to the discuss the HTN-OFF vs. HTN-ON results, the clinical significance of the SBP reduction effect size, and the relative importance ambulatory vs office BP measurements.

Additional Analyses

Table 17 shows a frequentist analysis of covariance (ANCOVA) for the baseline BP adjusted treatment effect for the HTN-ON Pilot, Expansion, and Full Cohorts. It should be noted that the HTN-ON Expansion Cohort consists of subjects randomized in 1:1 to rfRDN:Sham and subjects randomized 2:1 to rfRDN:Sham. The analysis methodology did not accommodate combining subjects that were randomized using different randomization ratios. Therefore, the results presented for Expansion and Full Cohorts may not be statistically accurate and should be interpreted with caution. Results of the HTN-ON Expansion Cohort considering randomization ratios are provided, where the ANCOVA results are presented for each randomization ratio cohort.

For 24-SBP, the Pilot Cohort results were discordant with the Expansion Cohort results with a significantly greater reduction in rfRDN treat-subjects vs Sham in the Pilot Cohort and no significant difference between treatment groups in the Expansion Cohort. For OSBP, the Pilot Cohort results were generally similar to the Expansion Cohort results.

Table 17. Frequentist ANCOVA Analyses for ASBP and OSBP at 6 Months for HTN-ON Cohorts

ITT Population	rfRDN	Sham	ANCOVA Difference (95% CI)	ANCOVA p-value
24Hr SBP Change				
HTN-ON Pilot Cohort	-9.3 ± 10.9 (36)	-1.6 ± 10.7 (36)	-7.3 (-12.2, -2.4)	0.0041
HTN-ON Expansion Cohort	-5.9 ± 10.6 (156)	-5.8 ± 10.0 (80)	0.0 (-2.8, 2.9)	0.9735
HTN-ON Expansion Cohort (1:1)	-8.2 ± 11.2 (N=13)	-7.4 ± 14.7 (N=9)	-1.3 (-12.5, 9.9)	
HTN-ON Expansion Cohort (2:1)	-5.9 ± 10.6 (N=143)	-5.6 ± 9.4 (N=71)	0.0 (-2.9, 3.0)	
HTN-ON Expansion Cohort (weighted average)	--	--	-0.1 (-2.9,2.7)	
HTN-On Full Cohort	-6.5 ± 10.7 (192)	-4.5 ± 10.3 (116)	-1.9 (-4.4, 0.5)	0.110
Office SBP Change				
HTN-ON Pilot Cohort	-9.2 ± 12.3 (38)	-2.6 ± 12.9 (40)	-6.6 (-12.3, -0.8)	0.0259
HTN-ON Expansion Cohort	-10.1 ± 14.3 (161)	-6.2 ± 13.2 (86)	-4.0 (-7.6, -0.4)	0.0280
HTN-ON Expansion Cohort (1:1)	-12.3± 10.7 (N=15)	-8.1 ± 10.9 (N=10)	-4.2 (-13.6, 5.1)	
HTN-ON Expansion (2:1)	-9.9± 14.6 (N=146)	-6.0 ± 13.5 (N=76)	-4.0 (-7.9, 0.2)	
HTN-ON Expansion Cohort (weighted average)	--	--	-4.1 (-7.6,0.5)	
HTN-On Full Cohort	-9.9 ± 13.9 (199)	-5.1 ±13.2 (126)	-4.9 (-7.9, -1.9)	0.001

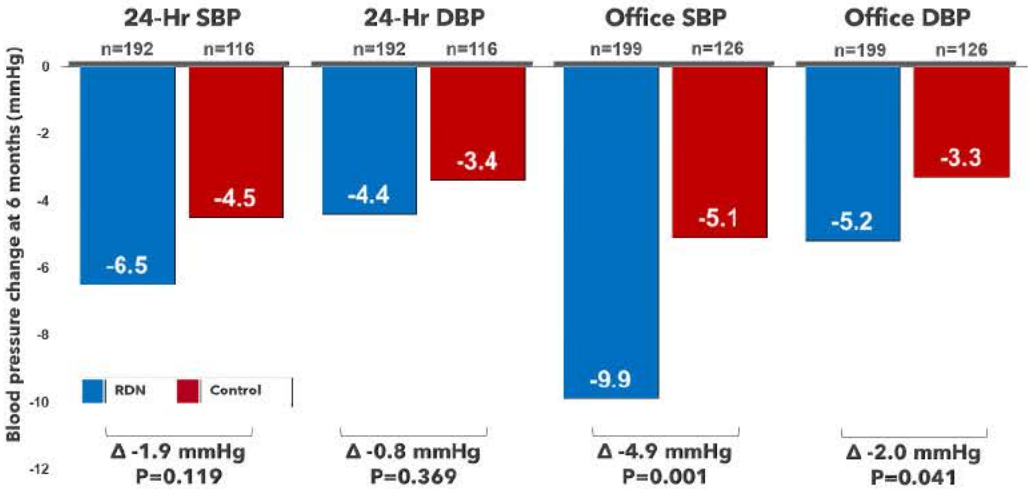
Data displayed as mean ± SD (N)
Difference and p-values are ANCOVA adjusted for the baseline BP values
Note that all p-values are not adjusted with multiplicity and all results of HTN-ON Expansion and Full cohorts are not adjusted for difference randomization ratios

7.2.4.2 Selected Secondary Effectiveness Endpoints

Secondary endpoints were evaluated in the HTN-ON Full Cohort. When considering a Full Cohort analysis, it should be noted that there were primary endpoint outcome differences in 24-hour ASBP observed in the Pilot Cohort and the Expansion Cohort.

Change in 24-hour and Office SBP and DBP

Changes in 24-hour ambulatory SBP and DBP and office SBP and DBP at 6 months are shown in Figure 14 for all evaluable subjects (Full Cohort) using a frequentist ANCOVA method.



Note that all p-values are not adjusted with multiplicity and all results of HTN-ON Full cohorts are not adjusted for difference randomization ratios
SBP changes are unadjusted absolute drops from baseline. Differences and p-values are determined from ANCOVA models adjusting for the baseline value

Figure 14. Changes in 24-hour and Office SBP and DBP through 6 Months – HTN-ON Full Cohort (ITT)

OSBP Reductions of ≥5-20 mmHg at 3 and 6 Months (Full Cohort)

Table 18 shows the proportion of subjects with OSBP reduction greater than 5, 10, 15, and 20 mmHg at 3 and 6 months for HTN-ON.

- At 3 and 6 months, a numerically higher proportion of rfRDN subjects had OSBP reduction at all levels of BP reduction. The differences in the number of subjects with ≥5 mmHg reduction between rfRDN and Sham was non-significant at 3 and 6 months, but the differences in the number of subjects with reductions ≥15 and ≥20 mmHg were significantly greater in the rfRDN group at 3 and 6 months.
- Significantly more rfRDN subjects achieved target OSBP <140 mmHg vs. Sham subjects.

Table 18. OSBP Reduction at 3 and 6 Months – HTN-ON Full Cohort

	rfRDN	Sham	p-value
HTN-ON (Full cohort)	**(n=206)**	**(n=131)**	
Reduction in OSBP @ 3 Months			
≥ 5 mmHg	63.8% (127/199)	54.5% (67/123)	0.102
≥ 10 mmHg	49.7% (99/199)	43.1% (53/123)	0.253
≥ 15 mmHg	33.7% (67/199)	22.8% (28/123)	0.044
≥ 20 mmHg	21.6% (43/199)	13.0% (16/123)	0.055
Achieving target SBP[1]	18.6% (37/199)	8.1% (10/123)	0.009

	rfRDN	Sham	p-value
Reduction in OSBP @ 6 Months			
≥ 5 mmHg	61.3% (122/199)	53.2% (67/126)	0.167
≥ 10 mmHg	50.8% (101/199)	38.9% (49/126)	0.040
≥ 15 mmHg	37.2% (74/199)	21.4% (27/126)	0.003
≥ 20 mmHg	23.6% (47/199)	14.3% (18/126)	0.04
Achieving target SBP[1]	19.6% (39/199)	6.3% (8/126)	0.001

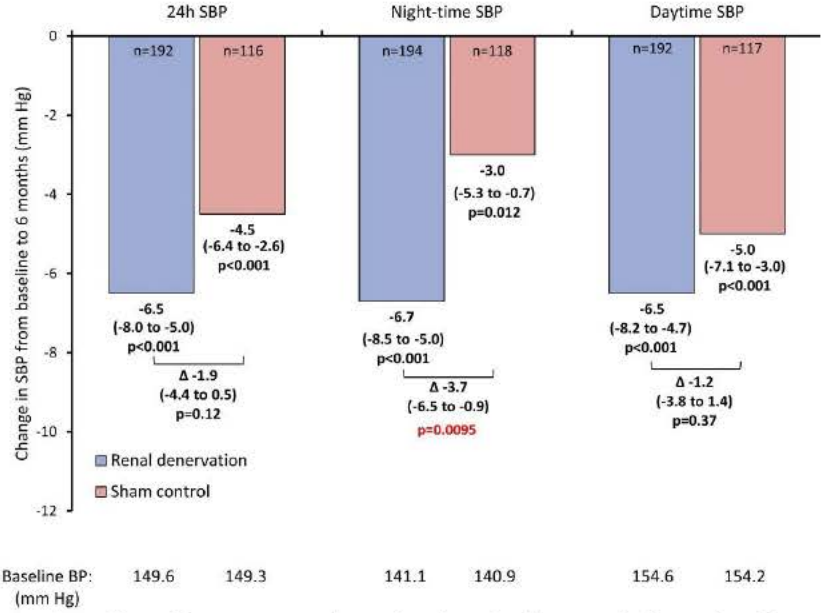
Data displayed as % (n/N)
[1] Target SBP is <140 mmHg
Note that all p-values are not adjusted with multiplicity

Daytime and Nighttime SBP

Figure 15 shows the changes of 24-hour, daytime and nighttime ASBP for the HTN-ON Full Cohort.

- Daytime was defined as any ABPM readings between 7 am and 10 pm.
- Nighttime was defined as any ABPM readings between 10 pm to 7 am.

The difference in rfRDN vs. Sham SBP reduction was greater for nighttime SBP (3.7 mmHg) vs. daytime SBP (1.2 mmHg).



Note that all p-values are not adjusted with multiplicity and all results of HTN-ON Full cohorts are not adjusted for difference randomization ratios
SBP changes are unadjusted absolute drops from baseline. Differences and p-values are determined from ANCOVA models adjusting for the baseline value

Figure 15. 24-hour, Night-time, and Daytime ASBP Changes at 6 Months – HTN-ON Full Cohort

7.2.4.3 Durability of Treatment and Medication Burden

Challenges interpreting the durability of BP reduction associated with rfRDN in HTN-ON include:

- Adding BP medications after the 6 months primary effectiveness endpoint assessment was reached
- Subject unblinding at 6 (Expansion Cohort) or 12 months (Pilot Cohort)

These factors can introduce confounders in interpreting BP reduction durability data. Further, allowing Sham subjects to crossover to rfRDN limits the durability analysis sample size. Additionally, the subjects that did not cross over, and who instead remained in the Sham group, may not represent a random sample. To help assess the durability of rfRDN effectiveness, ambulatory and office BP and medication burden were evaluated.

BP reduction durability data are not available for the HTN-ON Full Cohort beyond 6 months, so data beyond 6 months is limited to the HTN-ON Pilot Cohort. [31] Table 19 shows the medication burden at baseline, 3 months, and 6 months for the Full Cohort. At 6 months, the rfRDN group was prescribed a similar number of pills confirmed by drug testing (1.88 ± 1.03 for rfRDN vs 1.92 ± 0.91 for Sham), and the medication burden as calculated by Med Index 1 and Med Index 2 was not significantly different, with a difference in Med Index 1 from baseline to 6 months between rfRDN and Sham is 0.12 (~1/8 of a full dose).

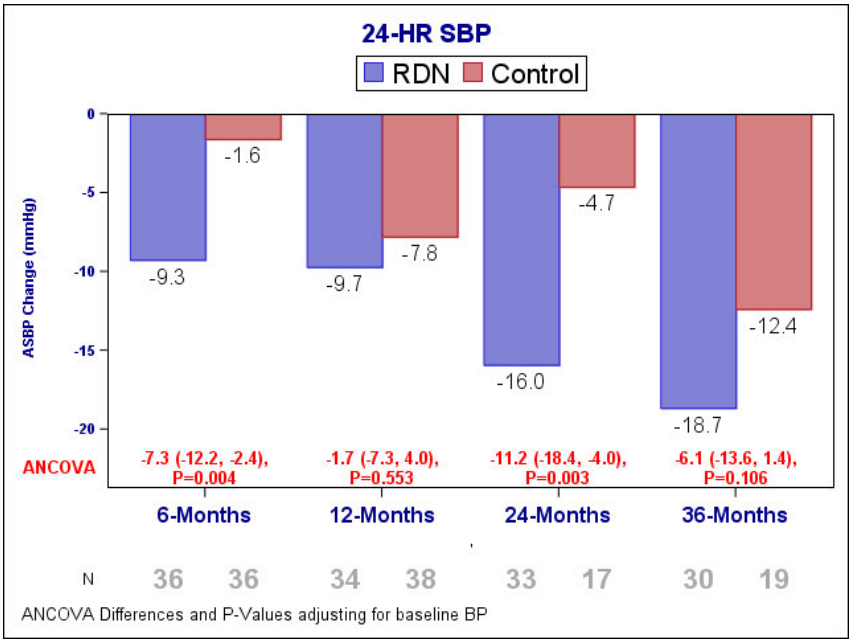
Table 19. Medication Burden Index (confirmed by drug testing) through 6 Months for HTN-ON Full Cohort

	Med Index 1			Med Index 2		
	rfRDN (n = 206)	**Sham (n = 131)**	**p-value**	**rfRDN (n = 206)**	**Sham (n = 131)**	**p-value**
Baseline	1.20 ± 0.85	1.17 ±0.87	0.737	2.92 ± 3.71	2.70 ± 3.15	0.573
3 months follow-up	1.22 ± 0.89	1.26 ± 0.86	0.150	3.03 ± 3.58	3.00 ± 3.30	0.372
6 months follow-up	1.25 ± 0.88	1.34 ± 0.83	0.073	3.14 ± 3.84	3.16 ± 2.95	0.445

Data displayed as mean ± SD
Note that all p-values are not adjusted with multiplicity and all results of HTN-ON Full cohorts are not adjusted for difference randomization ratios

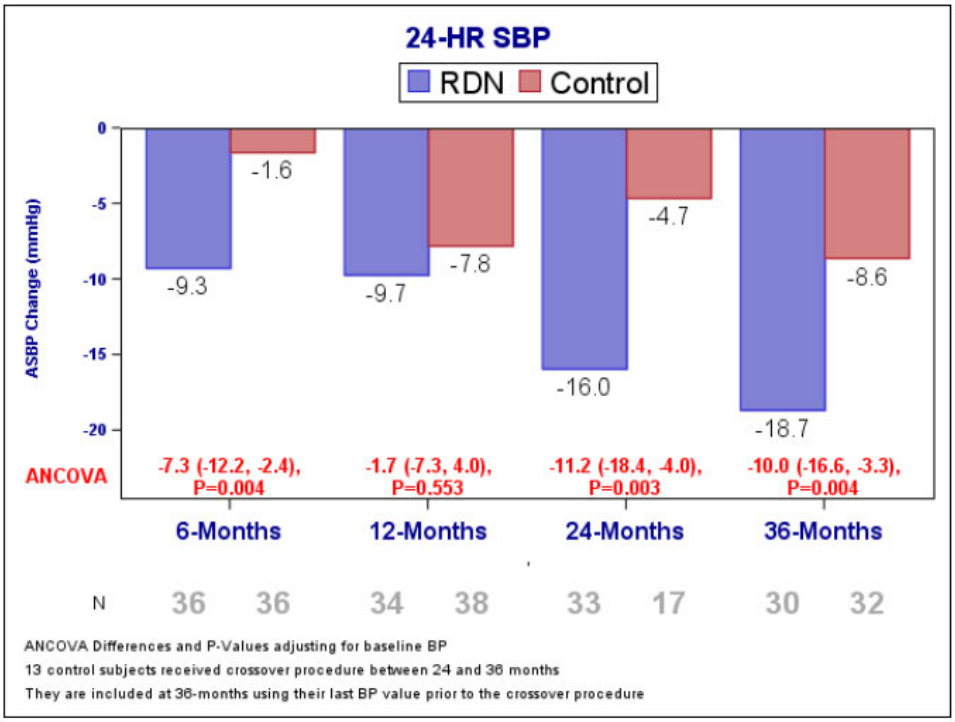
Figure 16 shows that the 24-hour SBP continued to decrease in both the rfRDN and Sham group through 36 months in the HTN-ON Pilot Cohort. The differences between rfRDN and Sham were significant at 6 and 24 months but not at 12 and 36 months. Figure 17 (reproduced from the Mahfoud, et al. publication) shows the same data except with imputation at 36 months for the 13 Sham subjects who later received rfRDN using the most recent pre-crossover measurement. [31] With imputations, the data showed a statistically significant difference between rfRDN and Sham groups at 36 months. The analysis was based on 30 subjects in the rfRDN group and 32 subjects in the sham control group. The 32 subjects in the sham control group includes 13 crossover subjects who later received rfRDN due to high BP and had their outcome imputed using their most recent pre-crossover measurement (last observation carried forward). Note that

none of the subjects in the rfRDN group were imputed, thus there is imbalance in the amount of complete data for the two groups. Moreover, since these 13 subjects had high BP measurement prior to crossover, due to the "regression towards the mean" effect the next measurement after the pre-crossover time point tends to be smaller. Therefore, the current approach of imputing the 36-month BP with the pre-crossover data could potentially introduce bias. Additionally, all the patients in the Pilot cohort were unblinded after 12 months, and the current 36-month analysis does not account for potential placebo effects. Of note, the study was not designed to answer questions related to durability of treatment effect. Due to the arguments provided above, the ANCOVA results based on the imputed data, and the p-values presented in Figure 17 should be interpreted with caution.



Note that all p-values are not adjusted with multiplicity
SBP changes are unadjusted absolute drops from baseline. Differences and p-values are determined from ANCOVA models adjusting for the baseline value

Figure 16. 24-hour SBP Changes through 36 Months (without imputation) – HTN-ON Pilot Cohort



Note that all p-values are not adjusted with multiplicity. SBP changes are unadjusted absolute drops from baseline.
SBP changes for 36 months are imputed as described above..

Figure 17. 24-hour SBP Changes through 36 Months (with imputation at 36 months) – HTN-ON Pilot Cohort [31]

Table 20 shows that in the HTN-ON Pilot Cohort, Med Indices 1 and 2 were numerically lower for the rfRDN group vs. the Sham group at all follow-up time points to 36 months, except Med Index 2 at 6 months. At 6 months (before unblinding and crossover) Med Index 1 was similar to baseline for rfRDN subjects and increased by 0.14 for Sham (~1/8 of a full drug dose). Compared to baseline, at 12 months, Med Index 1 increased by 0.28 in the rfRDN group and by 0.68 in the Sham group, corresponding to a 0.4 increase of a single standard dose medication in the Sham group vs. the rfRDN group.

At 6 months compared to baseline, Med Index 2 went down by 0.12 in the rfRDN group and increased by 0.51 in the Sham group. Compared to baseline, at 12 months, Med Index 2 increased by 0.36 in the rfRDN group and by 2.88 in the Sham group.

Table 20. Medication Burden Index using drug testing through 36 Months – HTN-ON Pilot Cohort

	MEDINDEX1			MEDINDEX2		
Mean ± SD (n)	RDN	Sham Control	p-value*	RDN	Sham Control	p-value*
Baseline	1.43 ± 1.19 (38)	1.38 ± 1.04 (42)	0.84	4.49 ± 6.32 (38)	3.66 ± 3.96 (42)	0.48
3 months	1.29 ± 1.14 (38)	1.42 ± 1.01 (42)	0.30	3.72 ± 4.98 (38)	3.75 ± 3.93 (42)	0.40
6 months	1.40 ± 1.11 (38)	1.52 ± 1.01 (42)	0.23	4.37 ± 5.65 (38)	4.17 ± 3.93 (42)	0.51
12 months	1.71 ± 0.91 (38)	2.06 ± 1.13 (42)	0.09	4.85 ± 3.50 (38)	6.54 ± 5.08 (42)	0.04
24 months	2.04 ± 1.16 (36)	2.19 ± 1.18 (41)	0.34	7.23 ± 6.40 (36)	7.52 ± 6.03 (41)	0.57
36 months	2.13 ± 1.15 (35)	2.55 ± 2.19 (39)	0.26	7.60 ± 6.14 (35)	10.31 ± 15.71 (39)	0.26

Data displayed as mean ± SD (n)
Note that all p-values are not adjusted with multiplicity

Caveats for Interpreting These Data

- Small sample sizes: <40 subjects at 6 months in both groups, and <20 in the Sham group beyond 12 months (due to subjects crossing over)
- Last available 24-hour SBP measurement at 36 months (Figure 17) was imputed for Crossover subjects (i.e., prior to crossing over after 24 months of follow-up)
- Discordance SBP reduction outcomes between the Pilot Cohort and the Expansion Cohort
  - Pilot Cohort: 7.3 mm greater 24-hour SBP reduction in rfRDN vs. Sham
  - Expansion Cohort: No difference in 24-hour SBP reduction in rfRDN vs. Sham
- Subject unblinding at 12 months

7.2.4.4 Additional Analyses

HTN-ON Win-Ratio Analysis at 6 Months

A Win-Ratio analysis compares subjects in a pairwise fashion on a set of multiple endpoints, ranked in order of importance. Each pair is compared to determine a winner or tie. The HTN-ON Win-Ratio analysis had two endpoints:

- Ambulatory SBP change of >5 mmHg in one treatment group vs. the other treatment group
- Change in Medication Index 2 (with BP medication use based on drug test)
  - The medication index was only compared if the SBP comparison resulted in a tie.
  - FDA was also interested in the results from the Win-Ratio analysis with Medication Index 1.

Table 21 and Table 22 shows the Win-Ratio analysis for the HTN-ON Full Cohort at 6 months using ASBP thresholds of 5.0 mmHg, 3.5 mmHg and 0 mmHg using Med Index 1 (Table 21a) and Med Index 2 (Table 21b).

Table 21. Win Ratio Analysis Sensitivity Analysis using Varying Thresholds (Med Index 1) – HTN-ON Full Cohort (ITT)

N = 206 X 131 = 26986 pairs	Threshold	% Pairs Win	% Pairs Lose	% Pairs Tied	WR	WR 95% CI	p-value
Scenario 1							
1. Δ 24-hour SBP (6-months)	5.0 mmHg	34.8	25.8	39.4	1.50	[1.13, 2.01]	0.006
2. ΔMedication Burden (6-months)	0.0	13.0	6.2	20.2			
Scenario 2							
1. Δ 24-hour SBP (6-months)	3.5 mmHg	38.2	28.9	32.9	1.46	[1.11, 1.93]	0.007
2. ΔMedication Burden (6-months)	0.0	11.1	4.8	17.1			
Scenario 3							
1. Δ 24-hour SBP (6-months)	0.0 mmHg	45.8	36.6	17.7	1.38	[1.07, 1.78]	0.012
2. ΔMedication Burden (6-months)	0.0	6.8	1.6	9.3			

Note that all p-values are not adjusted with multiplicity and all results of HTN-ON Expansion and Full cohorts are not adjusted for difference in randomization ratios

Table 22. Win-Ratio Analysis Sensitivity Analysis using Varying Thresholds (Med Index 2) at 6 months – HTN-ON Full Cohort (ITT)

N = 206 X 131 = 26986 pairs	Threshold	% Pairs Win	% Pairs Lose	% Pairs Tied	WR	WR 95% CI	p-value
Scenario 1							
1. Δ24-hour SBP (6-months)	5.0 mmHg	34.8	25.8	39.4	1.49	[1.13, 2.00]	0.005
2. ΔMed Index 2 (6- months)	0.0	13.2	6.5	19.7			
Scenario 2							
1. Δ24-hour SBP (6-months)	3.5 mmHg	38.2	28.9	32.9	1.45	[1.11, 1.91]	0.007
2. Δ Med Index 2 (6- months)	0.0	11.2	5.1	16.7			
Scenario 3							
1. Δ24-hour SBP (6-months)	0.0 mmHg	45.8	36.6	17.7	1.37	[1.07, 1.78]	0.013
2. Δ Med Index 2 (6-months)	0.0	6.8	1.7	9.1			

Note that all p-values are not adjusted with multiplicity and all results of HTN-ON Expansion and Full cohorts are not adjusted for difference in randomization ratios

The Win-Ratio using a 5.0 mmHg ASBP threshold was 1.49 (95% CI, 1.13 to 2.00; p=0.005) in favor of rfRDN. After back-transformation, this result corresponds to a 59.8% (95% CI, 53.0% to 66.6%) probability (1.49/(1.49+1)) of winning with rfRDN (conditional on not being a tie). In sensitivity analyses, Win-Ratios of 1.45 and 1.37 (using lower ASBP thresholds of 3.5 mmHg

and 0 mmHg, respectively) correspond to probabilities of 59.2% (95% CI, 52.5% to 65.6%) and 57.8% (95% CI, 51.7% to 64.0%) of winning with rfRDN.

FDA Comment:
In the win ratio methodology, the hierarchy of each endpoint should represent clinical superiority, and the patient who wins should be clinically better off. The Panel will be asked to comment on the interpretation of the win ratio outcome considering the clinical importance of changes in medication index.

HTN-ON Time in Target Range (TTR)

- Target SBP: OSBP ≤140 mmHg or 24-hour SBP ≤130 mmHg
- TTR methodology:
  - %TTR is calculated by linearly interpolating the blood pressure between times of measurement and calculating the percentage of time the BP is in therapeutic range.
  - %TTR calculated from baseline to 3 and 6 months.

Table 23 shows the TTR of OSBP (≤140 mmHg) and 24-hour ASBP (≤130 mmHg). For 0 to 3 months and 0 to 6 months, rfRDN subjects were in the SBP target range for a higher proportion of follow-up time vs. Sham subjects for OSBP and 24-hour ASBP.

Table 23. Percent Time in Target Range (%TTR) – HTN-ON Full Cohort

	rfRDN (TTR%)	Control (TTR%)	p-value
OFFICE SBP TTR (≤140 mmHg)[1]			
TTR 0-3 months	11.8 ± 22.6 (206)	5.8 ± 17.7 (128)	0.0004
TTR 0-6 months	13.8 ± 24.7 (206)	5.9 ± 16.5 (129)	0.0001
24hr SBP TTR (≤130 mmHg)[1]			
TTR 0-3 months	2.6 ± 9.6 (189)	1.4 ± 5.0 (113)	0.8471
TTR 0-6 months	5.8 ± 16.5 (196)	4.0 ± 12.8 (121)	0.3368
COMBINED OFFICE & 24HR TTR[2]			
Max (OSBP-140, ASBP-130) 0-3M	12.5 ± 22.9 (206)	6.8 ± 17.9 (129)	0.0073
Max (OSBP-140, ASBP-130) 0-6M	16.0 ± 26.3 (206)	8.5 ± 19.1 (129)	0.0012

Data displayed as mean ± SD (N)
[1] Analyses use all non-missing BP data from BL, 1M, 3M, 6M within time ranges
[2] The maximum value of Office TTR and 24-Hour TTR within each time period is used in combined analysis p-values from non-parametric Kruskal-Wallis test
Note that all p-values are not adjusted with multiplicity

FDA Comment:
As discussed above in Section 7.1.4.4, the panel will be asked to discuss the strengths and limitations of the TTR analysis methodology and its clinical significance as part of the totality of evidence for rfRDN effectiveness.

7.2.5 Subgroup Analyses

Subgroup Analyses by Baseline Characteristics

Figure 18 shows subgroup analyses for the difference of 24-hour SBP at 6 months for the HTN-ON Full cohort. The sample size is small for many of the subgroups, outcome differences between treatment were generally small.

Subgroup		RDN N	Sham N	24-h ambulatory systolic BP adjusted treatment difference mmHg (95% CI)	interaction p-value
Age	< 65	163	98		0.99
	≥ 65	29	18		
Sex	Male	157	88		0.84
	Female	35	28		
BMI	Tertile 1 (<28.9)	72	30		0.66
	Tertile 2 (28.9 to 33.1)	62	41		
	Tertile 3 (≥33.1)	58	45		
Type II Diabetes	Yes	21	19		0.28
	No	171	97		
Smoking Status	Current	28	19		0.29
	Former	68	36		
	Never	96	61		
Baseline eGFR(mL/min/1.73 m²)	<60	13	10		0.38
	≥ 60	179	106		
Obstructive Sleep Apnea	Yes	22	19		0.10
	No	170	97		
Geography	US	87	54		0.011
	OUS	105	62		
US Patients	Black Americans	31	15		0.21
	Non-Black Americans	56	39		
OUS location	Europe	78	46		0.37
	Japan	13	7		
	Australia	14	9		
Baseline 24-h SBP (mmHg) by tertiles	Tertile 1 (<145.3)	65	39		0.99
	Tertile 2 (145.3-151.7)	60	46		
	Tertile 3(≥151.7)	67	31		
Baseline 24-h SBP (mmHg) by median	<148.6	98	60		0.84
	≥148.6	94	56		
Baseline office SBP (mmHg) by tertiles	Tertile 1 (<159)	65	42		0.54
	Tertile 2 (159-166.3)	62	37		
	Tertile 3 (≥166.3)	65	37		
Baseline office SBP (mmHg) by median	<162	93	60		0.95
	≥162	99	56		
Baseline 24-h heart rate (bpm) by tertiles	Tertile 1 (<69.3)	71	31		0.86
	Tertile 2 (69.3-79.5)	64	42		
	Tertile 3 (≥79.5)	57	43		
Baseline 24-h heart rate (bpm) by median	<74.9	107	49		0.70
	≥74.9	85	67		
Baseline office heart rate (bpm) by tertiles	Tertile 1 (<68.7)	71	28		0.85
	Tertile 2 (68.7-79)	63	44		
	Tertile 3 (≥79)	58	44		
Baseline office heart rate (bpm) by median	<73.3	102	47		0.92
	≥73.3	90	69		
24-h pulse pressure (mmHg)	<60	160	94		0.42
	≥60	32	22		
Baseline orthostatic hypertension	Yes	61	42		0.82
	No	121	68		
Baseline orthostatic tachycardia	Yes	59	36		0.86
	No	123	74		
Medication Adherent at baseline and 6 mo	Yes	112	65		0.39
	No	80	51		
Accessory arteries treated	Yes	49	31		0.43
	No	143	85		
Number of prescribed AH medications at baseline	One	73	40		0.91
	Two	62	42		
	Three	57	34		

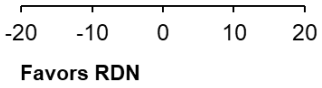


Figure 18. 24-hour SBP Subgroup Analyses at 6 Months – HTN-ON Full Cohort

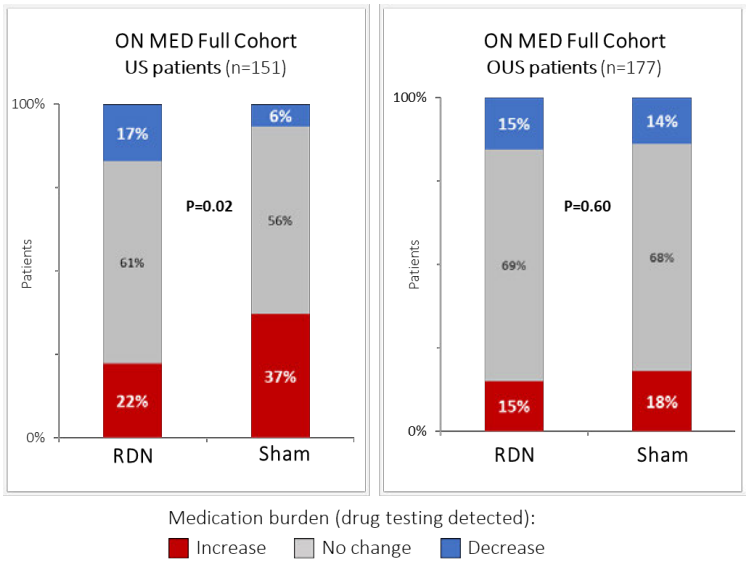
HTN-OFF and HTN-ON were not powered to assess BP responses stratified by subgroups. However, statistically significant differences in 24-hour SBP were noted in US vs OUS subjects for HTN-OFF and HTN-ON, and trends in 24-hour SBP were noted in African Americans vs non-African Americans in HTN-ON.

US vs. OUS Subjects at 6 Months (HTN-ON Full Cohort)

As shown in Figure 18 for the HTN-ON Full Cohort, significant differences were noted between the primary effectiveness endpoint in US and OUS subjects with an interaction p-value of 0.011. Sham US subjects (n=54) had a greater absolute 24-hour SBP reduction vs. OUS subjects (n=62) (6.7 vs. 2.6 mmHg, respectively).

Figure 19 shows that US patients had significant differences in medications between the rfRDN and Sham patients at 6 months (p=0.02) whereas the OUS patients did not have any significant differences in medications between the 2 groups (p=0.60) significantly.

- However, US rfRDN (n=87) subjects also had more BP medication increases vs. OUS subjects but had a smaller absolute 24-hour SBP reduction vs. OUS rfRDN subjects (n=105) (5.5 vs. 7.4 mmHg, respectively).
- The baseline adjusted difference in reduction of 24-hour ASBP between treatment groups for US subjects was 1.5 mmHg in favor of Sham and 4.8 mmHg for OUS subjects in favor of rfRDN.
- For OSBP, the baseline adjusted difference between treatment groups for subjects was 2.7 mmHg and 6.7 mmHg in favor of rfRDN for US and OUS subjects, respectively.

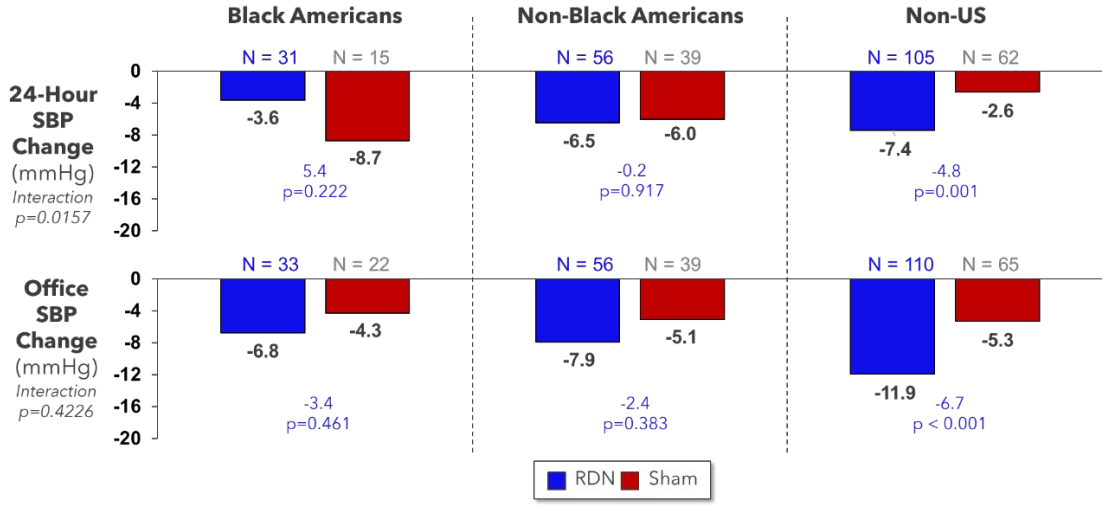


Note that all p-values are not adjusted with multiplicity

Figure 19. Antihypertensive Medication Change for US vs OUS Subjects through 6 Months – HTN-ON Full Cohort

African American Subgroup Analysis at 6 Months (HTN-ON Full Cohort)

The 24-hour SBP response was discordant between US African Americans (N=46) and US non-African Americans (N=95) at 6 months that favored the Sham group in US African Americans (Figure 20). In contrast, the OSBP reduction trend in favor of rfRDN at 6-months was generally similar between US African Americans and US non-African Americans.

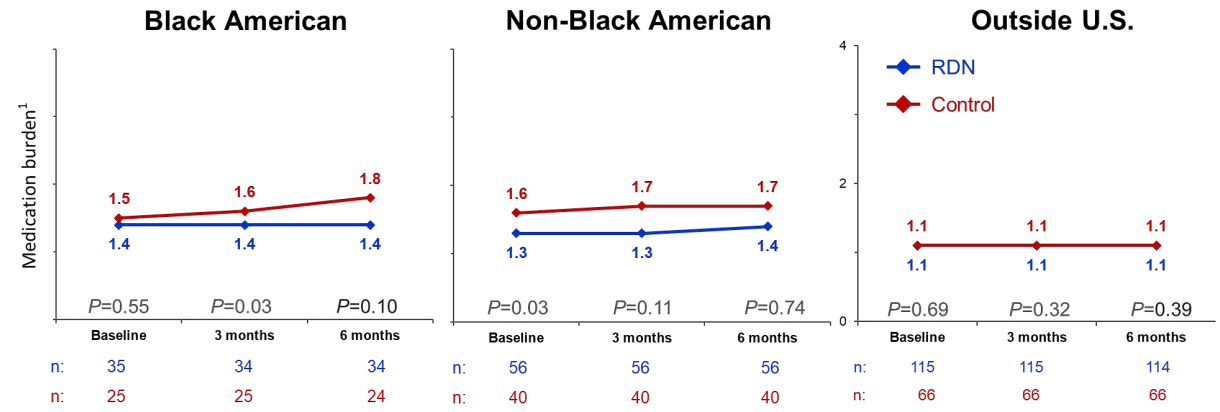


Note that all p-values are not adjusted with multiplicity
SBP changes are unadjusted absolute drops from baseline. Differences and p-values are determined from ANCOVA models adjusting for the baseline value

Figure 20. 24-hour SBP Changes for US African Americans, US Non-African Americans, and OUS Subjects at 6 Months – HTN-ON Full Cohort

Figure 21 and Figure 22 show changes in prescribed BP medication use at 6 months in US African Americans and US non-African Americans:

- US African Americans: The Sham group had a 0.3 Med Index 1 increase from baseline (corresponding to an average of ~1/3 of a maximal dose of one pill.) vs. no change in the rfRDN group.
- US non-African Americans: The Sham and rfRDN groups had a 0.1 Med Index 1 increase from baseline.



Note that all p-values are not adjusted with multiplicity

Figure 21. Prescribed Medication Changes (Med Index 1) in US African Americans, US Non-African Americans, and OUS Subjects at 6 Months – HTN-ON Full Cohort

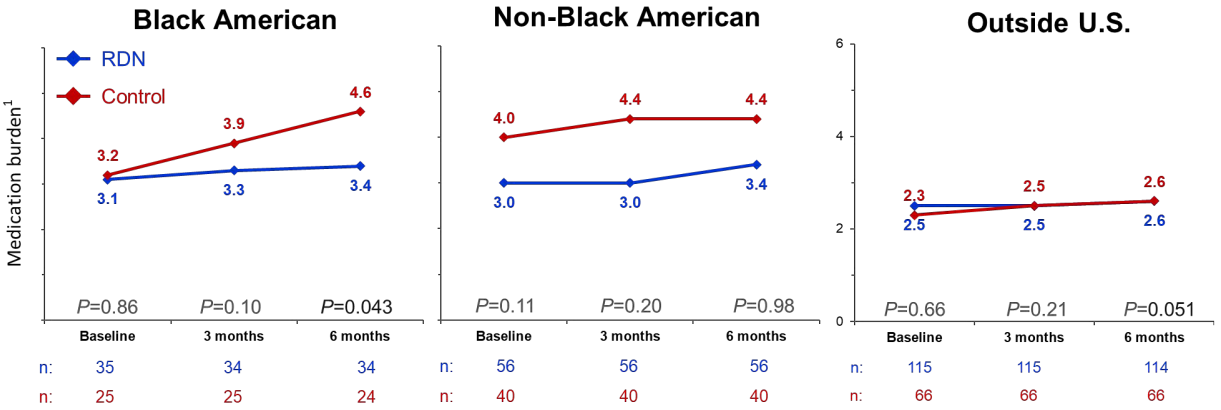
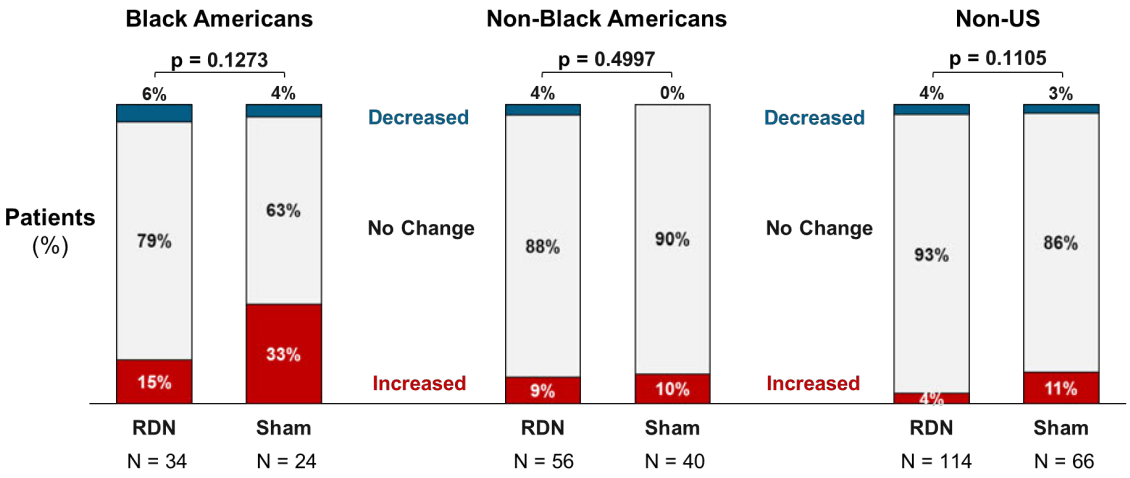


Figure 22. Prescribed Medication Changes (Med Index 2) in US African Americans, US Non-African Americans, and OUS Subjects at 6 Months – HTN-ON Full Cohort

Figure 23 shows prescribed medication changes based on Med Index 1, and Figure 24 shows these data confirmed by drug testing. A higher proportion of US African Americans in the rfRDN and Sham group had increased prescribed BP medications vs. US non-African Americans and OUS subjects. The results are similar using Med Index 2 (not shown). The BP medication increase was most pronounced in the US African American Sham group.



Note that all p-values are not adjusted with multiplicity

Figure 23. Prescribed Medication Changes (Med Index 1) in US Black Americans, US Non-Black Americans, and OUS Subjects at 6 Months – HTN-ON Full Cohort

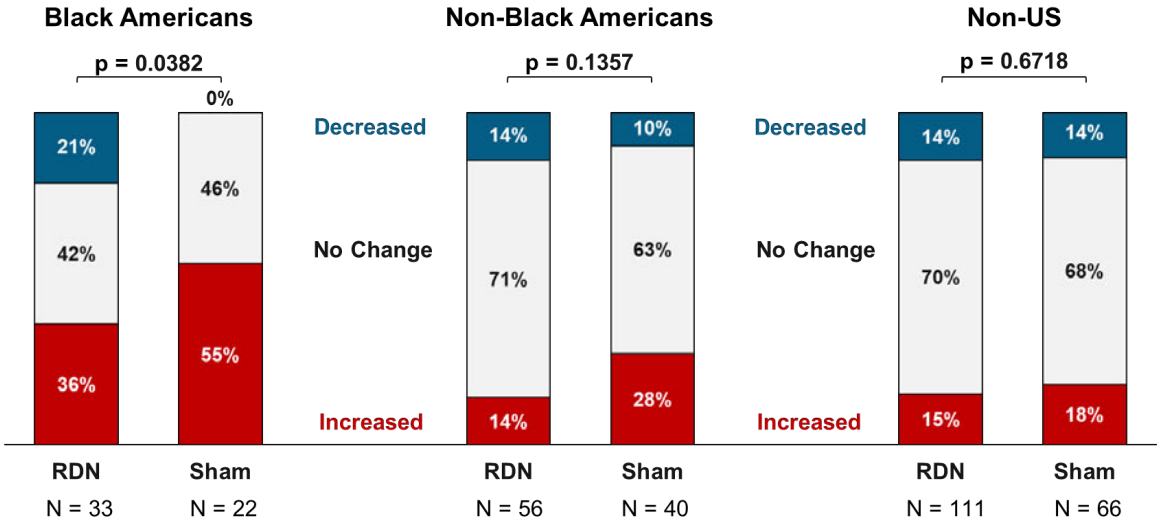


Figure 24. Prescribed Medication Changes (Med Index 1) Confirmed by Drug Testing in US Black Americans, US Non-Black Americans, and OUS Subjects at 6 Months – HTN-ON Full Cohort

These data suggest that the greater BP reduction noted for Black Americans in the Sham group may have been due to a larger increase in BP medication use vs. the rfRDN group.

FDA Comment: HTN-OFF and HTN-ON were not powered to assess BP responses stratified by subgroups. However, subgroup analyses suggest that rfRDN may be associated with a greater reduction in BP in non-US subjects vs. US subjects (HTN-OFF and HTN-ON), and BP reduction was attenuated in US rfRDN African Americans, possibly due more BP medication use in

African American Sham subjects. Subgroup sample sizes were small, and subgroup analyses should to be interpreted with caution. The Panel will be asked to discuss the clinical implications of the subgroup analyses.

Change in ASBP as a Function of Baseline Characteristics

Figure 25 shows the difference in in 24-hour SBP reductions as a function of baseline 24-hour SBP, office SBP, 24-hour HR, and office HR (stratified by tertiles). No interaction p-values reached statistical significance.

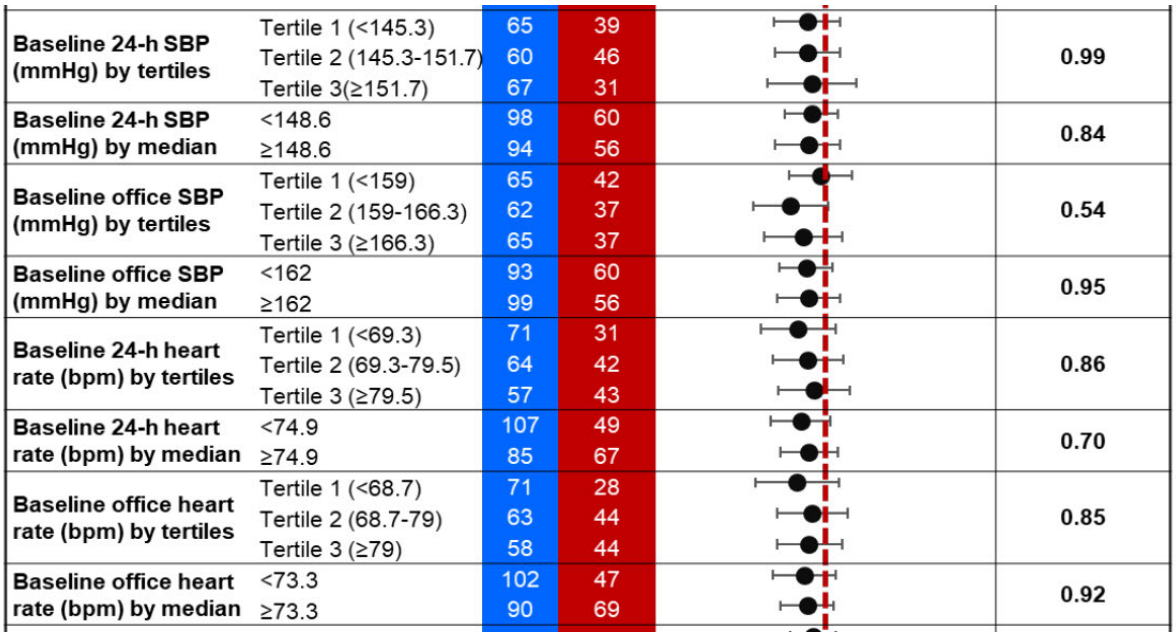
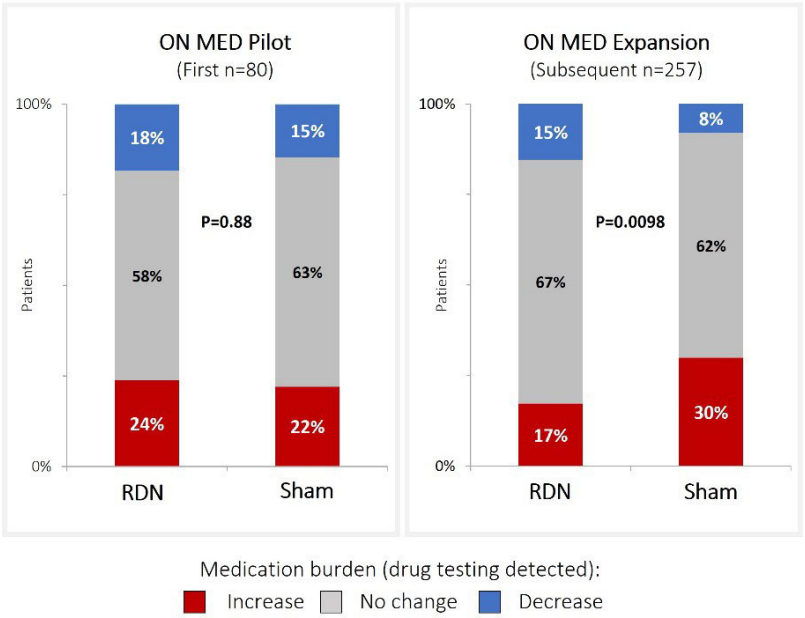


Figure 25. 24-hour SBP Reduction at 6 Months as a Function Tertiles of Baseline 24-hour SBP, Office SBP, 24-hour HR, and Office HR – HTN-ON Full Cohort

7.2.6 Potential Confounder Considerations for HTN-ON

Due the discordance between analyses for the Pilot and Expansion Cohorts, Medtronic conducted additional analyses to examine potential confounders in the HTN-ON study. Potential confounders include unbalanced medication changes between the two treatment groups and studies, non-evaluable ABPM data, and timing of pill intake related to ABPM monitoring.

Unbalanced antihypertensive medication changes: Based on drug testing, there was a higher proportion of Sham Expansion Cohort subjects that increased BP medications and a smaller proportion of Sham Pilot Cohort subjects that reduced BP medications vs the rfRDN subjects (Figure 26).



Note that all p-values are not adjusted with multiplicity

Figure 26. Medication Changes Assessed by Drug Testing at 6 Months – HTN-ON Pilot and Expansion Cohorts

Higher medication usage in Sham Expansion Cohort subjects vs. rfRDN subjects may explain the smaller effect size in 24-hour ASBP and OSBP in the Expansion Cohort compared to the Pilot Cohort (see Table 17).

Non-evaluable ABPM data: More HTN-ON Sham Expansion Cohort patients had non-evaluable ABPM data compared to the rfRDN group, related to a higher proportion of subjects meeting BP treatment escape criteria (increasing medications before planned ABPM) and due to subjects with missing ABPMs. The primary endpoint missing data rate at 6 months was 11.5% (15/131) in the Sham group vs. 6.8% (14/206) in the rfRDN group. In contrast, in HTN-OFF, the missingness rate for the primary effectiveness endpoint at 3 months was generally similar between treatment groups: 14.3% (26/182) in the rfRDN group and 16.7% (31/184) in the Sham group.

Timing of BP Medication Use in Relation to 24-hour BP Monitoring

- Medtronic notes that ABPM monitors were applied to subjects immediately after witnessed BP medication intake.
- The Sponsor suggests that the ABPM results were impacted by peak pharmacokinetic effects of drugs twice during 24 hour monitoring period: at the time of witnessed medication intake at the start and again the next morning (as shown in Figure 27).
- Sham group subjects had greater BP medication use vs rfRDN subjects, which may have resulted in a greater 24-hour SBP reduction in the Sham group.
- In contrast, office BP measurements were taken immediately prior to witnessed pill intake.

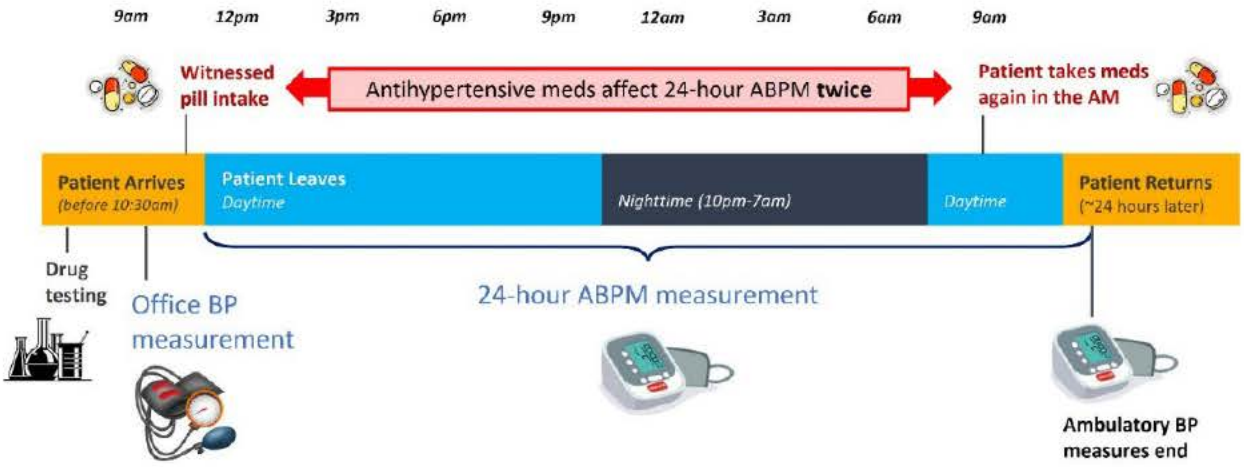


Figure 27. Timing of Pill Intake in Relation to ABPM

Medtronic conducted additional ABPM analyses using data from noon to 6 AM and midnight to 6 AM (Table 24), that eliminates a potential double medication effect. From midnight to 6 AM, there was a significant difference in ambulatory SBP in favor of rfRDN, while from noon to 6 AM, there was no significant difference in ambulatory SBP between treatment groups. Therefore, the impact of a potential doubling of BP medication effects on primary effectiveness endpoint is unclear.

Table 24. Additional Analyses of Timeframes with Reduced Impact of Medications on ABPM follow up

	Adjusted Treatment Difference (95% CI) Between RDN and Control Groups from Baseline to 6 months	**p-value**
12 PM (noon) – 6 AM Average ASBP		
Full Cohort	-1.9 (-4.5, 0.6)	0.1373
Pilot	-7.2 (-12.4, -2.0)	0.0071
Expansion Cohort	0.2 (-2.8, 3.1)	0.9117
12 AM (midnight) – 6 AM Average ASBP		
Full Cohort	-3.09 (-5.91, -0.26)	0.032
Pilot	-8.4 (-14.4, -2.4)	0.007
Expansion Cohort	-0.7 (-3.9, 2.5)	0.656

Data displayed as mean (95% CI)
Note that the p-values are not adjusted for multiplicity

7.3 Primary Safety Endpoint Results

7.3.1 Primary Safety Endpoint

The pre-specified primary safety analysis is a pooled analysis of first 253 evaluable rfRDN-treated subjects from the SPYRAL HTN-OFF and SPYRAL HTN-ON trials, defined as a patient-level composite of the incidence of the following major adverse events (MAEs):

- 1-month post-randomization adjudicated by the clinical events committee
    a. All-cause mortality
    b. End stage renal disease (ESRD)
    c. Significant embolic events resulting in end-organ damage
    d. Renal artery perforation requiring intervention
    e. Renal artery dissection requiring intervention
    f. Vascular complications (e.g., complications that require surgical repair, interventional procedures, thrombin injection or blood transfusion)
    g. Hospitalization for hypertensive crisis not related to non-adherence with BP medications or the study protocol

And

- Renal artery stenosis (RAS) at 6 months, as defined as >70% diameter stenosis by angiography confirmed by the angiographic core lab

The primary safety endpoint results are shown in Table 25. The primary safety endpoint rate was 0.4% with one-sided upper 95% confidence interval of 1.9%. The 7.1% performance goal was met (p-value < 0.001).

Table 25. Primary Safety Endpoint Analysis (Pooled rfRDN Evaluable)

	n/N	Event rate % [95% CI]	Performance goal	p-value
Composite MAE Rate	1/253	0.4% [0, 1.9%]	7.1%	<0.001

Table 26 shows the safety event rates from the pooled analysis for each study. There only reported event was a single vascular complication (pseudoaneurysm) in the HTN-ON Expansion Cohort.

Table 26. Safety Endpoint Event Rates for Each Study for the Pooled Primary Safety Analysis

Study	Safety endpoint events
HTN-OFF Pilot	0.0% (0/31)
HTN-OFF Expansion	0.0% (0/95)
HTN-ON Pilot	0.0% (0/35)
HTN-ON Expansion	4.2% (1/24)
SPYRAL HTN-OFF MED Crossovers	0.0% (0/51)
SPYRAL HTN-ON MED Crossovers	0.0% (0/17)
Total	**0. 4% (1/253)**

Data displayed as % (n/N)

Additional Analyses

FDA also requested a post-hoc analysis using the all rfRDN-treated subjects from the four studies. The results were similar across the studies, as shown in Table 27. There were 2 pseudoaneurysms requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion.

Table 27. Primary Safety Endpoint for the Pooled and Individual Studies (rfRDN Subjects)

	MAE Rate	One-sided upper 95% CI	p-value
Pre-specified Analysis of first 253 evaluable	0.4% (1/253)	1.9%	<0.001
All Studies Pooled	0.4% (2/537)	1.2%	<0.001
HTN-OFF Full Cohort	0.0% (0/182)	--	--
HTN-OFF Crossover	0.0% (0/125)	--	--
HTN-ON Full Cohort	1.0% (2/206)	--	--
HTN-ON Crossover	0.0% (0/24)	--	--

Data displayed as % (n/N)
Note that all p-values are not adjusted with multiplicity

The rates of the any pre-specified MAE through 6 months for the HTN-OFF and HTN-ON studies are shown in Table 28 for the RDN and Sham groups.

Table 28. HTN-OFF and HTN-ON MAEs through 6 months for rfRDN and Sham Subjects (Full Cohort)

	HTN-OFF % Subjects with Events (n/N)		HTN-ON % Subjects with Events (n/N)	
	rfRDN (n=182)	Sham (n=184)	rfRDN (n=206)	Sham (n=131)
All-cause mortality	0.0% (0/179)	0.0% (0/183)	0.0% (0/202)	0.0% (0/130)
New myocardial infarction	0.0% (0/179)	0.0% (0/183)	0.0% (0/202)	0.0% (0/130)
Major Bleeding	0.0% (0/179)	1.1% (2/183)	0.0% (0/202)	0.0% (0/130)
Significant embolic events resulting in end organ damage	0.0% (0/179)	0.0% (0/183)	0.0% (0/202)	0.0% (0/130)
Any renal artery reintervention	0.0% (0/179)	0.0% (0/183)	0.0% (0/202)	0.0% (0/130)
Vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion	0.0% (0/179)	0.5% (1/183)	1.0% (2/202)	0.8% (1/130)
Hypertensive emergency resulting in hospitalization	0.6% (1/179)	0.0% (0/183)	0.0% (0/202)	0.0% (0/130)
New Stroke	0.0% (0/179)	0.5% (1/183)	0.0% (0/202)	0.8% (1/130)
New renal artery stenosis (>70% diameter stenosis)	0.0% (0/163)	0.0% (0/125)	0.0% (0/187)	0.0% (0/91)

Data displayed as % (n/N)

7.3.2 Assessment of Renal Artery Stenosis

One risk of renal artery procedures is new and progression of renal artery stenosis (RAS), which could impact renal function and worsen hypertension. Duplex ultrasound (DUS) was the primary imaging modality used to assess renal artery responses to rfRDN in which a >70% diameter stenosis (DS) confirmed by angiography was considered hemodynamically significant.

However, during the FDA's 2018 Advisory Committee meeting on device treatment for HTN (Appendices 1 and 2) and during IDE protocol review with the sponsor, FDA noted that although DUS is a common screening tool for RAS, image quality can be highly operator-dependent and the methodology can lack sensitivity to identify non-hemodynamically significant <70% diameter stenoses. [32] [33] [34] [35] Additionally, during the 2018 meeting, FDA noted it remains unclear how to best evaluate for RAS in the distal renal arteries. Further, it has been recommended that the duplex diagnostic criteria utilized should be validated in individual vascular laboratories to assure the DUS results remain sensitive and accurate. [36] [37] Medtronic provided study sites with a renal artery and renal parenchymal imaging manual from an independent DUS core lab, and DUS operators received hands-on training (or remote training during the global Covid pandemic) from the DUS core lab or had several test cases evaluated and deemed of sufficient quality by the DUS core lab. The HTN-OFF and HTN-ON studies did not provide data comparing DUS with angiography, CTA, or MRA to correlate imaging sensitivity or accuracy.

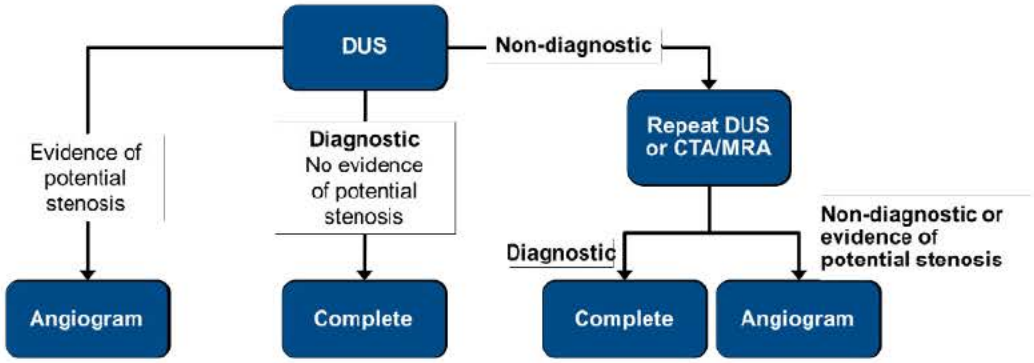
Additionally, while a 70% DS is considered hemodynamically significant, FDA is also concerned that lesions <70% could worsen over time. DUS lacks sensitivity for identifying <70% diameter renal arterial luminal narrowing. FDA recommended that computed tomography angiography (CTA) or magnetic resonance angiography (MRA) be used to assess the presence and progression of renal artery narrowing. Medtronic agreed to provide CTA or MRA data on ≥150 subjects at 12 months to better assess renal artery narrowing and the DUS sensitivity.

<u>SPYRAL HTN-OFF and HTN-ON renal artery imaging protocol</u>

Renal imaging was required at 6 and 12 months.

- First line imaging modality
  - 6 months – DUS
  - 12 months – CTA, MRA (or DUS for HTN-OFF)
- Repeat imaging modality
  - If first line was non-diagnostic, DUS, MRA, or CTA performed
  - If repeat imaging was non-diagnostic, renal angiography performed
- If a potential stenosis >60% DS by DUS or >70% DS by CTA or MRA was reported, renal angiography was required.
- Following crossover of Sham subjects to rfRDN, the imaging protocol timeline followed the schedule for subjects initially randomized to rfRDN.
- Imaging is considered *Diagnostic* if any of following criteria met:
  - Initial imaging study provided complete visualization and ability to evaluate patency for all treated renal artery segments

- Repeat imaging with either the same or an alternate imaging modality provided complete visualization of treated vessel segments that were not evaluable in the initial non-invasive imaging study
- Non-invasive imaging was not evaluable only in a vessel that did not receive renal Denervation
- For DUS images, renal flow for accessory main renal arteries and branch vessels were confirmed by visualization of uniform parenchymal flow within segments of the same kidney as well as between kidneys



Complete means no further imaging needed.

Figure 28. 6-month Imaging Protocol

Renal artery imaging quality

Table 29 shows types of renal artery imaging performed at the time of the rfRDN procedure and during follow-up. The procedural imaging modality was angiography in all subjects, and the vast majority of follow-up imaging was by DUS. Of the images evaluated by core labs, 100% of angiograms, 89% of DUS, 80% of CTAs, and 37% of MRAs met the criteria for being diagnostic.

Table 29. Total Number of Images for All Subjects through Follow-up (HTN-OFF and HTN-ON rfRDN subjects)

	ANGIO	DUS	CTA	MRA	TOTALS
Procedure Angiograms	920*	0	0	0	920
Follow-up Imaging	12	1152	252	190	1606
Percent Modality used for Follow-up Imaging	12/1606 (1%)	1152/1606 (72%)	252/1606 (15%)	190/1606 (12%)	NA
Percent Diagnostic for Follow-up Imaging	12/12 (100%)	1026/1152 (89%)	200/252(79 %)	72/190 (38%)	1310/1606 (82%)

Data displayed as n/N (%)

Of 604 rfRDN subjects that had diagnostic baseline angiograms, 519 (86%) had diagnostic follow-up imaging (the vast majority via DUS) at 6 months, and 474 (85%) had diagnostic follow-up imaging (55% DUS and 45% CTA or MRA) at 12 months.

The CTA/MRA core laboratory frequently identified study quality issues affecting the ability to confidently evaluate main and branch renal arteries, resulting in an 80% diagnostic rate for CTA and a 37% diagnostic rate for MRA. Although Medtronic suggests that CTA and MRA diagnostic rates may have been impacted by image quality issues, these rates are not consistent for sensitivity and specificity reported in literature, which often exceeds 90% for these imaging modalities. [38]

Renal artery DUS imaging results for HTN-ON and HTN-OFF

- No potential stenoses were identified with first line DUS at 6 months using the threshold of >60% diameter stenosis (DS).

Renal artery sub-study of 180 rfRDN patients with Diagnostic CTA/MRA at 12 months

- Medtronic provided results from diagnostic CTA or MRA studies on 180 rfRDN subjects at 12 months to more thoroughly evaluate the incidence of new RAS in rfRDN subjects. MDT compared 12-months post-randomization diagnostic CTA or MRA images to 6 months DUS images in the same subject.
    - Potential stenoses were identified in 31 of 180 rfRDN subjects with CTA (25/31) or MRA imaging (6/31) performed at least 12 months post rfRDN. Of these potential stenoses:
        - 22 subjects had potential stenoses of 1-25% DS, such that additional imaging was not performed
        - 2 subjects had potential stenoses of 26-50% DS, such that additional imaging was not performed
        - 2 subjects had potential stenoses of 51-75% DS
        - 5 subjects had potential stenoses >76% DS
        - None of the 31 subjects exhibited significant worsening of HTN
    - In 180 subjects with evaluable data at 12 months, no hemodynamically significant stenosis was detected by DUS at 6 months.
    - In the 7 subjects in the sub-study that had a potential stenosis >50% DS by initial 12-month CTA or MRA, subsequent imaging to assess the potential renal artery stenosis was as follows:
        - 3 subjects underwent follow-up angiography and reported no stenosis
        - 2 subjects underwent follow-up angiography and reported no stenosis, but imaging was of insufficient quality to calculate a DS
        - 1 subject underwent follow-up CTA/MRA, which confirmed 60% DS
        - 1 subject had no follow-up imaging; 12 month CTA result (60%DS) carried forward

There were 39 additional potential stenoses in 28 subjects that did not meet the analysis criteria above (both 6-month DUS and 12 month CTA/MRA). In total, there were 84 potential stenoses identified in 59 subjects, as described in the additional analyses of all subjects below.

Additional Analysis of Pooled HTN-OFF and HTN-ON rfRDN Subjects with a Potential >50% Diameter Stenosis Identified on Follow-up Imaging by CTA or MRA,

- There were 206 subjects that had CTA or MRA diagnostic images at least 12 months post rfRDN treatment.
    - 59 of 206 rfRDN subjects had potential stenoses identified by diagnostic CTA or MRA imaging
        - 8 subjects had a potential >76-99% DS
            - 5 subjects had renal angiograms ruling out a >70% DS
            - 1 subject refused a renal angiogram and exited the study
            - 1 subject refused renal angiography; follow-up DUS ruled out a potential stenosis >60% DS
            - 1 subject refused renal angiography, follow-up CTA and MRA ruled out a potential stenosis >70% DS
        - 5 subjects had a potential >50-76% DS
            - 1 subject had a renal angiogram ruling out a >70% DS
            - 2 subjects refused renal angiography; follow-up DUS ruled out a potential stenoses
            - 1 subject had a repeat CTA, which confirmed stenosis of 60%. Per protocol, an angiogram was not required.
            - 1 subject did not have repeat imaging, the initial CTA reported stenosis of 60%. Per protocol, an angiogram was not required.
        - In the 13 subjects in the additional pooled analysis that had a potential stenosis >50% DS by initial 12-month CTA or MRA, subsequent imaging to assess the potential renal artery stenosis was as follows:
            - 4 subjects underwent follow-up angiography and reported no stenosis
            - 2 subjects underwent follow-up angiography and reported no stenosis, but imaging was of insufficient quality to calculate a DS
            - 3 subjects underwent follow-up DUS
            - 2 subjects underwent follow-up CTA/MRA
            - 1 subject had no follow-up imaging; 12 month CTA result (60%DS) carried forward
            - 1 subject refused follow-up imaging

            - Overall, 4 of 13 subjects did not receive confirmatory imaging by angiogram or CTA/MRA to evaluate the stenosis
                - 3 of 13 subjects received a DUS instead of angiogram
                - 1 of 13 subjects refused follow-up imaging

Rates of renal artery stenosis

Sub-study of 180 CTA/MRA rfRDN subjects

- If stenosis is assumed to occur based on initial 12 month CTA or MRA imaging:
  - The per patient rate of a >50% DS could be as high as 3.9% (7/180 subjects)
- Considering the results of the subsequent confirmatory imaging performed:
  - The per patient rate of a >50% DS could be as high as 1.1% (2/180) since 2 subjects had 60% stenosis by CTA.
  - If one assumes that the 2 subjects in whom the angiography was of insufficient quality to calculate a DS had a >50% DS, the per patient rate could be as high as 2.2% (4/180).

Additional analysis of pooled HTN-OFF and HTN-ON rfRDN Subjects (N=206)

- If stenosis is assumed to occur based on initial 12 month CTA or MRA imaging:
  - The per patient rate of a >50% DS could be as high as 6.3% (13/206)
- Considering the results of the subsequent confirmatory imaging performed:
  - The per patient rate of a >50% DS could be as high as 2.9% (6/206) since 4 subjects did not receive confirmatory imaging by either angiogram or CTA/MRA, and 2 subjects had 60% stenosis confirmed by CTA.
  - If one assumes that the 2 subjects in whom the angiography was of insufficient quality to calculate a DS had a >50% DS, the per patient rate could be as high as 3.9% (8/206).

FDA comment: FDA recommended diagnostic CTA/MRA at 6 and 12 months on all rfRDN subjects. Medtronic developed a renal imaging protocol using DUS as a primary imaging method. As noted above, DUS may have less sensitivity for detecting renal artery stenosis than CTA, MRA, or invasive angiography and it has been recommended that DUS diagnostic criteria be validated by individual vascular laboratories to support its sensitivity and accuracy. The HTN-ON/OFF studies did not provide data to determine the correlation of DUS with angiography/CT/MRA. Considering the 12 month CTA/MRA sub-study results, the rate of a >50% diameter stenosis could be as high as 3.9% subjects based on initial 12 month imaging. The Panel will be asked to discuss the renal artery imaging results to support the safety profile of the device.

7.3.3 Secondary Safety Endpoints

Renal Function (Estimated Glomerular Filtration Rate, eGFR)

Changes in renal function vs. baseline, assessed by calculating eGFR from serum creatinine (in mL/min per 1.73m^2), were pooled for HTN-OFF and HTN-ON. Among 389 rfRDN subjects, 52 (13%) had a >10% decline in eGFR during follow-up. Comparatively, 74/297 (24.9%) Sham subjects had a >10% decline in eGFR during follow-up. FDA requested data on the change in eGFR slope for rfRDN and Sham subjects for available follow-up. For this analysis, changes in serum creatinine (SCr) and eGFR from baseline to 3-month follow up for both cohorts were evaluated by a linear mixed model. The average decline in the Sham group was numerically higher vs. the rfRDN group: -1.36 vs. -1.19 mL/min/1.73m^2 (p=0.2).

For comparison, a meta-analysis of 6 sham-controlled RDN trials showed no significant difference in eGFR between RDN-treated and controls (-0.40 mL/min/1.73m^2; 95% CI: -1.94 to 1.47; p=NS; N=543 subjects) 9 months post-RDN or Sham procedure. [39]

Figure 29 shows eGFR in rfRDN and Sham subjects for HTN-OFF and HTN-ON over the two-year period after randomization for all subjects (left-hand panel) and subjects with baseline eGFR <60 ml/min. (right-hand panel). The changes in eGFR are similar in rfRDN and Sham subjects, independent of baseline eGFR.

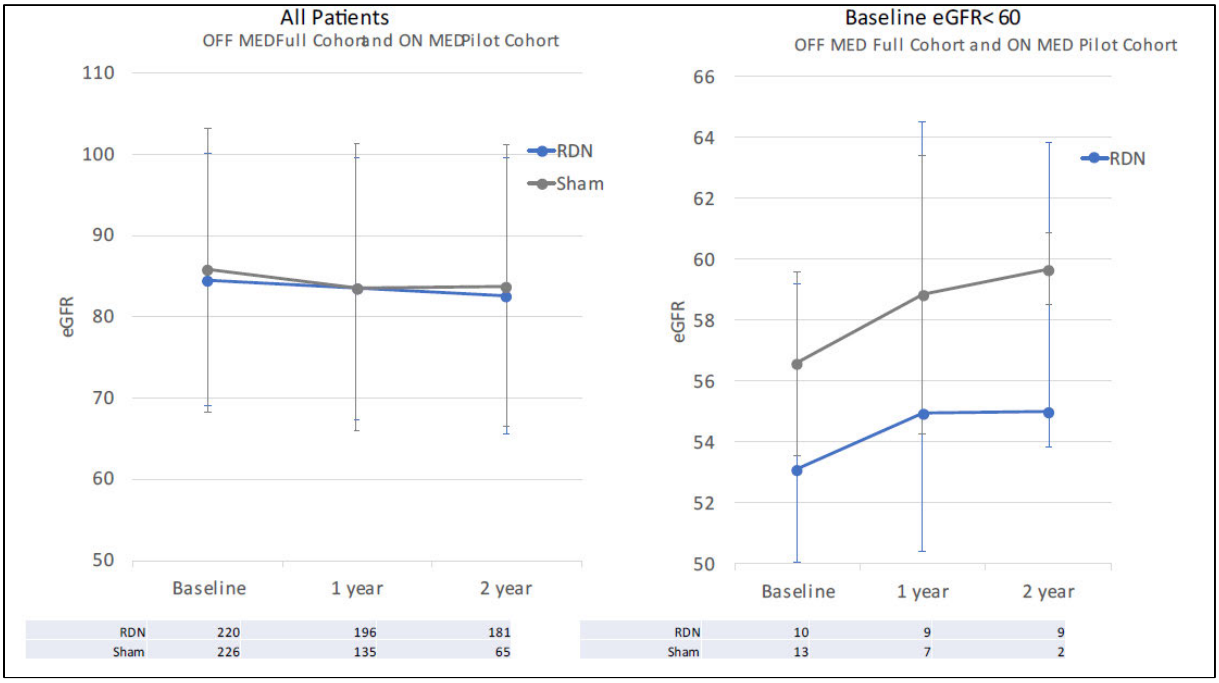


Figure 29. Change in eGFR for HTN-OFF (Full Cohort) and HTN-ON (Pilot) (Combined)

Hematoma

Hematomas were assessed in 960 subjects: 703 randomized subjects + 206 crossovers + 51 renal artery anatomical screen failures. Of these 960 subjects, 111 (11.6%) developed a hematoma. Hematomas were noted in 40 subjects in HTN-ON (25 rfRDN, 15 Control; 2:1 randomization) and 71 subjects in HTN-OFF (35 rfRDN, 36 Control; 1:1 randomization). Of the hematomas (subjects could have >1), 6% (58/960) were classified as 0 or 1 (bruise to mild); 4% (41/960; 17 rfRDN; 24 Sham) moderate; 6% (53/960) moderate to severe; <1% (6/960; 5 rfRDN; 1 Sham) severe, and <1% (6/960; 3 rfRDN; 3 Sham) severe, extending below the knee or above the hip. The incidence and severity of hematomas was similar between groups.

7.4 HTN-OFF and HTN-ON Study Blinding Analysis

Table 30 shows the subject and BP assessor blinding assessment at discharge, 3 months, and 6 months (HTN-ON only).

The James blinding index ranges from 0 (all patients correctly guessed their study-group assignments) to 1 (all patients incorrectly guessed their study-group assignments), with values greater than 0.5 indicating successful blinding. The results demonstrate that adequate blinding was maintained for most of the subjects and assessors.

Table 30. James Blinding Index for Subjects and Blood Pressure Assessors – HTN-OFF and HTN-ON Full Cohort

	Subject Blinding Index (95% CI)	**BP Assessor Blinding Index (95% CI)**
HTN-OFF		
Discharge	0.66 (0.61, 0.71)	0.82 (0.78, 0.86)
3-Months	0.53 (0.48, 0.59)	0.73 (0.68, 0.78)
HTN-ON		
Discharge	0.68 (0.63, 0.73)	0.82 (0.78, 0.87)
3-Months	0.58 (0.53, 0.63)	0.75 (0.70, 0.79)
6-Months	0.58 (0.53, 0.63)	0.73 (0.68, 0.78)

8 Patient Preference Study

Medtronic conducted a patient preference study as a discrete choice experiment on 400 US patients to view attitudes towards interventional treatment (i.e., rfRDN) versus pills only to treat hypertension. Recruiting and data collection were initiated on October 14, 2020, and the study was completed on March 17, 2021.

Table 31 shows selected subject demographics and HTN experience.

Table 31. Patient Preference Study Subject Demographics

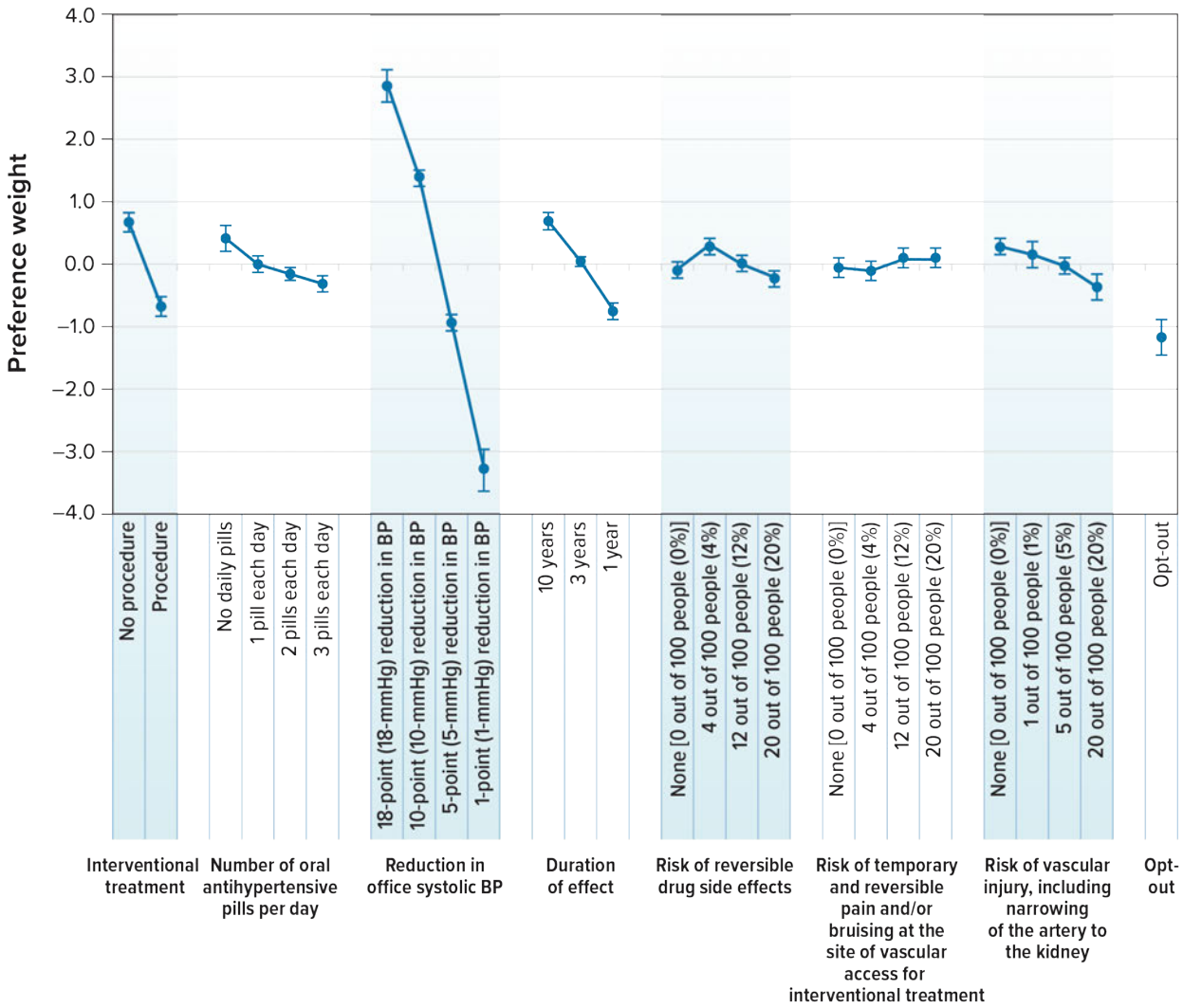
	Respondents (N=400)
Age	59.2 (13.0)
Minimum, maximum	25.0, 79.0
Sex	
Male	194 (48.5%)
Female	206 (51.5%)
Race or ethnicity	
American Indian or Alaska Native	3 (0.8%)
Asian	20 (5.0%)
Black or African American	59 (14.8%)
Hispanic or Latino	36 (9.0%)

	Respondents (N=400)
Middle Eastern or North African	4 (1.0%)
Native Hawaiian or other Pacific Islander	4 (1.0%)
White	269 (67.3%)
Other	5 (1.3%)
When did a doctor first tell you that you had high blood pressure?	
Less than a year ago	53 (13.3%)
1 to 5 years ago	118 (29.5%)
6 to 10 years ago	111 (27.8%)
11 to 15 years ago	52 (13.0%)
More than 15 years ago	66 (16.5%)
Do not know or not sure	0 (0.0%)
Which of the following have you ever used to try to reduce your blood pressure? (Select all that apply.)	
Lifestyle and dietary changes (for example, eating less salt, saturated fat, sweets; losing weight; drinking less alcohol; eating more fruits and vegetables)	279 (69.8%)
Exercise or physical activities	225 (56.3%)
Dietary supplements (for example, potassium, probiotics, fish oil)	173 (43.3%)
Stress reduction or relaxation techniques	111 (27.8%)
Prescription oral medicine	362 (90.5%)
Prescription medicine patch applied to the skin	30 (7.5%)
Other	46 (11.5%)
I have never tried to reduce my blood pressure using prescription medicines or other activities	5 (1.3%)

Data displayed as n (%)

Appendix 5, Table 5.1 includes the attributes and levels for the patient preference study. Attributes were chosen based on the clinical protocol, literature, and discussions with FDA. At a high level, the study was conducted in accordance with recommended practices, and patient preference results were generally as expected.

Figure 30 shows the results from the patient preference study.



BP = blood pressure; HTN = hypertension.
Note: The parameter estimates are the preference weights corresponding to the effects-coded attribute levels. The effects-coded variables are categorical variables ranging from −1 to 1. The preference weights corresponding to the effects-coded variables are log odds, which are distributed symmetrically around zero. The vertical bars surrounding each mean preference weight denote the 95% confidence interval about the point estimate. The opt-out, or no treatment, variable is dummy coded. So, the opt-out preference weight is a measure of the relative importance of no HTN treatment compared with the average HTN treatment in the survey.

Figure 30. Preference Weights for Treatment Attributes

In Figure 30, the longer the distance or length of each line representing an attribute labeled at the bottom of the figure, the greater importance that respondents on average gave to that attribute. The "Reduction in office systolic BP" has the largest vertical distance. Therefore, it was the attribute given the most weight on average by respondents.

Based on the overall patient preference study results, various clinical scenarios meant to be similar to possible hypertension treatments were developed. The preference weights were used to develop a model which was used to estimate the percentage of the sample likely to choose the treatment profile. One example scenario is described in Table 32.

Table 32. Example Scenario

Attribute	Interventional Treatment	Pills only: increase in pills	No treatment option
Interventional treatment	Yes	No	No treatment
Change in number of oral antihypertensive pills per day	No change	Increase	
Reduction in office SBP (mmHg)	9.4	10.0	
Duration of effect	1 year	1 year	
Risk of reversible drug side effects	10.0%	10.0%	
Risk of temporary and reversible pain and/or bruising at the site of vascular access for interventional treatment	13.0%	0.0% (N/A)	
Risk of vascular injury, including narrowing of the artery to the kidney	0.3%	0.0% (N/A)	
Average predicted likelihood of selecting treatment profile (95% CI)	**18.70% (31.61-23.80)**	**76.59% (70.90-82.28)**	**4.71% (3.14-6.27)**

In the example scenario above, assuming an 9.4 mmHg OSBP reduction for post-interventional procedure, 18.7% of patients prefer the interventional treatment. Models used safety and efficacy results from the HTN-OFF and HTN-ON studies. In general, the scenarios suggest that between 15.1% - 30.9% of patients would select a RDN system intervention based on expected outcomes.

FDA Comment: The Panel will be asked to discuss to what extent the results of the patient preference study support that the benefits outweigh the risks of the subject device for the proposed indication for use.

9 Additional Clinical Studies

9.1 SYMPLICITY HTN-3 Long-Term Follow-up

The SYMPLICITY HTN-3 study was a US multi-center, randomized (2:1) controlled trial in 535 subjects (364 rfRDN, 171 Sham. [25, 26] The study evaluated the Symplicity Flex RDN device, an earlier version of the current PMA device. The study failed to meet the primary and secondary endpoints of reductions in office and 24-hour ambulatory baseline-adjusted BP at 6 months with difference of -1.96 mmHg (p=0.98) between the rfRDN and Sham groups.

Bhatt et al described long-term SYMPLICITY HTN-3 BP outcomes. [26] Figure 31 and Figure 32 reproduced from the publication show the 24-hour SBP and BP medications, respectively, through 3 years follow-up. These data show a continued 24-hour SBP decline over 36-months follow-up in the RDN group and no change in the Sham group. Med Index 1 and Med Index 2 analyses showed a trend towards lower BP medication use in the rfRDN group.

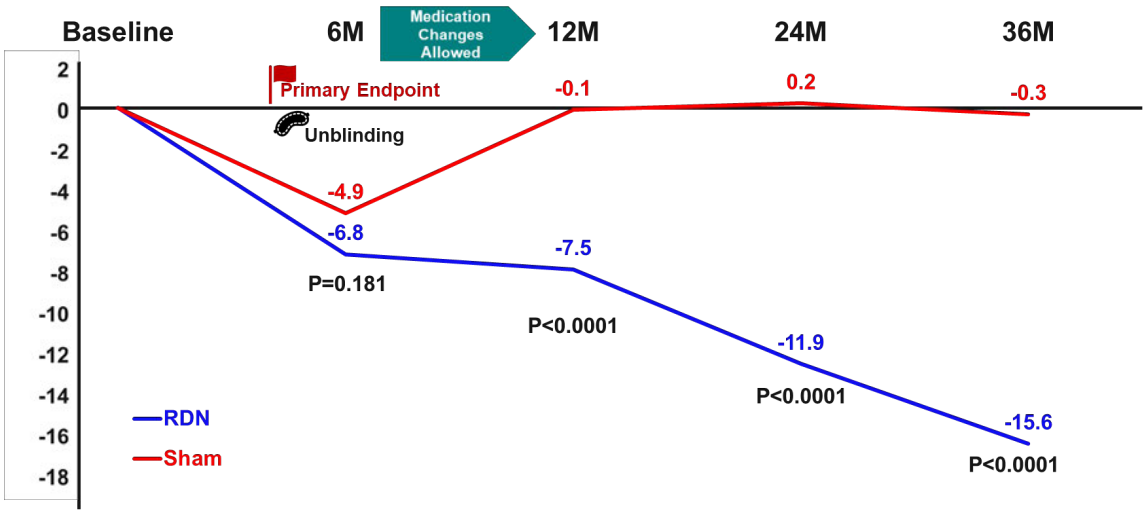


Figure 31. 24-hour SBP through 3 Years for SYMPLICITY HTN-3

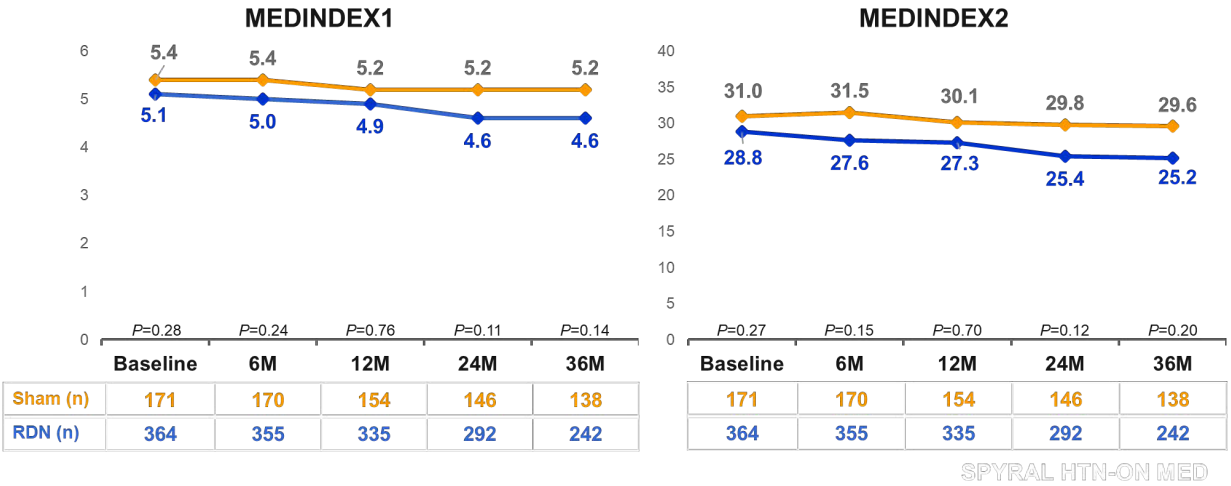


Figure 32. Anti-hypertensive Medications through 3 Years for SYMPLICITY HTN-3

Long-Term SYMPLICITY HTN 3 Outcome Considerations

As with HTN-ON, there were potential confounders that could bias the results against the Sham group including reduced Sham group size due to crossovers, unblinding, and imputation for missing data. The authors acknowledge that following unblinding at 6 months, BP increased in the non-crossover control group while the BP in the rfRDN group continued to decrease, suggesting placebo or Hawthorne effects affecting the long-term BP results. Additionally, SYMPLICITY HTN 3 studied an earlier version of the RDN device, and only the proximal portion of the renal artery underwent RDN treatment.

9.2 SPYRAL DYSTAL

Study design: Single-arm feasibility study evaluating Symplicity Spyral rfRDN catheter (subject device of the current PMA) in the distal main renal arteries and first order renal artery branches

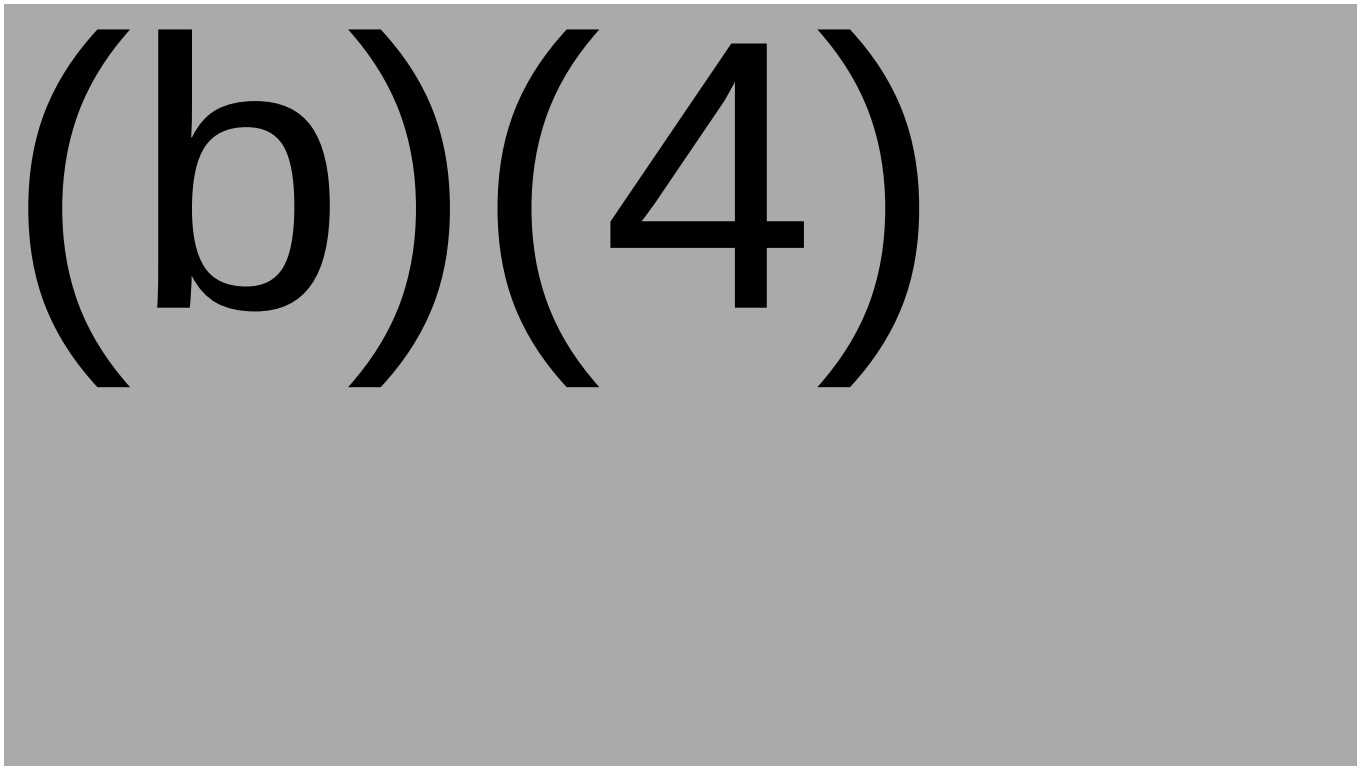
Subjects: 56 subjects (at 9 study sites) with uncontrolled HTN withdrawn from medication (similar to HTN-OFF) and followed through 12 months

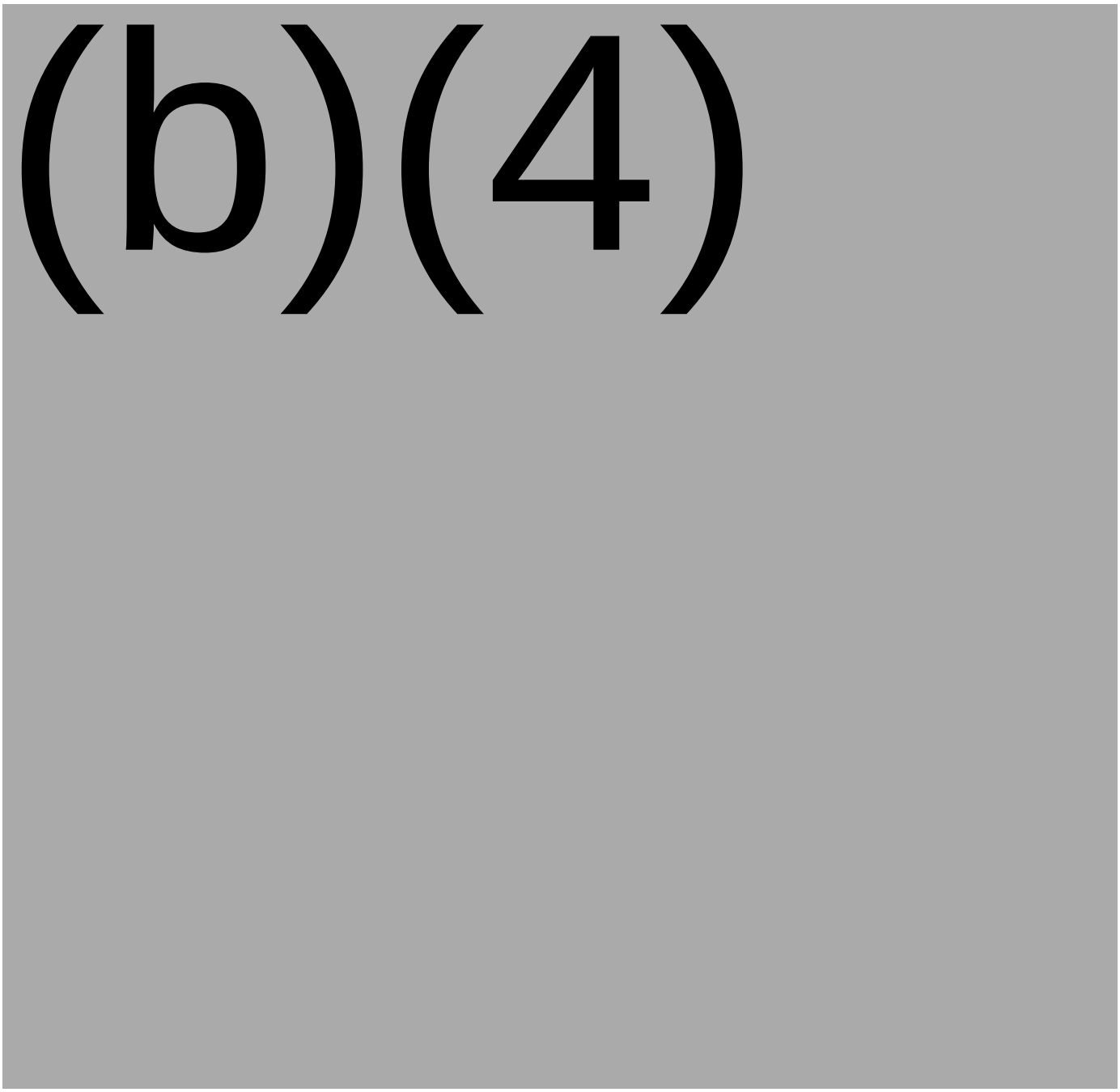
Safety Endpoint: Composite of MAE at 1 month:

- All-cause mortality
- End-stage renal disease
- Significant embolic event resulting in end-organ damage
- Renal artery perforation requiring intervention
- Renal artery dissection requiring intervention
- Vascular complications
- Hospitalization for hypertensive crisis not related to confirmed non-adherence with medications or the protocol
- New renal artery stenosis, defined as >70% diameter stenosis, confirmed by angiography and determined by the angiographic core lab at 6-months follow-up

Select effectiveness endpoints:

- Change in 24-hour ASBP at 3 months with a propensity score stratified analysis vs. the HTN-OFF rfRDN group (Full Cohort)
- Change in OSBP

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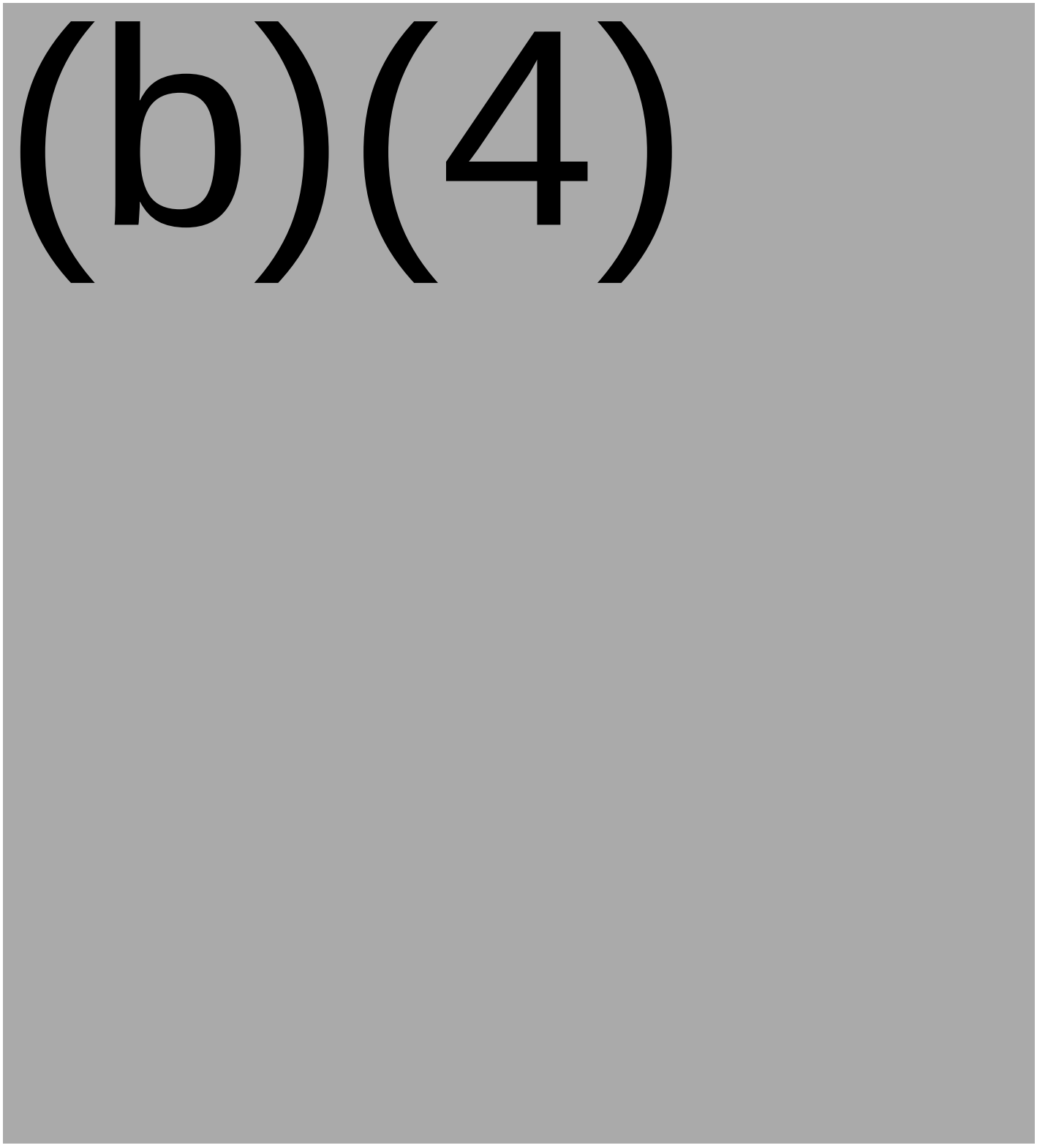
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9.3 Global SYMPLICITY Registry

The Global SYMPLICITY Registry (GSR) is a prospective, multi-center, single-arm, non-interventional and open label registry. The Global SYMPLICITY Registry aims to include a patient population resembling real world clinical practice. The GSR began enrolling subjects in 2012 in countries where Medtronic's renal denervation system is approved.

The GSR includes subjects treated using both the Symplicity Flex (single electrode) and Symplicity Spyral (multi-electrode) catheters and is intended to enroll up to 5000 subjects ≥18 years of age. In the GSR, subjects were included that have different comorbidities vs. the randomized controlled trials, and subgroup analyses were performed.

Subject follow-up is planned at 3, 6, and 12 months and then annually for 3-5 years. However, the actual follow-up visits are based upon the hospital's standard of care for renal denervation.

Table 35 shows the office SBP and DBP for the Symplicity Spyral catheter (subject of the current PMA) and the Symplicity Flex catheter. BP reduction was greater than observed in the sham-controlled HTN-OFF and HTN-ON RCTs and was similar to prior single-arm studies (such as HTN-2), which raises the potential for a placebo effect.

Table 35. GSR Office SBP and DBP from Baseline to 36-months in Subjects Treated with the Symplicity Spyral and Flex Catheters

	Baseline	Change at 6-months	Change at 12-months	Change at 24-months	Change at 36-months
Symplicity Spyral Catheter					
Ambulatory SBP	155.20 ± 20.10, N=542	-7.69 ± 18.72, N=289	-8.77 ± 18.04, N=242	-8.83 ± 17.96, N=132	-14.39 ± 21.93, N=74
Ambulatory DBP	88.10 ± 15.18, N=542	-4.88 ± 10.76, N=289	-4.90 ± 10.62, N=242	-4.42 ± 10.05, N=132	-6.12 ± 12.33, N=74
Office SBP	165.83 ± 24.82 (792)	-14.23 ± 25.76 (517)	-15.18 ± 26.54 (475)	-13.99 ± 27.59 (331)	-18.07 ± 26.76 (200)
Office DBP	91.19 ± 17.44 (792)	-5.52 ± 14.07 (515)	-6.42 ± 14.77 (473)	-7.67 ± 15.06 (326)	-7.79 ± 15.68 (195)
Symplicity Flex Catheter					
Ambulatory SBP	153.99 ± 18.18, N=1554	-7.21 ± 17.76, N=965	-8.06 ± 18.87, N=880	-8.89 ± 19.83, N=609	-8.13 ± 19.83, N=459
Ambulatory DBP	86.51 ± 14.17, N=1555	-4.21 ± 10.45, N=966	-4.47 ± 11.66, N=881	-4.88 ± 11.42, N=610	-4.30 ± 12.05, N=460
Office SBP	165.48 ± 24.81 (2169)	-12.85 ± 26.20 (1691)	-13.68 ± 26.67 (1617)	-15.62 ± 27.52 (1275)	-16.42 ± 28.69 (1068)
Office DBP	89.79 ± 16.51 (2170)	-4.55 ± 14.31 (1686)	-5.12 ± 15.01 (1616)	-6.21 ±16.00 (1273)	-6.13 ± 16.18 (1064)

Data displayed as mean ± SD (n); SBP/DBP: Systolic/diastolic blood pressure

GSR Considerations

- The GSR includes two different versions of the device – Symplicity Flex (single electrode) and Symplicity Spyral (multi-electrode).
- The GSR evaluates changes in OBP and ABP (when available) whereas in the HTN-OFF and HTN-ON studies, the primary effectiveness endpoint is ASBP in every subject.
- Patients enrolled in the GSR were unblinded, and there is no concurrent control group.

10 Postmarket Study

Medtronic plans to continue follow-up of subjects in HTN-OFF and HTN-ON trials for an additional 24 months to assess long-term safety, effectiveness, and BP reduction durability at 5 years post rfRDN. In addition, they plan to transition the AFFIRM continued access study to a postmarket study. The AFFIRM study is a multi-center, international, prospective, interventional, single-arm study designed to evaluate renal denervation in a real-world population aiming to enroll up to 1200 subjects at 100 sites with varying severities of uncontrolled hypertension and associated cardiovascular risk factors and comorbidities, including patient populations with chronic kidney disease, isolated systolic HTN, and type 2 diabetes mellitus. Patients are to continue BP medications through 6 months similar to the HTN-ON study. ABPM will be performed in the first 250 subjects and OBM in the remaining subjects.

To evaluate effectiveness, the change in OSBP, home BP, 24-hour ASBP will be analyzed for newly enrolled AFFIRM subjects through 36 months follow-up. Other endpoints include procedural characteristics, BP medication burden, proportion of subjects requiring repeat RDN, and TTR (defined as OSBP < 140 mmHg). The following powered analyses are planned with the primary endpoint being the change in OBP from baseline to 6 months with the following performance goals:

- Isolated systolic hypertension: Difference of at least -4.2 mmHg
- Chronic kidney disease: Difference of at least -4.1 mmHg
- Diabetes mellitus type 2: Difference of at least -4.9 mmHg

For safety, the incidence of MAEs will be evaluated throughout the trial.

11 Conclusion

HTN-OFF and HTN-ON were designed to demonstrate the safety and effectiveness of the Symplicity Spyral System compared to sham control in subjects with uncontrolled hypertension.

The pooled safety analysis of the first 253 evaluable rfRDN treated subjects of the composite of MAEs through 30 days and 6-month RAS was 0.4%. The results for the individual Pilot, Expansion, and Full Cohorts were similar. The safety endpoint rate met the performance goal of 7.1%. In both HTN-OFF and HTN-ON, the incidence of post-RDN safety events was low and generally of transient nature. FDA is seeking Panel input on rfRDN safety profile (device and procedure-related major adverse events and renal vascular response).

Regarding effectiveness, HTN-OFF met its primary effectiveness endpoint of the difference in 24-hour ASBP. Subjects treated with rfRDN had a statistically significant greater reductions in 24-hour (3.9 mmHg) and office SBP (6.5 mmHg) at 3 months compared to Sham subjects during the time of medication withdrawal. This BP reduction effect in favor of rfRDN was attenuated when BP medications were restarted, and patients were treated to goal (<140 mmHg).

HTN-ON did not meet its primary effectiveness endpoint. There was no difference in 24-hour SBP (0.03 mmHg) between the rfRDN and Sham groups in HTN-ON who maintained their BP medications, although there was a 4.1 mmHg difference in reduction for OSBP, favoring rfRDN-treatment. There were several confounders that may have impacted the HTN-ON outcomes, including unbalanced medication changes between the two treatment groups, unbalanced missing ABPM data, and timing of pill intake related to ABPM monitoring.

To assess the durability of BP lowering effectiveness, 24-hour and office SBP and medication burden were evaluated. While there tended to be little difference between 24-hour and office SBP at the later timepoints between rfRDN subjects and Sham subjects, medication burden trended slightly higher in the Sham group in the HTN-OFF trial. Limited long-term data are available for the HTN-ON Full Cohort.

FDA is seeking Panel input on the magnitude and potential clinical impact of rfRDN effectiveness, the relative importance of BP measurement methods (ambulatory BP vs. office BP assessment), and the durability of BP reduction.

Because of the importance of HTN treatment for US public health and FDA's mission to bring new safe and effective treatments to patients, we seek Panel input on the assessment of benefits and risks rfRDN and whether the information provided demonstrates a reasonable assurance of device 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, the benefits to health outweigh the risks, and there is an absence of unreasonable risk (safety), and that there are clinically significant results in a significant portion of the target population (effectiveness).

FDA is seeking input on the device labeling and a post-approval study (if the device is approved). It is important to understand the benefits and the risks of the device in a diverse patient population. 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.

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13 Appendices

Appendix 1. 2018 Panel Pack
Appendix 2. Panel 24-hour Summary
Appendix 3. HARC Document
Appendix 4. Bayesian Power Prior Methodology
Appendix 5. Supplemental Clinical Data