SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Ablation catheter, renal denervation
Device Trade Name:	Symplicity Spyral™ Renal Denervation System
Device Procode:	QYI
Applicant's Name and Address:	Medtronic Vascular 3576 Unocal Place Santa Rosa, CA 95403 USA
Date of Panel Recommendation:	August 23, 2023
Application: (PMA) Number:	P220026
Date of Notice of Approval:	11/17/2023

Breakthrough Device: Granted breakthrough device status on March 27, 2020 for the reduction of blood pressure in patients with uncontrolled hypertension despite the use of anti-hypertensive medications or in patients who may have documented intolerance to anti-hypertensive medications.

II. INDICATIONS FOR USE

The Symplicity Spyral Multi-Electrode Renal Denervation Catheter and the Symplicity G3 RF Generator are indicated to reduce blood pressure as an adjunctive treatment in patients with hypertension in whom lifestyle modifications and antihypertensive medications do not adequately control blood pressure.

III. CONTRAINDICATIONS

The Symplicity Spyral Multi-Electrode Renal Denervation Catheter and the Symplicity G3 RF Generator are contraindicated in any of the following:

- Renal artery diameter <3mm or >8mm
- Renal artery fibromuscular dysplasia (FMD)
- Stented renal artery (<3 months prior to RDN procedure)
- Renal artery aneurysm
- Renal artery diameter stenosis >50%
- Pregnancy
- Presence of abnormal kidney (or secreting adrenal) tumors
- Iliac/femoral artery stenosis precluding insertion of the catheter

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Symplicity Spyral multi-electrode renal denervation catheter and Symplicity G3 RF generator labeling.

V. DEVICE DESCRIPTION

The Symplicity Spyral Renal Denervation (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 radiofrequency (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.

Symplicity Spyral Multi-Electrode Renal Denervation Catheter

The Symplicity Spyral multi-electrode rfRDN catheter is designed to be used with the Symplicity G3 RF generator. The catheter connects to the generator using the integrated cable attached to the catheter handle. The catheter requires the use of a 0.36 mm (0.014 in) guidewire for delivery, preferably without hydrophilic coating. For a straighter electrode array during delivery, Medtronic recommends using an extra support guidewire such as the Medtronic Thunder guidewire. In addition, an adult-sized dispersive electrode (also known as a neutral electrode, return electrode pad, or grounding pad) must be placed on the patient and connected to the generator for the therapy to be delivered.

The catheter has an effective length of 117 cm and is compatible with a 6 Fr guide catheter. It is designed for treating vessels with diameters ranging from 3 mm to 8 mm. As shown in Figure 1 the catheter features 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 treatment length (the distance between the most distal and proximal electrodes) of a function of the vessel diameter (Table 1). A radiopaque tip marker is located 1 mm proximal to the catheter tip and assists in catheter positioning using fluoroscopic guidance. The catheter also features a straightening tool that facilitates safe insertion of the guidewire into the catheter (Figure 2). This tool is located near the handle and slides along the catheter shaft to straighten the distal end. Refer to the Symplicity Spyral catheter Instructions for Use for additional details.

Figure 1. Representative Image of Self-Expanding Electrode Array Assembly (Spiral Configuration)

Table 1: Symplicity Spyral Catheter Treatment Length

Vessel Diameter (mm)	Treatment Length (mm)
3	21
4	20
5	20
6	19
7	18
8	17

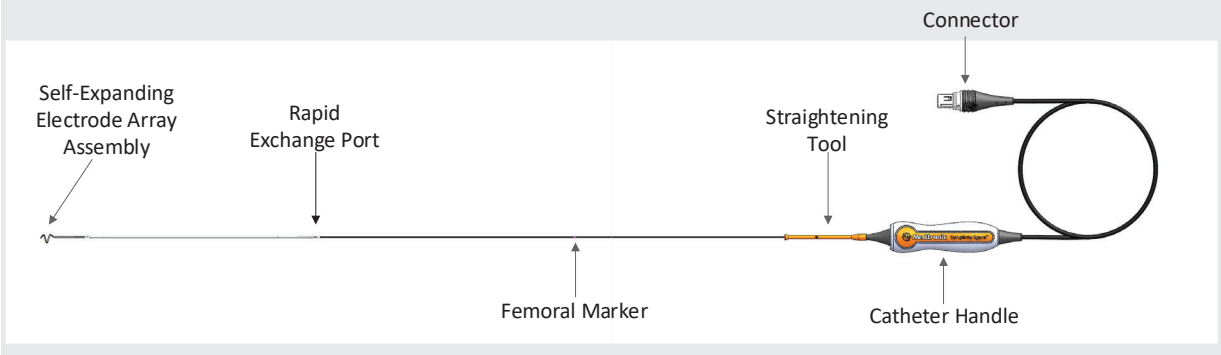


Figure 2. Overview of Symplicity Spyral Catheter

Symplicity G3 RF Generator and Touch Screen

The generator uses an automated algorithm to control the treatment based on real-time temperature and impedance feedback. Refer to the Symplicity G3 RF generator user manual for further information.

The front panel of the Symplicity G3 RF generator touch screen shows information such as impedance, temperature, ablation time, and messages. The front panel also features an RF activation button. Channels on the generator screen correspond to each electrode on the catheter. The generator touch screen and remote control allow the user to navigate different options, such as the selection or deselection of channels, viewing previous ablation data sets, or selecting the left or right kidney.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of hypertension including lifestyle modifications and pharmacological therapy. Each approach has its advantages and disadvantages.

A patient should fully discuss hypertension treatment options with their health care provider to select the method(s) that achieve blood pressure control and meets expectations and lifestyle.

VII. MARKETING HISTORY

The Symplicity Spyral Renal Denervation System was first CE Marked in the European Union on 15 October 2013. The Symplicity G3 RF generator data in this section is for the predicate Symplicity G3 RF generator, which is currently commercially available in the countries listed in Table 2.

Table 2. Commercialized Geographies for the Symplicity Spyral Renal Denervation System

Countries			
Australia	Dominican Republic	Kazakhstan	Romania
Argentina	Ecuador	Kuwait	Russia
Austria	Egypt	Latvia	Saudi Arabia
Bangladesh	El Salvador	Liechtenstein	Singapore
Bahamas	Estonia	Lithuania	Slovakia
Belgium	Finland	Luxembourg	Slovenia
Brazil	France	Malaysia	South Africa
Brunei	Germany	Malta	South Korea
Bulgaria	Greece	Mexico	Spain
Cayman Islands	Guatemala	Netherlands	Sweden
Chile	Hong Kong	New Zealand	Switzerland
Colombia	Hungary	Nicaragua	Taiwan
Costa Rica	Iceland	Norway	Thailand
Croatia	India	Panama	Turkey
Curacao	Indonesia	Peru	United Kingdom
Cyprus	Ireland	Philippines	Venezuela
Czech Republic	Israel	Poland	
Denmark	Italy	Portugal	

The Symplicity Spyral Renal Denervation System has not been withdrawn from commercial distribution for any reason related to safety or effectiveness.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device (listed in alphabetical order).

- Allergic reaction to contrast
- Arterial damage, including injury from energy application
- Hypotension
- Hypotension causing end organ hypoperfusion

- Arterial dissection or perforation
- Arterial spasm
- Arterial stenosis
- Arterio-enteric fistula
- Arteriovenous fistula
- Bleeding
- Blood clots or embolism
- Bruising
- Cardiopulmonary arrest
- Complications associated with medications commonly utilized during the procedure, such as narcotics, anxiolytics, or other pain or anti-vasospasm medications
- Death
- Deep vein thrombosis
- Edema
- Electrolyte imbalance
- Heart rhythm disturbances, including bradycardia
- Hematoma
- Hematoma - retroperitoneal
- Hematuria
- Hypertension
- Hypotension – orthostatic
- Infection
- Kidney damage including renal failure
- Kidney perforation
- Myocardial infarction
- Nausea or vomiting
- Pain or discomfort
- Peripheral ischemia
- Pulmonary embolism
- Proteinuria
- Pseudoaneurysm
- Radiocontrast neuropathy
- Renal artery aneurysm
- Skin burns from a failure of the dispersive electrode pad
- Stroke

There may be other potential adverse events that are unforeseen at this time. For the specific adverse events that occurred in the clinical studies, please see Section X, Summary of Primary Clinical Studies, below.

IX. SUMMARY OF NONCLINICAL STUDIES

Nonclinical testing of the Symplicity Spyral Renal Denervation System included verification and validation (device, system, and software), biocompatibility of patient-contacting materials, sterilization, packaging, shelf life testing, and animal studies. Performance testing was conducted to demonstrate design integrity. Tests that were identified in standards or guidance documents were performed based on design inputs.

A. Biocompatibility

Biocompatibility testing of the Symplicity Spyral Renal Denervation System was evaluated based on device contact and duration in accordance with ISO 10993-1: 2009 and (R)2013 and FDA Guidance, Use of International Standard ISO 10993-1, "Biological Evaluation of Medical Devices Part 1: Evaluation and testing within a risk management process".

The Symplicity Spyral catheter test samples were derived from the finished product. The catheter is classified according to ISO 10993-1 as an externally communicating medical device with limited contact (≤24 hours) with circulating blood. The Symplicity G3 RF generator, remote control, DVI-D cable, power cord and cart do not have any direct or

indirect tissue contact and are provided non-sterile; therefore, biocompatibility testing was not required for these components.

A summary of the results is provided in Table 3 and demonstrates that the Symplicity Spyral catheter is biocompatible per ISO 10993-1. Biocompatibility testing was completed according to Good Laboratory Practice (GLP) requirements 21 CFR 58, and the results provide objective evidence that the catheter is biocompatible per its intended use.

Table 3. Summary of Biocompatibility Testing - Symplicity Spyral Catheter

Test Performed	Test Method (applicable ISO Part Number)	Acceptance Criteria	Results
Cytotoxicity	MEM Elution Using L 929 Fibroblast Cells (ISO 10993-5; ISO 10993-12)	The test article must result in a grade of 2 or less	Pass Non-cytotoxic
Sensitization	ISO Guinea Pig Maximization Sensitization Test (ISO 10993-10; ISO 10993-12)	A grade of ≥1 in the test group indicates sensitization provided the corresponding control group is grade <1	Pass Non-sensitizing
Irritation or Intracutaneous Reactivity	ISO Intracutaneous Irritation Reactivity Test (ISO 10993-10; ISO 10993-12)	The difference between the test extract mean score and corresponding control mean score must be ≤1.0	Pass Non-irritant
Acute Systemic Toxicity	ISO Acute Systemic Injection Test (2 Extracts) (ISO 10993-11; ISO 10993-12)	If during the observation period, none of the test animals shows a significantly greater reaction than the corresponding control animals, the test article meets the test requirements	Pass Non-toxic
Material-Mediated Pyrogenicity	ISO Materials Mediated Rabbit Pyrogenicity (ISO 10993-11; ISO 10993-12)	If no animal shows an individual rise in temperature of 0.5°C or more above its baseline temperature, the test article meets the requirements for the absence of pyrogens	Pass Non-pyrogenic
Hemocompatibility	Complement Activation SC5b-9 with supplied comparison (ISO 10993-4; ISO 10993-12)	If the SC5b-9 concentration in the test article is statistically similar to at least the negative control, inactivated NHS control, or the sponsor-provided control, the test article is not considered an activator of the complement system.	Pass Not a complement activator

B. *In vitro* Engineering and Bench Testing

Symplicity Spyral Renal Denervation (rfRDN) System

Testing was conducted on the Symplicity Spyral Renal Denervation System (generator, catheter, and optional accessories) according to harmonized test standards for active medical devices and to software verification/validation requirements, following uniquely designed test protocols for the device. The Symplicity Spyral Renal Denervation system met international certification requirements for safety in compliance such as: ANSI/AAMI ES60601-1:2005/A1:2012-08, IEC 60601-1:2005, COR1:2006, COR2:2007, AMD1:2012, IEC 60601-6:2010/AMD1:2013 IEC 60601-1-2:2014.

The Symplicity Spyral Renal Denervation System passed design verification (functional) bench testing including dimensional, strength, reliability, mechanical, and electrical integrity. Testing included performance of the Symplicity G3 RF generator used in conjunction with the Symplicity Spyral multi-electrode renal denervation catheter and all other system components. Table 4 shows the tests performed on the Symplicity Spyral Renal Denervation (rfRDN) system, the purpose of the tests, the acceptance criteria, and the test results (pass/fail). Pass denotes the device and systems met the established product specification and/or performance criteria.

Table 4. Summary of Functional Testing - Symplicity Renal Denervation (rfRDN) System

Test	Test Summary/Purpose	Acceptance Criteria	Results (Pass/Fail)
Tip Length	The purpose of this test is to measure the distance from the distal end of the catheter to the distal end of the tip bond.	Lower Spec: 4 mm Upper Spec: 8 mm	Pass
Tip to Marker Band Distance	The purpose of this test is to measure the distance from the distal end of the catheter to the distal end of the marker band.	Upper Spec: 1.5 mm	Pass
Catheter Working Length (Straight)	The purpose of this test is to measure the distance from the distal end of the catheter to the distal end of the straightening tool in the straight configuration.	Lower Spec: 114 cm Upper Spec: 120 cm	Pass
Exchange Joint Distance from Tip (Straight)	The purpose of this test is to measure the distance from the catheter tip to the exchange joint in the straight configuration.	Lower Spec: 25 cm Upper Spec: 35 cm	Pass
Tip to Femoral Marker Distance (Straight)	The purpose of this test is to measure the distance from the distal end of the catheter to the distal end of the femoral marker in the straight configuration	Lower Spec: 45 cm Upper Spec: 65 cm	Pass
Catheter Max Profile (Intermediate Bond OD)	The purpose of this test is to measure the outside diameter of the intermediate bond which represents the maximum catheter profile.	Upper Spec: 1.55 mm (0.061”)	Pass

Test	Test Summary/Purpose	Acceptance Criteria	Results (Pass/Fail)
Cable to Handle Tensile	The purpose of this test is to measure the tensile strength of the catheter cable and handle connection.	Lower Spec: 15N (3.37lbs)	Pass
Deployed Array Length/Compliance	The purpose of this test is to measure the array length in the deployed configuration.	Lower Spec: 5 mm Upper Spec: 26.5 mm	Pass
Compatibility with accessories	The purpose of this test is to ensure that the device does not lock-up in or on standard procedural accessories during simulated use in a transfemoral bench top model.	Catheter interfaces with accessories without damaging catheter.	Pass
Loading Tool Compatibility	The purpose of this test is to ensure that the loading tool allows for a guidewire to be loaded during simulated use.	Able to insert wire into device without damaging catheter.	Pass
Catheter Integrity	The purpose of this test is to perform a visual assessment of the catheter to identify damage to the device after simulated use in a transradial bench top model.	Catheter does not exhibit visual damage post simulated use.	Pass
Tip Bond Tensile	The purpose of this test is to measure tensile strength of the bond between the distal tip and the catheter per ISO 10555-1.	Lower Spec: 5N (1.12 lbs)	Pass
Electrode Tensile	The purpose of this test is to measure tensile strength of the bond between the electrode and the catheter.	Lower Spec: 5N (1.12 lbs)	Pass
Intermediate Bond Tensile	The purpose of this test is to measure tensile strength of the intermediate bond of the catheter per ISO 10555-1.	Lower Spec: 5N (1.12 lbs)	Pass
Exchange Joint Tensile	The purpose of this test is to measure tensile strength of the exchange joint bond of the catheter per ISO 10555-1.	Lower Spec: 5N (1.12 lbs)	Pass
Proximal Shaft to Handle Tensile	The purpose of this test is to measure tensile strength of the bond between the catheter shaft and the handle per ISO 10555-1.	Lower Spec: 5N (1.12 lbs)	Pass
Kink Resistance	The purpose of this test is to perform a visual assessment of the catheter to ensure that no kinks are observed on the device after simulated use in a transradial bench top model.	No kinking Post Simulated Use	Pass
Impedance Measurement	The purpose of this test is to ensure that the generator and system are able to measure the simultaneous impedance accurately between each RF channel and return electrode from 175 to 1200 ohms before and during RF energy delivery.	175 Ω to 250 Ω, ±20% 251 Ω to 700 Ω, ±10% 701 Ω to 1200 Ω, ±15%	Pass

Test	Test Summary/Purpose	Acceptance Criteria	Results (Pass/Fail)
RF output power	The purpose of this test is to ensure that the generator and system are able to deliver power with the specified accuracy to all four channels	6.5W maximum per electrode ±20% accuracy with impedance of 175 Ω to 200 Ω ±10% accuracy with impedance of 201 Ω to 1200 Ω	Pass
Temperature range	The purpose of this test is to ensure that the system is able to measure temperature of each electrode accurately before and during RF delivery.	Measurement 37°C to 65°C ±3°C	Pass
RF output frequency	The purpose of this test is to ensure that the generator and system are able to deliver RF power of 6.5 W at a frequency of 460 ±5 kHz	455-465 kHz	Pass
RF Treatment duration	The purpose of this test is to ensure that the system is able to deliver RF power for the specified treatment time.	60 seconds (+/-1 second)	Pass

C. Software Testing

The software for Symplicity G3 RF generator and remote control was verified/validated and documented according to the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices." The software testing included a full suite of safety and performance tests. The software was evaluated through unit, integration, verification and validation testing to demonstrate that the performance and safety of the Symplicity G3 RF generator and remote control passed specifications.

Cybersecurity risk analysis and testing was conducted per FDA guidance document "Guidance of Premarketing Submissions for Management of Cybersecurity in Medical Devices." Risk analysis and verification testing of risk controls performed ensures that the Symplicity Spyral Renal Denervation system is secure and trustworthy throughout its full life cycle. As described in the Symplicity G3 RF generator user manual, the following security information is included to help manage cybersecurity risks and/or to ensure the safe and effective use of the device.

Data security

The Symplicity G3 generator uses and stores treatment data. The system does not protect exported data. Exported data should be handled in accordance with your facility's security policy for data handling and storage. Medtronic recommends that you always export data to an encrypted mass storage device.

Cybersecurity events

If you suspect a cybersecurity event has occurred (such as strange or unexpected behavior, even if a fault or check status condition is not generated), stop using the

generator (if possible). Contact your IT department or Medtronic support for information on how to confirm and respond to the suspected incident. If you have further questions related to cybersecurity, contact your IT department or Medtronic support.

Security Risk Considerations

In addition to following the intended use and instructions necessary for the safe and effective use of the Symplicity G3 Generator, the following compensating controls for product implementation in the user's environment are recommended by Medtronic:

- The Symplicity G3 Generator does not support hospital network or other ethernet connectivity.
- Only personnel authorized by the hospital should access, use, or move the Symplicity G3 Generator, to avoid exposing the system to security risks. Medtronic recommends maintaining good physical access controls over the Symplicity G3 Generator.
- Software updates are to be installed by authorized Medtronic service personnel only. DO NOT install any software on the system, to avoid unintended system behavior.

D. Sterilization and Shelf Life

The Symplicity Spyral catheter is provided as a sterile, single use medical device and is not intended for reuse or re-sterilization. The Symplicity Spyral catheter is sterilized using a validated electron beam irradiation (E-beam) sterilization process that provides a sterility assurance level (SAL) of 10^{-6}. Sterilization validation was completed in accordance with the requirements of EN556, ISO11137/TIR13004.

The Symplicity G3 RF generator, remote control, DVI-D cable, power cord and cart are provided as non-sterile.

A shelf life of 3 years has been established for the Symplicity Spyral catheter based on product and package shelf life testing. The Symplicity Spyral catheter was tested following accelerated aging to an equivalent of 3 years per an approved shelf life protocol. Testing demonstrated the Symplicity Spyral catheter met the established acceptance criteria.

The Symplicity G3 generator is re-usable durable medical equipment and was designed and validated to provide a useful life of 5 years or more based on actual usage.

The Symplicity Spyral catheter is a single use, disposable, sterile device. Catheter packaging was designed and validated to ensure the sterility and integrity of individually packaged and sealed devices. The packaging validation was performed in accordance with ISO 11607-1:(2022) and applicable packaging standards (ISO 2233, ASTM F88, ASTM 2096, ASTM D4169, ASTM D4332, and F1929). The packaging validation supports the 3 year shelf life for the Symplicity Spyral catheter.

The Symplicity G3 RF generator, remote control, DVI-D cable, and power cord are provided non-sterile and protected by a Pelican case. The packaging validation demonstrates the selected packaging provides basic protection of the unit during expected transit cycles. Packaging validation was completed in accordance with applicable packaging standards (ISO 2233, ASTM D4169, and ASTM D4332).

E. Animal Studies

Medtronic conducted several in-vivo animal studies in a porcine model to develop the RF treatment parameters and characterize the performance and safety of the Symplicity Spyral Multi-Electrode Renal Denervation Catheter, utilized in conjunction with the Symplicity G3 RF Generator:

1. A long-term GLP (180-day timepoint) study was designed to characterize the safety of the treatment parameters and device performance of the Symplicity Spyral Renal Denervation System and to evaluate the physiological effects of RF renal denervation on the renal sympathetic functionality, as compared to untreated animals.

2. A series of non-GLP design studies (7 and 28 days timepoints) were completed to confirm the device design concepts and system specifications.

For each preclinical study, the following were evaluated to assess device and procedure safety: clinical observations, clinical pathology, angiography, gross pathology, and histopathology/histomorphometry. Renal cortical axonal density and renal cortical norepinephrine concentrations were also evaluated. A summary and description of animal studies are provided in Table 5.

Table 5. Summary of *In Vivo* Animal Studies

Study Type	No. and Type of Animals	Study Follow-up Duration	Study Purpose	Study Arms Evaluated	Results
GLP Chronic Study in Domestic Swine (FS235)	17 Domestic Farm Swine	180 days	A design validation study to demonstrate the long term safety of the Spyral Multi-Electrode Denervation Catheter as well as the physiological effects of renal denervation	Arm 1: Symplicity Spyral Renal Denervation Catheter with the Symplicity RF Generator Arm 2: Untreated control	No clinically significant complications in the treated vessels, adjacent structures, and kidneys based on arteriography, histopathology and blood biochemistry. Successful assessment and treatment of post-operative clinical concerns (e.g., pain, postoperative abnormalities). Successful determination of bilateral renal cortical norepinephrine concentration for each study arm.
Non-GLP Chronic Swine Study (PS629)	20 Domestic Swine	28 days	Comparison of the Symplicity Spyral Catheter and Generator System performance to the multi-electrode RF and Symplicity Flex RF Catheters / Generators Systems.	Arm 1: Symplicity Spyral Renal Denervation Catheter with the Symplicity RF Generator Arm 2: Multi-electrode RF catheter with Symplicity G2X4 Generator Arm 3: Symplicity Flex Catheter with Symplicity G2 Generator Arm 4: Untreated control	Successful Delivery of treatment modalities in 90% of animal. No clinically significant complications in the treated renal vessels, adjacent structures, and kidneys based on arteriography, histology, and blood chemistries. Renal cortical NE concentration for Arm1 equivalent or lower than Arm 2 and Arm 3.
Non-GLP Sub-Acute Swine Study (PS701)	59 Domestic Swine	7 days	Evaluation of treatment locations and various renal denervation parameters and duration combinations using the Symplicity Spyral RF Catheter System.	Arm 1-4: Symplicity Spyral Renal Denervation Catheter with the Symplicity RF Generator (multiple treatment parameters and locations)	No clinically significant complications in the treated renal vessels, adjacent structures, and kidneys based on arteriography, histology, and blood chemistries. Successful determination of renal cortical NE concentration and histology assessment (renal cortical axon quantification).

Study Type	No. and Type of Animals	Study Follow-up Duration	Study Purpose	Study Arms Evaluated	Results
				Arm 5: Symplicity Flex Catheter with Symplicity G2 Generator Arm 6: Contralateral untreated vessels	
Non-GLP Sub-Acute Swine Study PS716)	48 Domestic Swine	7 days	Confirm location of renal denervation and compare ablation parameters and application combinations using the Symplicity Spyral RF Catheter System.	Arm 1-4: Symplicity Spyral Renal Denervation Catheter with the Symplicity RF Generator (multiple treatment parameters and locations) Arm 5: Contralateral untreated vessels (left renal)	Successful delivery of treatment modalities in 90% of animals. No clinically significant complications in the treated renal vessels, adjacent structures, and kidneys based on arteriography, histology, and blood chemistries. Reduced norepinephrine concentration and renal nerve viability and cortical axon density following RF treated group compared to the untreated group.
Non-GLP Chronic Swine Study (PS717)	16 Domestic Swine	28 days	Subacute evaluation of RF parameters and methodology selected for renal ablation delivery using the Symplicity Spyral Catheter System.	Arm 1: Symplicity Spyral Renal Denervation Catheter with the Symplicity RF Generator. Arm 2: Untreated Control	No clinically significant complications in the treated renal vessels, adjacent structures, and kidneys based on arteriography, histology, and blood biochemistries. Reduced norepinephrine concentration and renal nerve viability and cortical axon density following RF treated group as compared to the untreated group

Collectively, the preclinical studies demonstrate the safety of RF delivery to the target renal vessels and the physiological impact of RF ablations on renal cortical norepinephrine concentration and cortical axon density.

Safety evaluation of RF ablations demonstrated the following:

- Clinical pathology results at pre-screen and terminal time points were within normal limits. No significant pain was exhibited by the animals.
- Post-treatment and terminal angiography indicated normal vessel perfusion for all treated animals. No clinically significant abnormal findings were attributed to RF changes.
- Histopathology and histomorphometry evaluation of treated renal arteries showed complete healing following RF ablations. No clinically significant complications attributed to the RF treatment were observed in the kidneys and surrounding tissues.

Bioanalytical and immunohistochemistry analyses consistently showed a significant and sustained reduction in sympathetic function at each study timepoint evaluated (7 days, 28 days, and 180 days). Renal norepinephrine concentrations and cortical axon density were significantly reduced in the group treated with Symplicity Spyral Renal Denervation Catheter and the Symplicity RF Generator compared to non-treated vessels.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The applicant performed two clinical studies—SPYRAL HTN-OFF MED and SPYRAL HTN ON-MED—to evaluate the safety and effectiveness of rfRDN with the Symplicity Spyral Renal Denervation System for reduction of blood pressure in patients with uncontrolled hypertension compared to a sham-controlled population, in the absence and presence of anti-hypertensive medications, respectively. The studies were conducted in the US, Canada, Japan, Europe, and Australia under IDE # G150036. Data from these clinical studies were the basis for the PMA approval decision. Summaries of the clinical studies are presented below.

A. Study Design

The HTN-OFF MED and HTN-ON MED studies were conducted in two cohorts: an initial Pilot Cohort to determine the feasibility of the study design and a second prospectively powered Expansion Cohort that expanded the study via an adaptive Bayesian design. Pilot and Expansion Cohorts were designed as a multi-center, international, prospective, single blinded, randomized, interventional, sham-controlled cohorts. The sham control procedure consisted of an aortogram and selective renal angiography performed with subjects blinded to treatment allocation to confirm eligible renal artery anatomy. Eligible subjects randomized to sham control remained blinded and on the catheterization lab table for at least 20 minutes prior to the inducer sheath removal. Patients, follow-up physicians, and research staff remained blinded through 6 months in the Expansion Cohorts or 12 months in the Pilot Cohorts.

HTN-OFF MED Study Design

In both Pilot and Expansion Cohorts, patients were randomized 1:1 to rfRDN or Sham. Antihypertensive medications were withdrawn from 3-4 weeks prior to the rfRDN or sham procedure through 3 months post-treatment (unless pre-specified elevated BP escape criteria (defined as office SBP ≥180 mmHg or <115 mmHg associated with symptoms of hypotension or safety concern requiring medication changes) were met).

The HTN-OFF MED study utilized a Bayesian adaptive design, and the Expansion cohort interim analyses could be performed at 210 and 240 evaluable subjects to determine if the enrollment could be stopped prior to a maximum study size of 300 subjects. HTN-OFF enrollment was stopped after the first interim analysis.

Patients were treated between June 2015 and January 2020. The database for this PMA reflected data collected through May 2022 and included 366 patients. There were 41 investigational sites.

HTN-ON MED Study Design

In the HTN-ON MED study, Pilot Cohort patients and the first 26 patients in the prospectively powered Expansion Cohort (patients 81–106) were randomized 1:1 to rfRDN or Sham, and patients 107 onward were randomized 2:1 to rfRDN or Sham rfRDN. The randomization scheme was changed to allow for more rfRDN safety data for primary safety endpoint. Antihypertensive medication was to remain unchanged between baseline and the 6-month primary endpoint assessment unless pre-specified elevated BP escape criteria (defined as Office SBP ≥180 mmHg or <115 mmHg associated with symptoms of hypotension or safety concern requiring medication changes) were met.

A Bayesian adaptive design was used for the primary analysis, and expansion cohort interim analyses could be performed at 110 and 149 evaluable subjects to determine if the enrollment could be stopped. HTN-ON enrollment continued to full enrollment (257 subjects).

Patients were treated between October 2015 and March 2022. The database for this PMA reflected data collected through November 2022 and included 337 patients. There were 42 investigational sites.

In both HTN-OFF MED and HTN-ON MED, Pilot Cohorts remained blinded through 12 months, and Expansion Cohort subjects remained blinded through 6 months.

For both studies, the cohorts and definition used in this clinical summary are described in Table 6.

Table 6. Study Cohorts and Number of Subjects for HTN-OFF MED and HTN-ON MED

	HTN-OFF MED	HTN-ON MED
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	Up to 331 Based on Bayesian analysis	Up to 337 Based on Bayesian analysis
Full Cohort: All enrolled subjects	366	337

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the studies was limited to subjects who met the following inclusion criteria:

Table 7. Key Inclusion Criteria for the HTN-OFF MED and HTN-ON MED Studies

	HTN-OFF MED	HTN-ON MED
Age	Individual is ≥20 and ≤80 years old at time of enrollment (consent	
OBP[1]	OSBP ≥150 mmHg and <180 mmHg ODBP ≥90 mmHg	
ABP[2]	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] Baseline OBP and ABPM (ambulatory blood pressure monitoring) are determined at Screening Visit 2
[2] ABP 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, OSBP: office systolic BP, ODBP: office diastolic BP

Subjects were not permitted to enroll in the studies if they met any of the following exclusion criteria:

- Individual has undergone prior renal denervation (RDN)
- Ineligible renal artery anatomy, including:
  - Main renal artery for each kidney less than 3 mm or greater than 8 mm
  - Lacking a main renal artery that does not allow 4 simultaneous quadrantic RF ablations in the main renal artery or equivalent
- Presence of fibromuscular dysplasia (defined as visible beading of the artery on angiography)

- >50% stenosis in any treatable vessel
- Renal artery stent placed <3 months prior to procedure.
- Renal artery aneurysm (defined as any localized increase in diameter of vessel)
- Treatment within 5 mm of a segment in the renal artery which contains any of the following: atheroma, calcification, or renal artery stent
- eGFR <45 mL/min/1.73m^2 using 4 variable MDRD calculation
- Type 1 diabetes mellitus or Type 2 diabetes mellitus with HbA1C > 8.0%
- Individual with ≥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 (at screening visit 2)
- Individual requires chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea (e.g. CPAP, BiPAP).
- History of narcotic drug abuse, is currently on Methadone, or who has used narcotic drugs more than once in the month prior to screening visit 1
- Individual is taking SGLT2 inhibitors or GLP-1 agonists that have been prescribed <90 days prior to screening visit 1 or who does not plan to remain on these drugs for the duration of the trial
- Individual with primary pulmonary hypertension
- Individual with untreated secondary cause of hypertension (either known or suspected) or is taking drugs that increase sympathetic tone that could contribute to hypertension
- Individual with frequent intermittent or chronic pain that results in treatment with non-steroidal anti-inflammatory drugs for two or more days per week over the month prior to screening visit 2. (Patients are permitted to take aspirin or clopidogrel for cardiovascular risk reduction.)
- Individual with HIV on anti-retroviral drug therapy without documentation that hypertension preceded initiation of anti-retroviral drug treatment
- Individual has one or more of the following conditions: stable or unstable angina within 3 months of enrollment, myocardial infarction within 3 months of enrollment; heart failure, cerebrovascular accident or transient ischemic attack, or atrial fibrillation at any time. Patients are permitted to take aspirin or clopidogrel for cardiovascular risk reduction. Patients who received catheter or surgical treatment for atrial fibrillation and are in sinus rhythm are not excluded.
- Individual has a scheduled or planned surgery that, in the opinion of the Investigator, may affect study endpoints
- Individual has a documented condition that would prohibit or interfere with ability to obtain an accurate blood pressure measurement using the protocol-specified automatic/office blood pressure monitor (e.g., upper arm circumference outside cuff size ranges available by geography or arrhythmia such as atrial fibrillation that interferes with automatic monitor's pulse sensing and prohibits an accurate measurement)
- Individual works night shifts

- Individual has severe cardiac valve stenosis for which, in the opinion of the investigator, a significant reduction of blood pressure is contraindicated
- Individual has a documented confounding medical condition, which in the opinion of the investigator, may adversely affect the safety of the participant (e.g., patients with clinically significant peripheral vascular disease, aortic aneurysm, bleeding disorders such as thrombocytopenia, hemophilia, or significant anemia)
- Individual is pregnant, nursing or planning to become pregnant during the course of the study follow-up. (Pre-menopausal female participants must have a negative serum or urine human chorionic gonadotropin pregnancy test prior to angiography.)
- Individual has a known unresolved history of drug use or alcohol dependency, lacks the ability to comprehend or follow instructions, or would be unlikely or unable, in the opinion of the investigator, to comply with study follow-up requirements
- Individual is currently enrolled in a concurrent investigational drug or device study, unless approved by the study sponsor. (For the purpose of this protocol, participants involved in extended follow-up studies for products that were investigational but are currently commercially available are not considered enrolled in an investigational study.)
- Individual is currently taking mineralocorticoid receptor antagonists. (Subjects may be enrolled as long as mineralocorticoid receptor antagonists are weaned off at least 8 weeks prior to screening visit 1.)
- Individual has an active peptic ulcer or gastrointestinal (GI) bleeding within the prior six months from consent
- Individual has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions
- Individual has polycystic kidney disease, unilateral kidney, atrophic kidney, or history of renal transplant

2. Follow-up Schedule

The follow-up schedule for selected endpoints from the HTN-OFF MED and HTN-ON MED studies is shown in Table 8 and Table 9, respectively. Subjects initially randomized to Sham control who underwent crossover to rfRDN were followed according to the same schedule as subjects initially randomized to rfRDN.

Table 8: HTN-OFF MED Follow-up Schedule

Required Assessments	Screening visit 1	2 Wk visit (Screening) ± 3 days	Screening visit 2 (within 3-4 weeks of SV2)	rfRDN or Sham Procedure	Prior to Discharge	2 Wk, 4Wk, 6 Wk, 8 Wk	3M	4M visit (for SBP ≥140 mmHg at 3M ±7days	6M	12M-36M
Medical History	X									
Clinical Assessment		X	X			X	X	X	X	X
Prescribe BP Medications							X	X		
Witnessed pill intake (if subject is taking antihypertensive medications), Complete after OBP measurements.									X	X
Renal Denervation or Sham Procedure				X						
Office Blood Pressure	X	X	X		X	X	X	X	X	X
24-Hour ABPM			X				X		X	X
Blood Tests (uric acid, lipid panel and high-sensitivity CRP[7] (hs-CRP))			X							
Blood Tests (Chem-7)[4]			X		X	X (4 wk only)	X		X	X
Blood Tests (renin and aldosterone)			X				X			
Serum or Urine Pregnancy Test			X							
Drug testing			X				X	X	X	X
Renal Artery Imaging -Angiogram				X						
Renal Artery Imaging			X[5]					X	X[1]	[5]
Blinding Assessment					X		X		X	
EQ-5D and SF-36			X				X		X	X
Mortality Assessment[2]						X (4 weeks and 8 weeks)	X		X	X
Medication Review, Event Review	All adverse events (AE) and medication review. After 12 months, previously reported AEs will need to be reviewed and updated as needed								SAE and all Medication Review	
3 Months (90 days): 76-104 days, 4 Months (120 days): 113 -127 days, 6 Months (180 days): 166-194 days, 12 Months (360 days): 330-390 days, 24 Months (720 days): 690-750 days, 36 Months (1080 days): 1050-1110 days					Post-Procedure Assessment Windows: Wk= ± 3 days; M months ± 14 days for 3M and 6M visits; ±30 days for 12M-36M visits					

Table 9. HTN-ON MED Study Follow-Up Schedule

Required Assessments	Screening visit 1	Screening visit 2	rfRDN or Sham Procedure	Prior to Discharge	1M	3M	6M	12M-36M
Medical History	X							
Clinical assessment		X			X	X	X	X
Renal Denervation or Sham Procedure			X					
Office Blood Pressure	X	X		X	X	X	X	X
24-Hour ABPM		X				X	X	X
Witnessed pill taking		X				X	X	X
Blood tests (uric acid, lipid panel and high sensitivity CRP[6])		X						
Blood Tests (Chem-7)[3]		X		X	X	X	X	X
Serum or Urine Pregnancy Test		X						
Drug testing		X				X	X	X
Renal Artery Imaging - Angiogram			X					
Renal Artery Imaging – Duplex Ultrasound		X[4]				X	X[1]	[5]
Blinding Assessment for Subjects and Assessors				X		X	X	
EQ-5D		X				X	X	X
Mortality Assessment[2]					X	X	X	X
Medication Review and Event Review	All adverse events (AE) and all medication review After 12 months, previously reported AEs need to be reviewed and updated as needed. Serious AEs and all medication review continue at 24M and 36M.							
1 month (30 days): 16-44 days, 3 months (90 days): 76-104 days, 6 months (180 days): 166-194 days, 12 months (360 days): 330-390 days, 24 months (720 days): 690-750 days, 36 months (1080 days): 1050-1110 days.	Post-Procedure (M=months ± 14 days for 1M, 3M and 6M visits, months ± 30 days for 12M-36M visits)							

[1] DUS required as first line imaging modality at 6M. Repeat DUS, MRA, CTA or angiogram to be used if DUS is nondiagnostic. Renal angiography used if repeat DUS/CTA/MRA nondiagnostic or >60-70% diameter stenosis suspected. The 6M DUS not required for subjects crossing over at 6M if crossover is completed within 30 days of 6M visit.
[2] Conduct if follow-up missed.
[3] Bicarbonate not measured for subjects enrolled in Japan and Europe.
[4] Baseline duplex ultrasound, CTA, or MRA submitted if obtained per standard of care prior to procedure within one year from the date of screening visit 1.
[5] CTA/MRA required as first line imaging modality at 12M (and 24M and 36M as applicable). For treatment and crossover subjects only: Repeat DUS, MRA, or CTA used if prior imaging modality nondiagnostic. If repeat DUS/CTA/MRA nondiagnostic or evidence of a clinically significant stenosis (>60-70%) seen, an angiogram must be obtained and submitted to the Angiographic Core Laboratory. Subjects who have already completed their 12-month follow-up without renal imaging required to undergo renal imaging at next scheduled follow-up unless they have a renal angiogram due to crossover. For the participating sites in Germany and the UK, only renal MRA imaging at the 12-month follow-up visit (or 24 or 36M follow-up as applicable) performed. For these countries, if the initial MRA is non-diagnostic, a repeat MRA should be performed. If the initial MRA or repeat renal MRAs are non-diagnostic and an additional repeat MRA is not expected to yield the required information for a diagnostic study, a DUS can be completed.
[6] High-sensitivity CRP not required for subjects enrolled at sites where high-sensitivity CRP test cannot be locally performed.

3. Clinical Endpoints

Primary Safety Endpoint

The pre-specified primary safety analysis was a pooled analysis of first 253 evaluable rfRDN-treated subjects (initial procedure or crossover) from the HTN-OFF MED and HTN-ON MED 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
  - 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

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. 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.

Primary Effectiveness Endpoint

The primary effectiveness endpoints for HTN-OFF MED and HTN-ON MED were evaluated on the intent-to-treat (ITT) population, which included all randomized patients analyzed according to their randomized treatment, using a Bayesian power prior approach adjusting for baseline BP (primary analysis), frequentist analysis of covariance (ANCOVA) adjusting for baseline BP, and other alternative approaches. The primary effectiveness endpoint was defined as:

- HTN-OFF MED: Change in SBP from baseline to 3-months post-procedure (prior to restarting BP medications) measured by 24-hour ABPM between the rfRDN and Sham groups
- HTN-ON MED: Change in SBP from baseline to 6-months post-procedure measured by 24-hour ABPM between the rfRDN and Sham groups

Powered Secondary Effectiveness Endpoint for HTN-OFF MED

- Change in office SBP from baseline to 3 months post-procedure compared between treatment groups using a Bayesian power prior approach adjusting for baseline SBP

Secondary Effectiveness Endpoint for HTN-OFF MED and HTN-ON MED

- 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
- Proportion of subjects 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 MED only)
- Antihypertensive medication usage throughout the study, including elevated BP escape patients and subjects with medication changes within 3-months (HTN-OFF MED) and 6-months (HTN-ON MED) follow-up. Medication burden is reported using two indices:

MedIndex 1: The ratio of prescribed daily doses to maximum recommended daily dose, summed for all prescribed antihypertensive drugs	$MedIndex\ \mathbf{1} = \sum_{no.\,meds}\left(class\ weight\left[\frac{prescribed\ dose}{maximum\ dose}\right]\right)$
MedIndex 2: MedIndex1 multiplied by number of medications	$MedIndex\ \mathbf{2} = \sum_{no.\,meds} no.\,meds\left(class\ weight\left[\frac{prescribed\ dose}{maximum\ dose}\right]\right)$

Secondary Safety Endpoints for HTN-OFF MED and HTN-ON MED

- 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, ≥5 g/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), 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. A sub-study was performed on at least 150 HTN-OFF MED or HTN-ON MED rfRDN patients to assess renal artery damage and diameter stenosis <70%.

B. Accountability of PMA Cohort

HTN-OFF MED

At the time of database lock, of 366 patients randomized in the HTN-OFF MED study, 99.7% (365) patients are available for analysis at the 3 month/ follow-up visit (*final visit evaluated for safety and effectiveness as the basis for the PMA submission*). Figure 3 shows subject accountability through 12 months for the HTN-OFF MED Full Cohort, including the crossover group which received rfRDN >6-months the post-sham procedure.

Of the first 80 Pilot Cohort patients, 38 were randomized to the rfRDN group and 42 to the Sham group.

In the Expansion Cohort, 251 patients were randomized for a total of 331 patients (166 patients to rfRDN and 165 patients to Sham). An additional 35 patients were randomized

prior to stopping enrollment for success (182 rfRDN and 184 Sham = 366 total), which comprise the Full cohort (Figure 3).

At the 3-month timepoint, 155 patients in the rfRDN group and 147 patients in the Sham group completed an evaluable 24-hour BP assessment (Figure 4).

After 6 months, patients were unblinded and Sham patients were given the option to receive rfRDN procedure (cross over) if they met the anatomical and kidney function criteria. Over 75% of Sham patients opted to crossover to receive rfRDN.

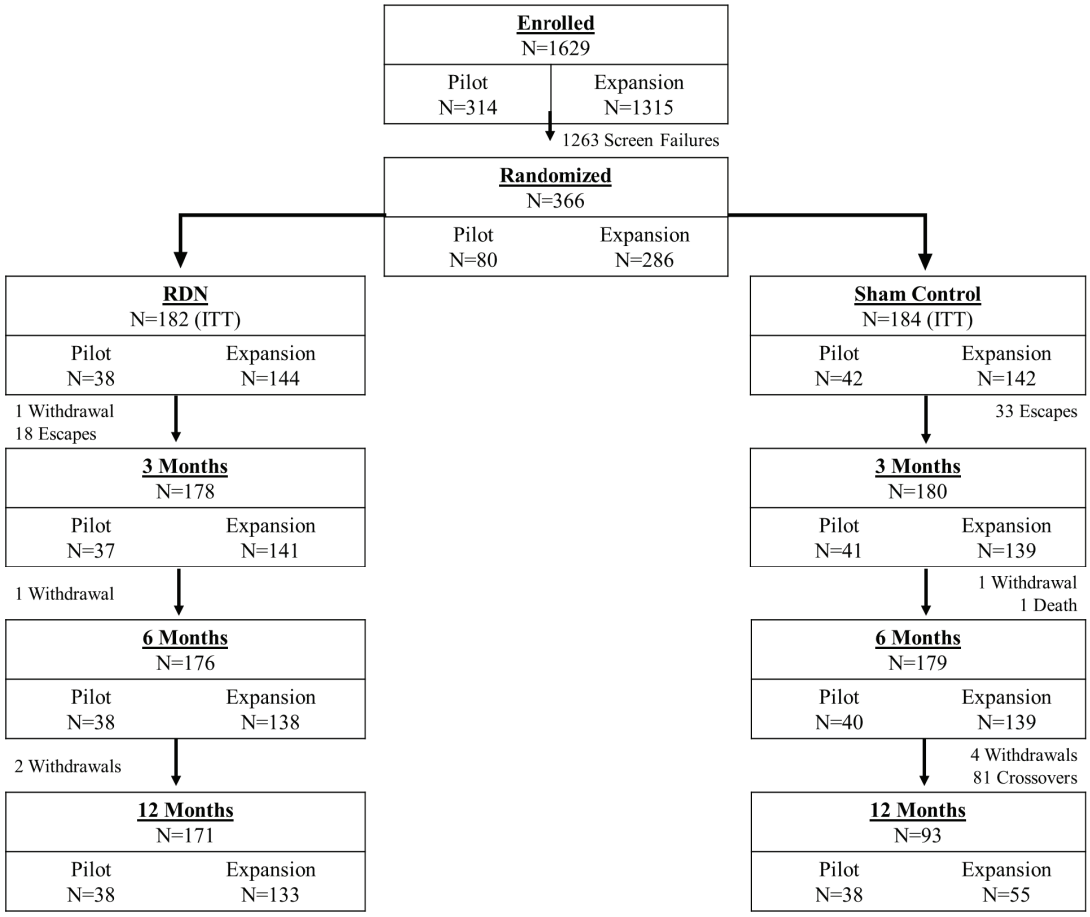
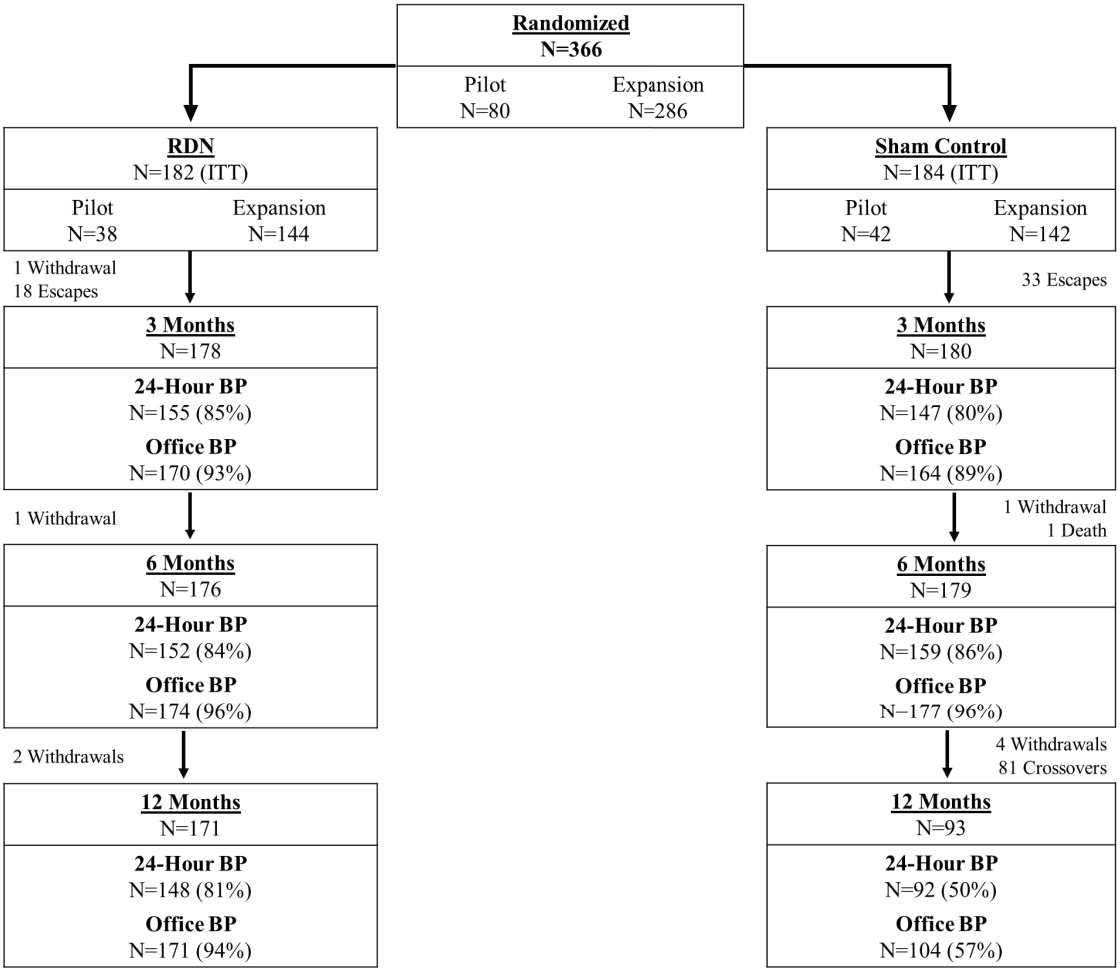


Figure 3. HTN-OFF MED Full Cohort Subject Accountability through 12 Months



Escape defined as Office SBP ≥180 mmHg OR <115 mmHg associated with symptoms of hypotension or safety concern requiring medication changes.

Figure 4: HTN-OFF MED Full Cohort Blood Pressure Endpoint Data Capture Through 12 Months

HTN-ON MED

At the time of database lock, of 337 patients enrolled in the HTN-ON MED study, 97.9% (330) of patients were available for analysis at the 6 month follow-up visit (*final visit evaluated for safety and effectiveness as the basis for the PMA submission*). Figure 5 shows subject accountability through 12 months for the HTN-ON MED Full Cohort.

Of the first 80 Pilot Cohort patients, 38 were randomized to the rfRDN group and 42 to the Sham group.

An additional 257 patients were randomized in the Expansion Cohort for a total of 337 patients forming the Full Cohort (206 patients in the rfRDN group and 131 in the Sham group, Figure 5). A total of 181 (54%) patients were enrolled outside the US.

At the 6-month timepoint, 192 patients in the rfRDN group and 116 patients in the Sham group completed an evaluable 24-hour BP assessment (Figure 6). Notably, 80% of patients in the Expansion Cohort had primary endpoint visits during the COVID-19 pandemic.

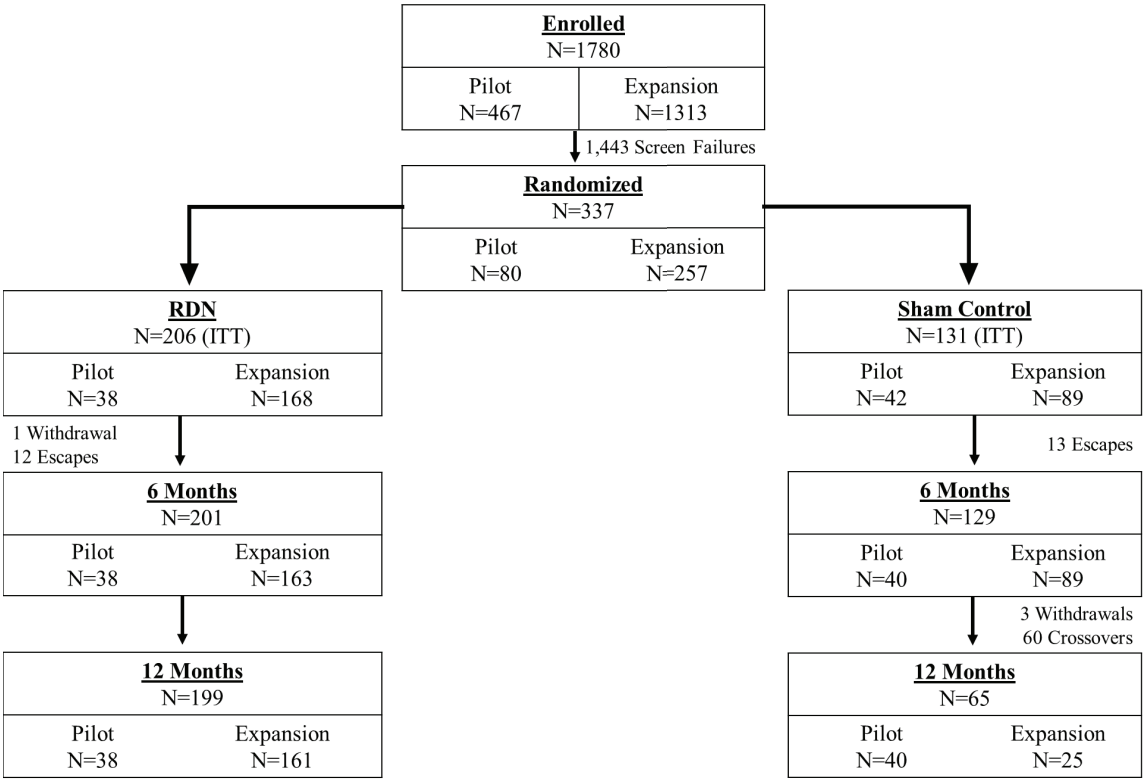
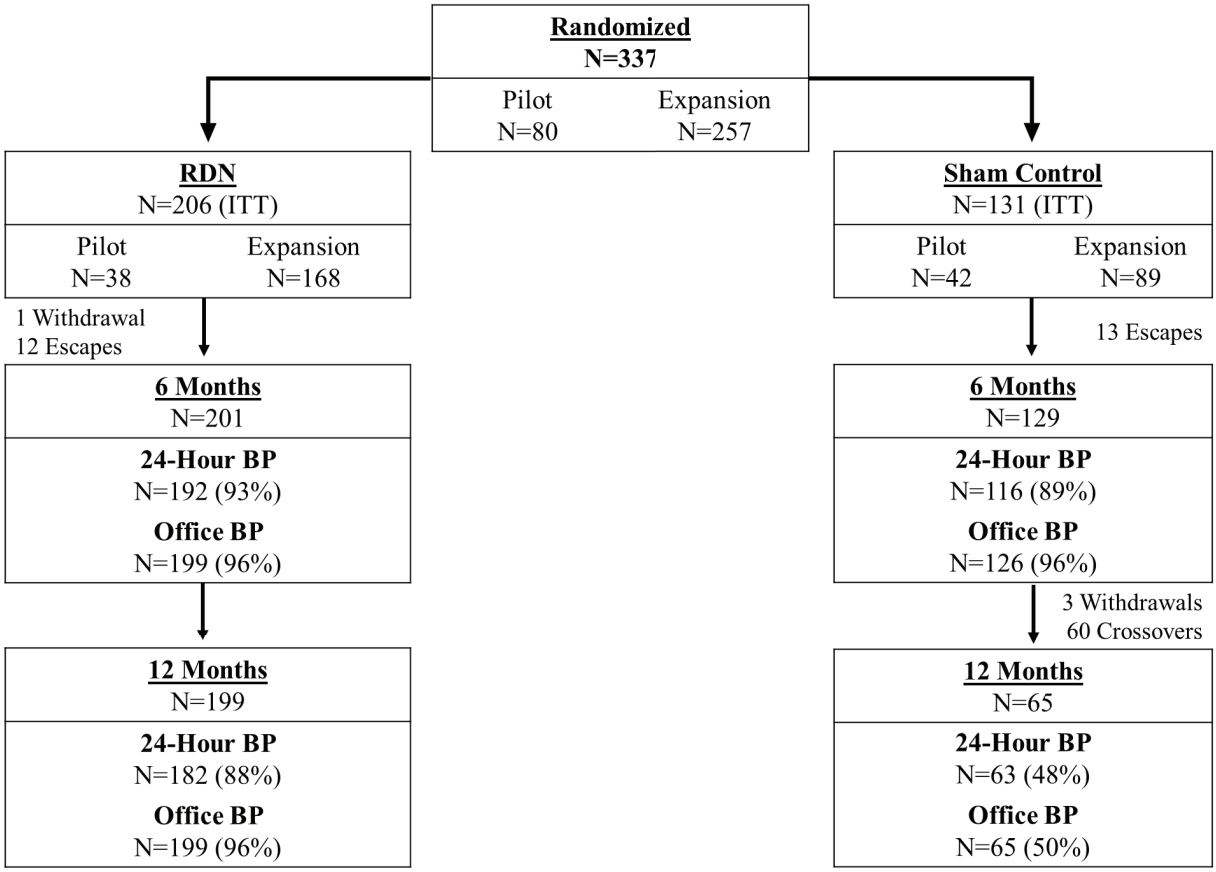


Figure 5: HTN-ON MED Full Cohort Subject Accountability Through 12 Months



Escape defined as Office SBP ≥180 mmHg OR <115 mmHg associated with symptoms of hypotension or safety concern requiring medication changes.

Figure 6: HTN-ON MED Full Cohort Blood Pressure Endpoint Data Capture Through 12 Months

C. Study Population Demographics and Baseline Parameters

1. HTN-OFF MED

Baseline Demographics / Characteristics

Baseline characteristics were well-balanced between the rfRDN and Sham groups and between Pilot and Expansion Cohorts. The majority of patients were male and white, and the median age was 53 years (Table 10).

Most patients had hypertension for >5 years, and there was a low incidence of comorbidities such as diabetes and sleep apnea.

Coronary artery disease was the only characteristic that was significantly different in the Full Cohort (p=0.007) between the two treatment groups (0% in the rfRDN group; 4.3% (8/184) in the Sham group).

Table 10. HTN-OFF MED 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% (102/182)	56.0% (103/184)
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
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)

	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)**
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)

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

Table 11: HTN-OFF MED Patient Baseline Blood Pressure

	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)**	**Sham (N=184)**
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)						
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
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

Procedure Characteristics

The mean procedure time, defined as the time from when arterial access was obtained until arterial closure, was 99 minutes in the rfRDN group. The denervation time was approximately 1 hour (Table 12). Pain medication requirements were significantly greater in the rfRDN group.

Table 12: HTN-OFF MED Procedure Characteristics (Full Cohort)

Treatment	rfRDN (N=182)	Sham (N=184)	Crossover (N=125)
Procedure Time[1] (minutes)			
Mean ± SD	99.3 ± 36.2	52.9 ± 16.6	80.2 ± 26.1
Median (min, max)	93.0 (40, 239)	51.5 (25, 128)	77.0 (32, 196)
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)
Procedural Success[4]	100.0% (181/181)	--	100.0% (125/125)
Denervation Time[4] (minutes)			
Mean ± SD	59.7 ± 24.3	NA	53.1 ± 19.1
Median (min, max)	55.0 (10, 207)		49.0 (20, 135)
Number of Ablation Attempts			
n[5]	181	NA	125
Mean ± SD	46.6 ± 15.3		47.2 ± 16.1
Median (min, max)	45.0 (18, 109)		45.0 (22, 117)
Number of Main Arteries Treated			
n[5]	181	NA	125
Mean ± SD	2.2 ± 0.6		2.3 ± 0.6
Median (min, max)	2.0 (1, 5)		2.0 (2, 4)
Number of Main Arteries Ablations			
n[5]	181	NA	125
Mean ± SD	18.2 ± 9.7		17.8 ± 8.8
Median (min, max)	16.0 (1, 62)		16.0 (5, 60)
Number of Branches Treated			
n[5]	181	NA	125
Mean ± SD	5.8 ± 2.6		6.0 ± 2.5
Median (min, max)	6.0 (0, 17)		6.0 (0, 14)

Treatment	rfRDN (N=182)	Sham (N=184)	Crossover (N=125)
Number of Branch Ablations			
n[5]	181	NA	125
Mean ± SD	28.4 ± 15.1		29.4 ± 15.5
Median (min, max)	28.0 (0, 94)		27.0 (0, 79)
NA: not applicable; SD: standard deviation [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 [5] Number of main arteries treated, not number of patients			

2. HTN-ON MED

Baseline Demographics / Characteristics

Baseline characteristics were well-balanced between the rfRDN and Sham groups and between Pilot and Expansion Cohorts (Table 13), except there was a slightly higher proportion of US subjects in the Expansion Cohort compared with Pilot Cohort (data not shown).

In the Full Cohort, both the rfRDN and Sham groups were predominantly male (81.1% vs 78.6%) with median ages of 56 and 55 years, respectively. Subjects were mostly white or race not reported. The rate of patients reported as Black or African American was 17.0% and 19.1% in the rfRDN and Sham groups, respectively.

Table 13: HTN-ON MED 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)

	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)**
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)
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)

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

Baseline systolic and diastolic BPs and rates of comorbidities were similar between groups (Table 14). The majority of patients in the rfRDN and Sham groups had hypertension for >5 years (69.9% vs 79.4%, respectively, Table 13).

Table 14: HTN-ON MED Patient Baseline Blood Pressure

Subject Baseline Blood Pressure(mmHg)	Pilot Cohort		Expansion Cohort		Full Cohort	
	rfRDN N = 38	Sham N = 42	rfRDN N = 168	Sham N = 89	rfRDN N = 206	Sham N = 131
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)						
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
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

Both the rfRDN and Sham groups were prescribed an average of 1.9 anti-hypertensive medication classes at baseline, and drug testing for medication adherence showed that rfRDN patients were taking an average of 1.7 anti-hypertensive medication classes vs. 1.6 in the Sham group (Table 15).

Table 15: HTN-ON MED Full Cohort Baseline Anti-Hypertensive Medications Detected by Drug Testing

Category	Baseline Prescribed Regimen		Medications Detected by Drug Testing at Baseline	
	rfRDN (N=206)	Sham (N=131)	rfRDN (N=206)	Sham (N=131)
Number of anti-hypertensive medication classes				
Mean ± SD	1.9 ± 0.8	1.9 ± 0.8	1.7 ± 0.9	1.6 ± 0.9
Median	2.0	2.0	2.0	1.0
Min, Max	1, 4	1, 4	0, 5	0, 5
Number of medication classes, n (%)				
1	80 (38.8%)	47 (35.9%)	80 (38.8%)	57 (43.5%)
2	67 (32.5%)	47 (35.9%)	78 (37.9%)	41 (31.3%)
3	58 (28.2%)	36 (27.5%)	29 (14.1%)	20 (15.3%)
4**	1 (0.5%)	1 (0.8%)	6 (2.9%)	2 (1.5%)

Category	Baseline Prescribed Regimen		Medications Detected by Drug Testing at Baseline	
	rfRDN (N=206)	Sham (N=131)	rfRDN (N=206)	Sham (N=131)
Medication class, n (%)				
Diuretic	84 (40.8%)	57 (43.5%)	49 (23.8%)	34 (26.0%)
Calcium Channel Blocker	110 (53.4%)	73 (55.7%)	106 (51.5%)	59 (45.0%)
ACE-I/ARB	158 (76.7%)	99 (75.6%)	145 (70.4%)	87 (66.4%)
Beta Blocker	37 (18.0%)	24 (18.3%)	38 (18.4%)	26 (19.8%)
Other	1* (0.5%)	0	9 (4.4%)	2 (1.5%)

ACE-I: angiotensin-converting enzyme inhibitor; ARB; angiotensin receptor blocker; SD: standard deviation
*Vasodilator
**One patient was prescribed Metoprolol at baseline for a "Heart Disease" indication in addition to 3 other anti-hypertensive medication classes.

Procedure Characteristics

The mean procedure time, defined as the time from when arterial access was obtained until arterial closure, was 91 minutes in the rfRDN group. The denervation time was 54 minutes (Table 16). At the time of the PMA submission, crossover data were only available from 24 subjects in the Pilot Cohort.

Table 16: HTN-ON MED Full Cohort Procedure Characteristics

Treatment	rfRDN (N=206)	Sham (N=131)	Pilot Crossover (N=24)
Procedure Time[1] (minutes)			
Mean ± SD	91.3 ± 31.2	51.2 ± 19.5	82.9 ± 26.9
Median (min, max)	88.5 (33, 210)	48.0 (23, 162)	80.0 (40, 160)
Amount of Contrast used (cc)	204.2 ± 81.4	69.9 ± 35.8	196.0 ± 93.7
Intra-procedural medication			
Pain meds	21.8% (45/206)	17.6% (23/131)	33.3% (8/24)
Sedatives/Anxiolytics	98.5% (203/206)	98.5% (129/131)	95.8% (23/24)
Atropine	2.9% (6/206)	0.0% (0/131)	12.5% (3/24)
Hospital Stay (days)	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.0
Device success[2]	100.0% (205/205)	--	100.0% (24/24)
Procedure success[3]	99.5% (204/205)	--	100.0% (24/24)
Denervation Time[4] (minutes)			
Mean ± SD	54.4 ± 19.2	NA	53.1 ± 27.0
Median (min, max)	52.0 (17, 133)		52.0 (0, 141)
Number of Ablation Attempts			
n[5]	205	NA	24
Mean ± SD	47.4 ± 16.5		50.8 ± 21.6

Treatment	rfRDN (N=206)	Sham (N=131)	Pilot Crossover (N=24)
Median (min, max)	44 (16, 107)		45 (17, 115)
Number of Main Arteries Treated			
n[5]	205	NA	24
Mean ± SD	2.3 ± 0.6		2.2 ± 0.4
Median (min, max)	2.0 (1, 5)		2.0 (2, 3)
Number of Main Arteries Ablations			
n[5]	205	NA	24
Mean ± SD	19.4 ± 9.5		18.5 ± 7.8
Median (min, max)	18.0 (5, 82)		18.5 (0, 33)
Number of Branches Treated			
n[5]	205	NA	24
Mean ± SD	5.8 ± 2.7		7.4 ± 4.3
Median (min, max)	6.0 (0, 14)		6.0 (2, 19)
Number of Branch Ablations			
n[5]	205	NA	24
Mean ± SD	28.0 ± 14.6		32.3 ± 18.2
Median (min, max)	25.0 (0, 82)		28.5 (7, 86)

NA: not applicable; SD: standard deviation;
[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
[5] Number of main arteries treated, not number of patients

D. Safety Results

Safety was evaluated in the pre-specified pooled safety population, which included the first 253 consecutive patients treated with rfRDN in the OFF and ON-MED studies. Safety evaluations were also performed for the individual studies comparing rfRDN to Sham and independently adjudicated by the CEC.

1. Primary Safety Endpoint Analysis

The primary safety endpoint was the incidence of major adverse events (MAE) at 1-month post-procedure and renal artery stenosis evaluated at 6 months for the first 253 consecutive patients treated with rfRDN (initial procedure or crossover) in the HTN-OFF MED and HTN-ON MED studies.

The primary safety endpoint results are shown in Table 17. 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).

Additional Analyses

FDA also requested a post-hoc safety analysis on rfRDN-treated subjects from the four studies and all studies pooled using the same endpoint definitions. The results were similar across the studies, as shown in Table 17. There were 2 pseudoaneurysms 1 required surgical repair and 1 required thrombin injection.

Table 17: 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 Subjects 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)
p-value for all pooled subjects not adjusted for multiplicity

2. Secondary Safety Endpoint Results

The rates of pre-specified MAE through 6 months for the HTN-OFF MED and HTN-ON MED (Full Cohorts) studies are shown in Table 18 for the rfRDN and Sham groups. The rates of MAEs were low and similar between the cohorts and studies.

Table 18: HTN-OFF MED and HTN-ON MED MAEs through 6 months for rfRDN and Sham Subjects

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

	HTN-OFF % Subjects with Events (n/N)		HTN-ON % Subjects with Events (n/N)	
	rfRDN (n=182) n (%)	Sham (n=184) n (%)	rfRDN (n=206) n (%)	Sham (n=131) n (%)
New Stroke	0 (0%)	1 (0.5%)	0 (0%)	1 (0.8%)
New renal artery stenosis (>70% diameter stenosis)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Data displayed as % (n/N)

In HTN-OFF MED, the incidence of serious AEs (SAEs) was similar between treatment groups and the majority of events were only experienced by one patient. The only SAEs that occurred in more than one patient were sepsis, vascular site hematoma, and arthralgia. SAEs were reported in 8.7% and 11.5% of patients randomized to rfRDN and Sham groups, respectively, in the HTN-ON MED study. The only event that was experienced by more than one patient was vascular access site pseudoaneurysm (Table 19).

Table 19: HTN-OFF MED (24 Months) & HTN-ON MED (6 Months) Serious Adverse Events in >1 Patient

	HTN-OFF (24 Months) % Subjects with Events (n/N)		HTN-ON (6 Months) % Subjects with Events (n/N)	
	rfRDN (N=182) n (%)	Sham (N=184) n (%)	rfRDN (N=206) n (%)	Sham (N=131) n (%)
Any Serious Adverse Event	**31 (17%)**	**27 (14.7%)**	**18 (8.7%)**	**15 (11.5%)**
Sepsis	2 (1.1%)	2 (1.1%)	0 (0%)	0 (0%)
Vascular Access Site Hematoma	1 (0.5%)	2 (1.1%)	2 (1.0%)	1 (0.8%)
Arthralgia	1 (0.5%)	5 (2.7%)	0 (0%)	0 (0%)
Vascular Access Site Pseudoaneurysm	0 (0%)	0 (0%)	**2 (1.0%)**	**1 (0.8%)**

Data displayed as % (n/N)

3. Adverse effects that occurred in the PMA clinical studies

In the HTN-OFF MED study, 82% of patients in the rfRDN group and 84% of patients in the Sham group experienced an AE. The most common AEs reported were headache and vascular access site hematoma (Table 20). The incidence and severity of hematomas was similar between groups and is expected for arterial interventional procedures. Overall, AEs were balanced across study groups.

Table 20: HTN-OFF MED (12 Months) & HTN-ON MED (6 Months) Pivotal Adverse Events (> 5 % in either arm) - Enrollment to 12 Months (Full Cohort)

	HTN-OFF (12 Months) % Subjects with Events (n/N)		HTN-ON (6 Months) % Subjects with Events (n/N)	
Events	**rfRDN (N=182)** n (%)	**Sham (N=184)** n (%)	**rfRDN (N=206)** n (%)	**Sham (N=131)** n (%)
Any Adverse Event	149 (81.9%)	154 (83.7%)	129 (62.6%)	89 (67.9%)
Headache	32 (17.6%)	31 (16.8%)	7 (3.4%)	9 (6.9%)
Vascular access site hematoma	16 (8.8%)	22 (12.0%)	10 (4.9%)	10 (7.6%)
Dizziness	15 (8.2%)	12 (6.5%)	0 (0%)	0 (0%)
Back pain	12 (6.6%)	8 (4.3%)	12 (5.8%)	4 (3.1%)
Peripheral edema	12 (6.6%)	15 (8.2%)	6 (2.9%)	12 (9.2%)
Arthralgia	11 (6.0%)	13 (7.1%)	0 (0%)	0 (0%)
Hypertension	11 (6.0%)	11 (6.0%)	0 (0%)	0 (0%)
Nasopharyngitis	11 (6.0%)	14 (7.6%)	0 (0%)	0 (0%)
Hypokalemia	0 (0%)	0 (0%)	12 (5.8%)	8 (6.1%)

Data displayed as % (n/N)

One renal artery occlusion was reported in the rfRDN group; no arterial dissection was identified by the Investigator. The Angio Core Lab identified dissection in branch L1A that was not denervated. After reviewing the angiography and procedure, the site concluded that the vascular damage was in a small peripheral renal branch (estimated diameter 1 mm) of the left accessory artery. According to the site, the insertion of the guide wire and the pullback afterwards caused the vascular complication and was not related to the study device. Six-month duplex ultrasound was non-diagnostic, and a repeat CTA did not identify a stenosis. The 24-months DUS was diagnostic with no stenosis identified.

In HTN-ON MED, AEs were reported for a total of 63% of rfRDN patients and 68% of Sham patients. The most frequently reported AEs in the rfRDN group were back pain, hypokalemia, and vascular access site hematoma (Table 20). The incidence and severity of hematomas was similar between groups and is expected for arterial interventional procedures.

There were 2 renal dissection events reported in rfRDN patients. One was identified by the angiographic core lab and reported by the site after further review, and the other was identified and reported by the site. These events did not meet the criteria to be reported as “serious adverse events” and did not require intervention.

In the HTN-OFF study, 1 non-cardiovascular death occurred in the Sham group through 24-month follow-up. In the HTN-ON study, no deaths occurred through the 6-month timepoint.

4. Additional Safety Analyses

Assessment of Renal Artery Stenosis

Renal imaging was required in the HTN-OFF MED and HTN-ON MED studies at 6 and 12 months post-procedure. DUS was the first-line imaging modality in the majority of subjects, with repeat imaging via DUS, CTA, or MRA if the initial imaging was non-diagnostic. Renal angiography was required when measured diameter stenosis (DS) > 60% when assessed by DUS or > 70% when assessed by CTA or MRA.

Imaging was considered diagnostic if any of following criteria were 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
- For rfRDN patients, imaging evaluability was assessed only for vessels treated with renal denervation.
- For DUS images, renal flow for accessory main renal arteries and branch vessels was confirmed by visualization of uniform parenchymal flow within segments of the same kidney as well as between kidneys

Of the images evaluated by imaging core laboratories, 100% of angiograms, 89% of DUS, 80% of CTA, and 37% of MRA results met the criteria for being diagnostic. 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.

DUS image quality can be highly operator-dependent in the renal vasculature, and this methodology can lack sensitivity to identify non-hemodynamically significant <70% diameter stenoses. HTN-OFF MED and HTN-ON MED studies did not provide data comparing DUS with angiography, CTA, or MRA to correlate imaging sensitivity or accuracy. In addition, the diagnostic imaging rates for CTA and MRA were affected by image quality issues as reported by the CTA/MRA core laboratory. These factors increased the uncertainty of renal artery stenosis assessment.

At 6 months, no potential stenoses of >60% were identified by DUS in either study.

In a separate 12-month analysis of 206 subjects who had diagnostic CTA/MRA, 13 subjects had potential stenosis of >50%. Seven of these subjects had follow-up imaging with angiography, CTA, or MRA that ruled out a stenosis > 70%, though 2

patients had renal angiograms read by the site as "no stenosis," but angiography was of insufficient quality for core lab to calculate diameter stenosis. Four subjects had follow-up imaging with only DUS or refused follow-up imaging. Two subjects had 60% stenosis confirmed by CTA. Carrying forward the results of subjects who did not have adequate follow-up imaging (6) and those with insufficient detail to determine diameter stenosis (2), the rate of renal artery stenosis >50% could be as high as 2.9% (6/206) to 3.9% (8/206) through 12 months.

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 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 of eGFR in the Sham group was numerically higher vs. the rfRDN group: -1.36 vs. -1.19 mL/min/1.73m^2 (p=0.2), but the difference in decline is not clinically-meaningful.

E. HTN-OFF MED Effectiveness Results

1. Powered Primary and Secondary Endpoint Results

The primary effectiveness endpoint and the powered secondary effectiveness endpoint were based on difference between randomized groups (rfRDN and Sham, ITT Cohort) using the Bayesian power prior methodology.

Primary Effectiveness Endpoint: Change in SBP measured by 24-hour ABPM from baseline to 3-months post-procedure, compared between rfRDN and Sham groups.

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

Table 21 shows the HTN-OFF ITT Cohort Bayesian analysis for the primary and secondary effectiveness endpoints. The power prior 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 an estimated 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 an estimated 6.5 mmHg greater reduction in OSBP at 3 months vs. the Sham group.

For both primary and secondary effectiveness endpoints, the treatment differences in favor of rfRDN met the study success criteria for superiority with posterior probability of superiority >0.999.

Table 21: Powered Primary and Secondary Effectiveness Results at 3 Months – HTN-OFF MED Primary (Bayesian) Analysis

	Power prior parameter	Prior N[b]	N	Bayesian treatment effect[a]	Posterior probability of success
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] Posterior mean and 95% Bayesian credible interval
[b] Effective prior sample size after discounting

Table 22 shows frequentist analyses for the HTN-OFF MED Pilot, Expansion, and Full Cohorts for 24-hour SBP and Office SBP. The treatment differences in favor of rfRDN among the cohorts were generally similar.

Table 22: Frequentist ANCOVA Analyses for ASBP and OSBP at 3 Months for HTN-OFF MED Cohorts (ITT)

ITT Population	rfRDN	Sham	ANCOVA difference[a]	ANCOVA p-value*
24Hr SBP Change				
HTN-OFF MED Pilot Cohort	-5.5 ± 10.3 (N=35)	-0.1 ± 10.0 (N=35)	-4.9 (-9.6, -0.3)	0.0370
HTN-OFF MED Expansion	-4.4± 10.5 (N=105)	-0.8 ± 8.1 (N=99)	-3.6 (-6.2, -1.0)	0.0065
HTN-OFF MED 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 MED Pilot	-10.0 ± 15.4 (N=37)	-2.3 ± 12.1 (N=41)	-7.1 (-13.2, -1.1)	0.0212
HTN-OFF MED Expansion	-9.2 ± 14.4 (N=119)	-2.6 ± 13.2 (N=109)	-6.6 (-10.2, -3.0)	0.0003
HTN-OFF MED Full Cohort	-9.4 ± 14.8 (N=170)	-2.3 ± 12.7 (N=164)	-7.1 (-10.0, 4.2)	<0.001

[a] Estimated treatment effect and 95% confidence interval
* p-values not adjusted for multiplicity

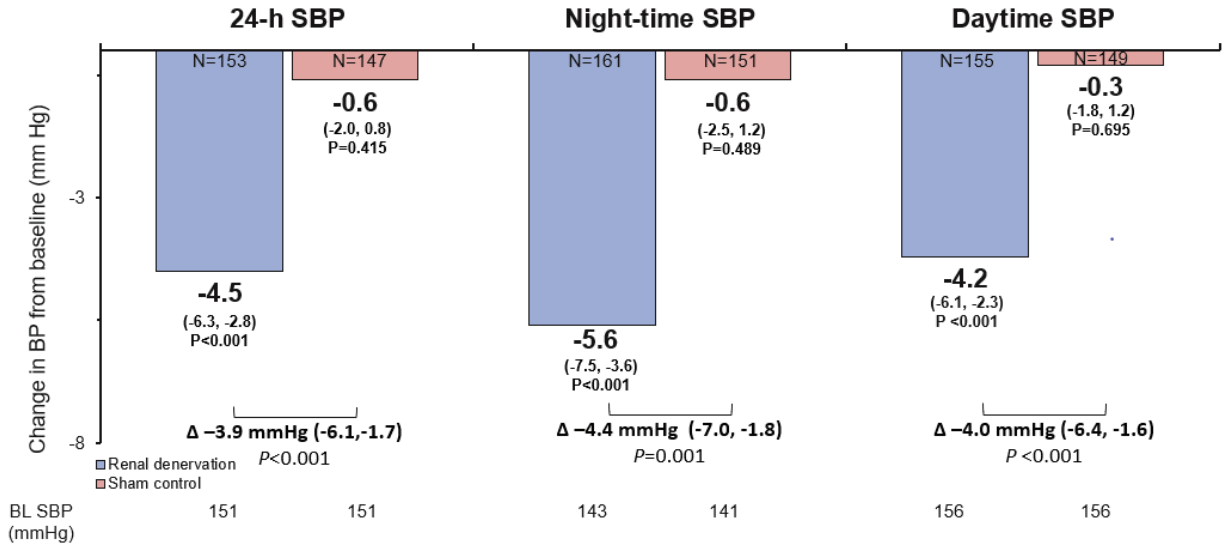
2. Secondary Effectiveness Endpoints

Daytime and Nighttime ASBP

Figure 7 and Figure 8show the changes in the 24-hour, daytime and nighttime ASBP for the HTN-OFF MED Full Cohort.

- Daytime was defined as any ABPM readings between 7 am and 10 pm (includes morning ABPM readings between 7 am and 9 am).
- Nighttime was defined as any ABPM readings between 10 pm to 7 am.

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



p-values not adjusted for 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: HTN-OFF MED Full Cohort 24-hour, Night-time, and Daytime ASBP Change at 3 Months

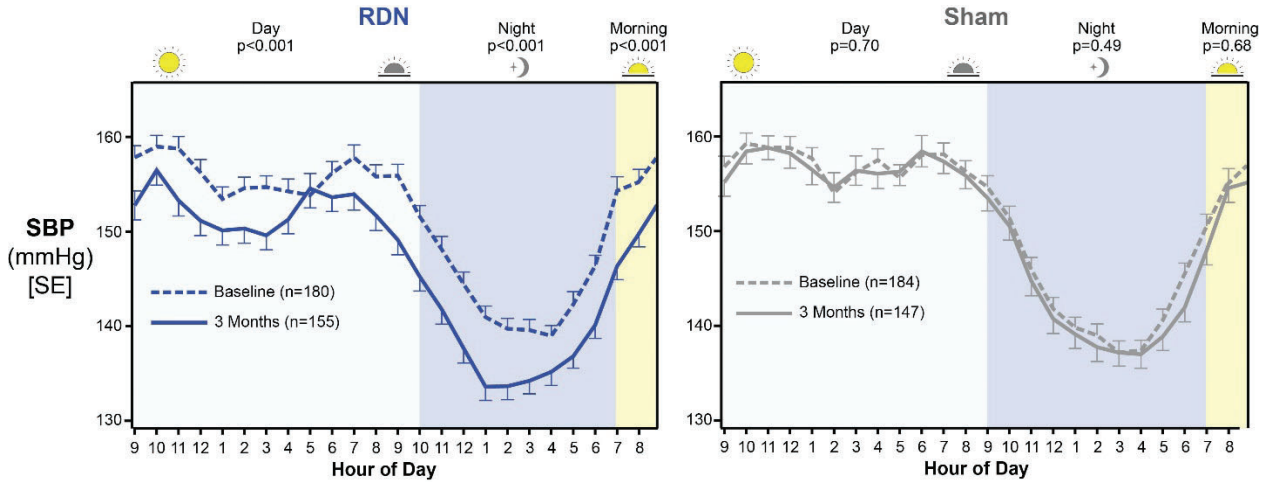


Figure 8: HTN-OFF MED Full Cohort 24-Hour SBP Baseline vs 3 Months

Distribution of Magnitude of SBP Reduction

Figure 9 and Figure 11 show the proportion of subjects with BP reductions in office and 24-hour SBP, respectively, ≥5, 10, 15, and 20 mmHg and patients who achieved goal SBP (<140 mmHg) at 3 months in HTN-OFF. Figure 10 shows the waterfall distribution of office SBP change at 3-months in the rfRDN and Sham groups.

Significantly more rfRDN subjects achieved office SBP reductions than the Sham group ($p<0.001$) with 65% of rfRDN-treated subjects achieving an office SBP reduction of at least 5 mmHg. rfRDN subjects treated achieved target office systolic blood pressure (OSBP) <140 mmHg at statistically higher rates than Sham subjects .

An evaluation of progressive reductions measured by 24-hour ambulatory monitoring in HTN-OFF (Figure 10) showed similar results to those seen in office SBP for reductions of ≥5, ≥10 and ≥15 mmHg with rfRDN significantly outperforming the Sham group. The proportion of rfRDN subjects with BP reductions of ≥20 mmHg was numerically greater than Sham subjects.

Figure 9

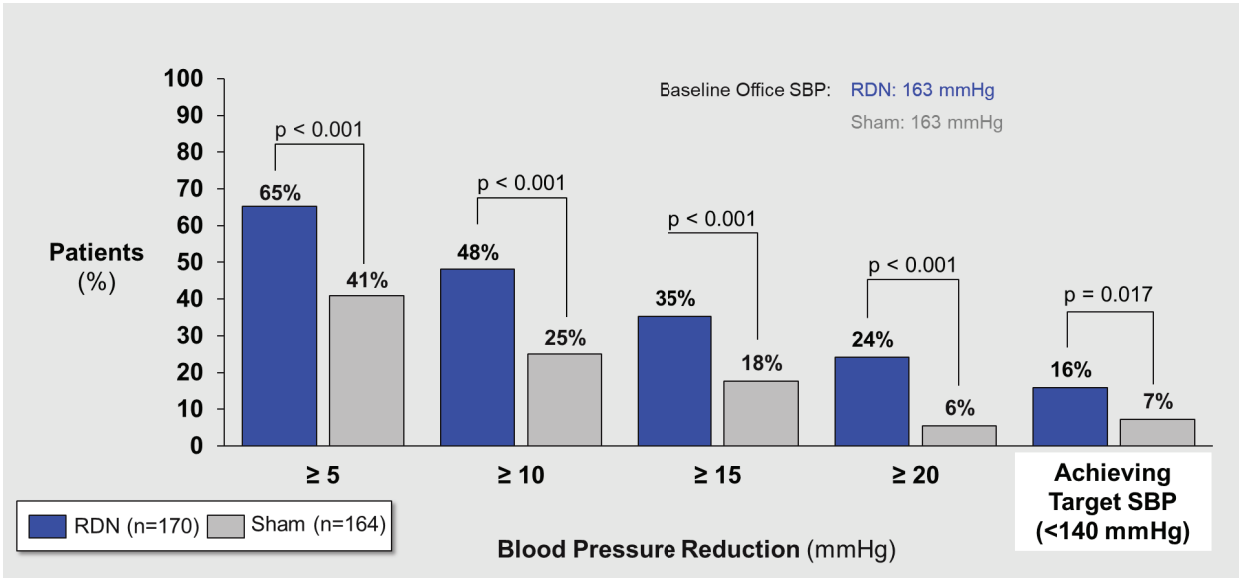
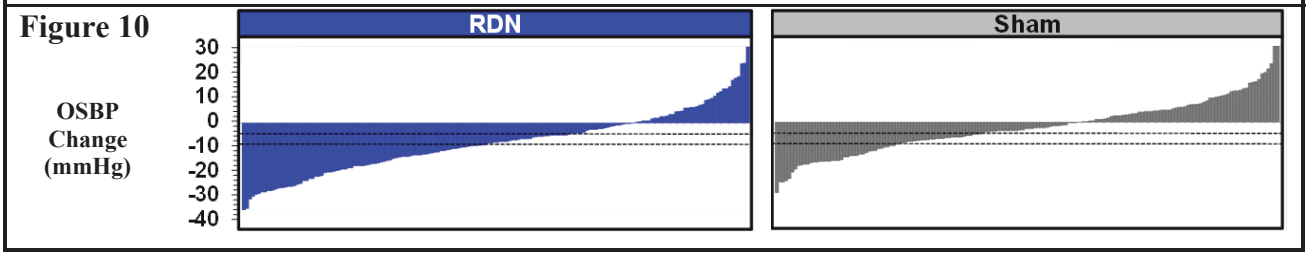


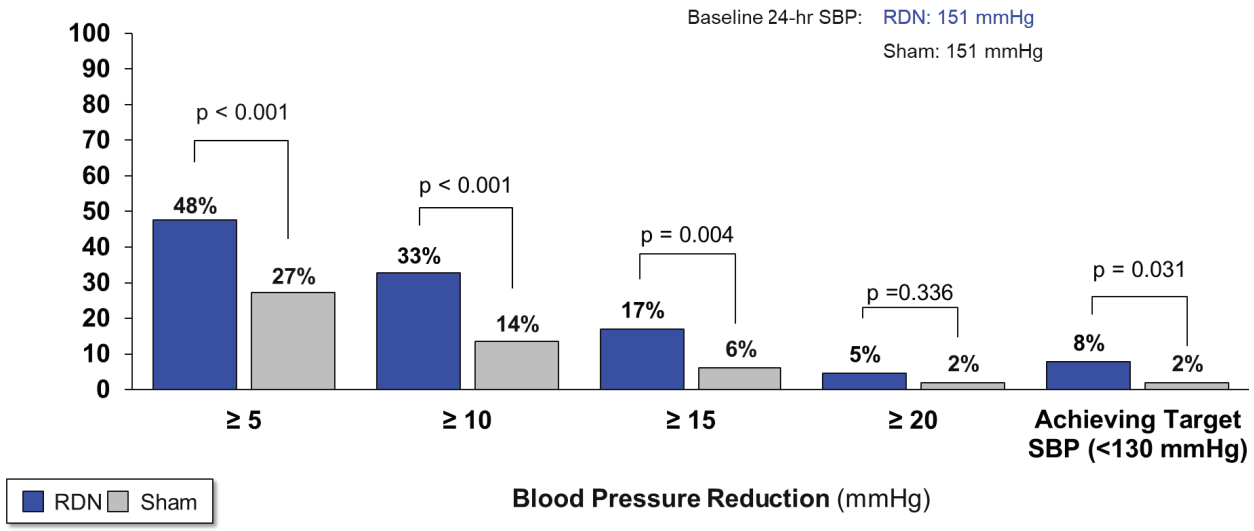
Figure 10



p-values not adjusted for multiplicity

Figure 9: HTN-OFF Full Cohort Tiers of Office SBP Reduction and Achievement of Target SBP at 3 Months

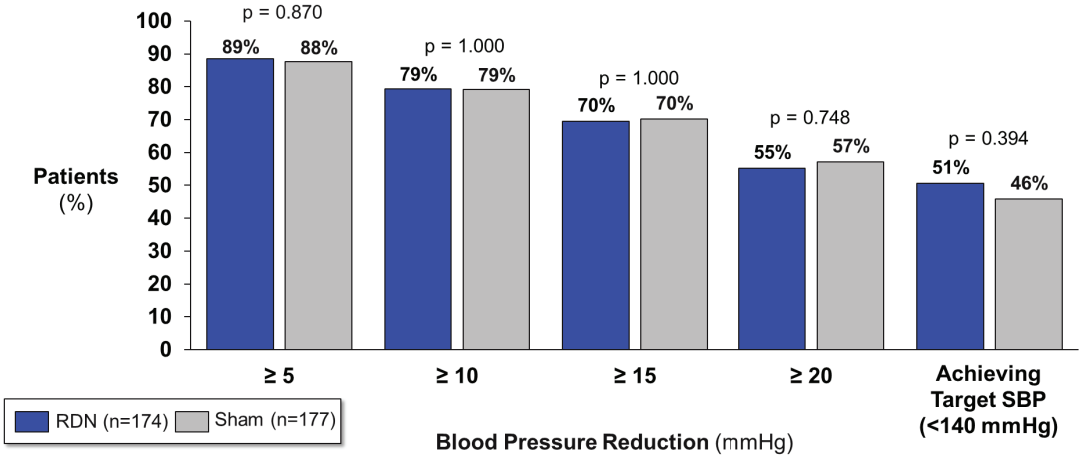
Figure 10: Waterfall Plots for HTN-OFF Full Cohort at 3-Months (Prior to Reintroducing Antihypertensive medications)



p-values not adjusted for multiplicity

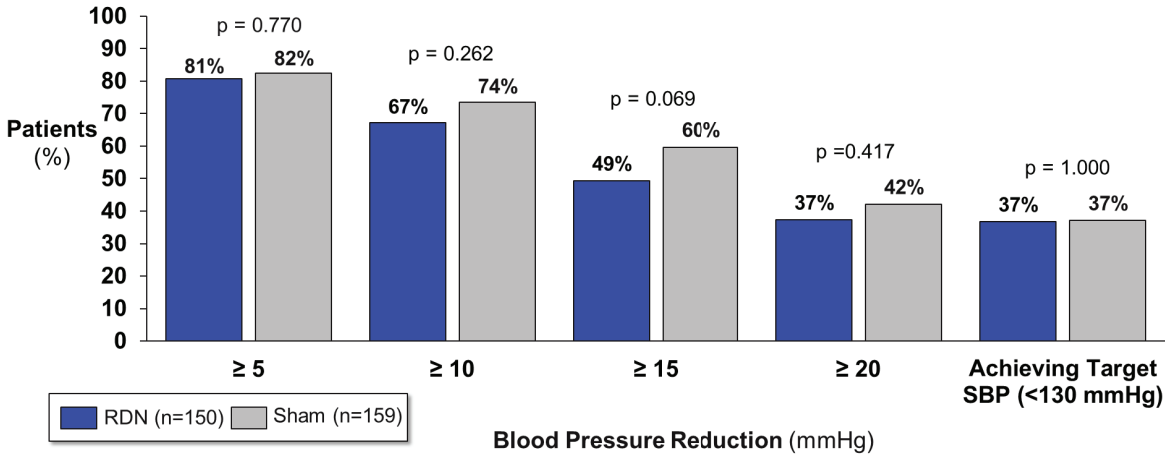
Figure 11: Tiers of 24-Hour SBP Reduction and Achievement of Target SBP: HTN-OFF Full Cohort at 3-Months

Figure 12 and Figure 13 show the proportion of subjects with BP reductions in office and 24-hour SBP, respectively, ≥5, 10, 15, and 20 mmHg and patients who achieved goal SBP (<140 mmHg) at 6 months in HTN-OFF.



p-values not adjusted for multiplicity

Figure 12: Tiers of Office SBP Reduction and Achievement of Target SBP: HTN-OFF Full Cohort at 6-Months



p-values not adjusted for multiplicity

Figure 13: Tiers of 24-Hour SBP Reduction and Achievement of Target SBP: HTN-OFF Full Cohort at 6-Months

Box plots provide another means of viewing patient level data where each patient's observation is represented with a dot. The box plot gives a visual summary of the distribution of each group by quartiles and the median. Figure 14 shows box plots of the change in 24-hour SBP and Office SBP for the HTN-OFF study at 3 months. For 24-hour SBP changes, the median and IQR for the rfRDN and sham groups were -4.8 mmHg (-12.4, 2.4) and -0.1 mmHg (-5.7, 4.05) respectively. For Office SBP changes, the median and IQR for the rfRDN and sham groups were -9.0 mmHg (-19.3, -0.7) and -3.0 mmHg (-9.77, 5.08), respectively.

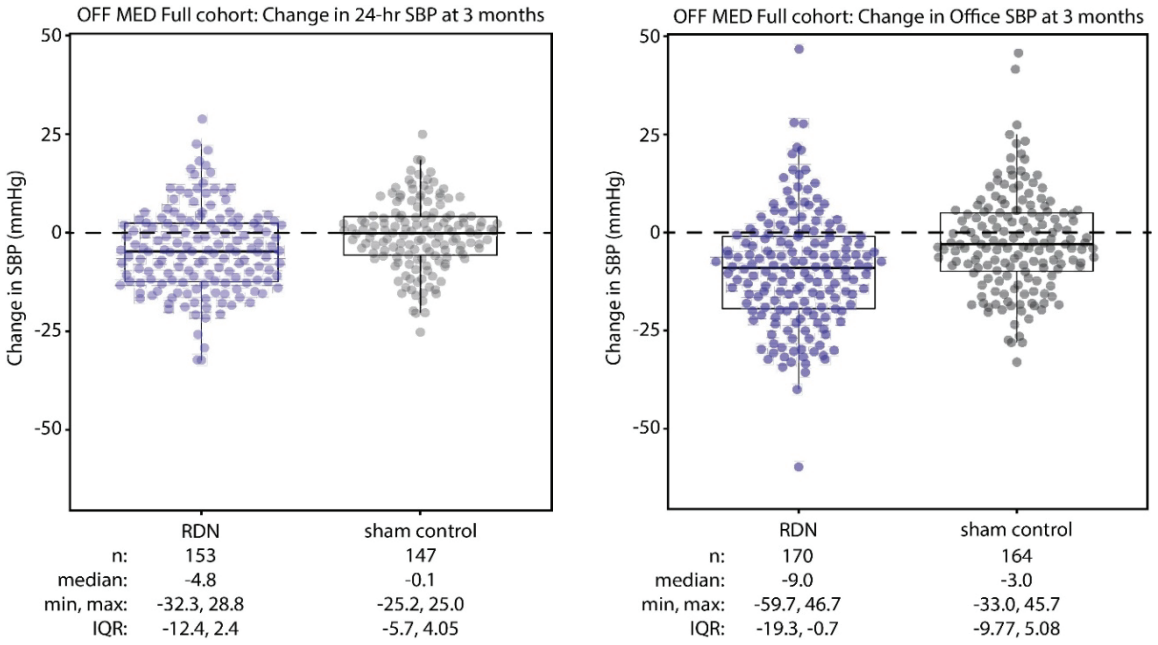


Figure 14: HTN-OFF MED Full Cohort Box plots of 24-Hour and Office Systolic Blood Pressure Change at 3-Months

The box plot shows the distribution of BP change with each individual patient observation represented as a dot. The box contains the middle 50% of the patient BP changes (between the 25th and 75th percentiles, the inter-quartile range or IQR). The median is represented by a horizontal line within that box. Observations that extend above or below the vertical lines outside the box (± 1.5*IQR) are considered to be outliers.

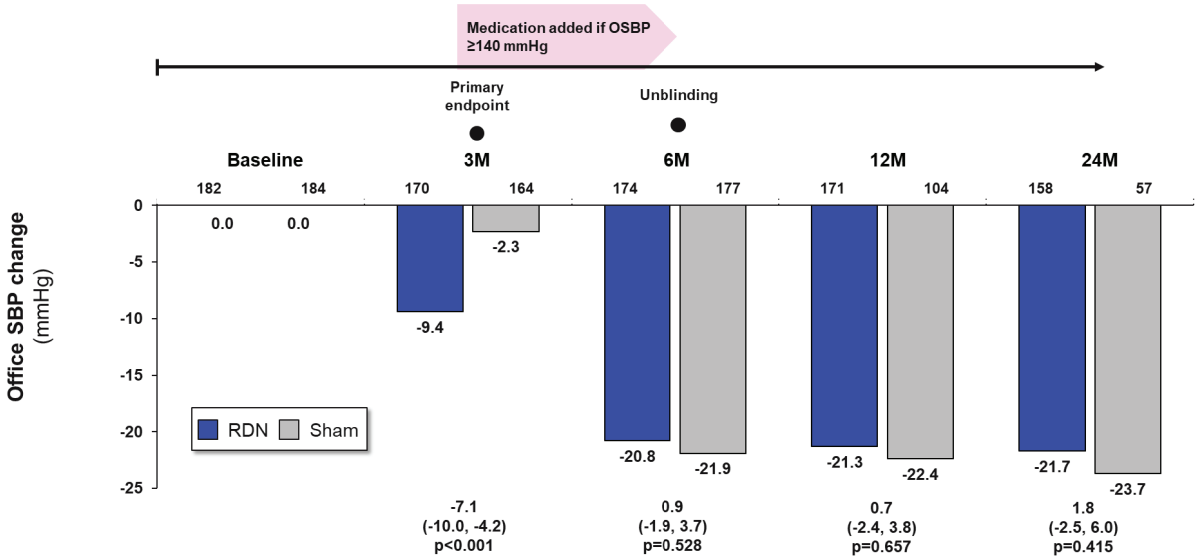
3. Long-Term Effectiveness Results

The HTN-OFF MED study was not designed to assess the durability of blood pressure reduction, as the effect of rfRDN at later timepoints may be challenging to interpret because of the use and escalation of BP medications beyond after 3 months, unblinding of study subjects to their treatment assignment, and crossover of many Sham subjects to rfRDN treatment.

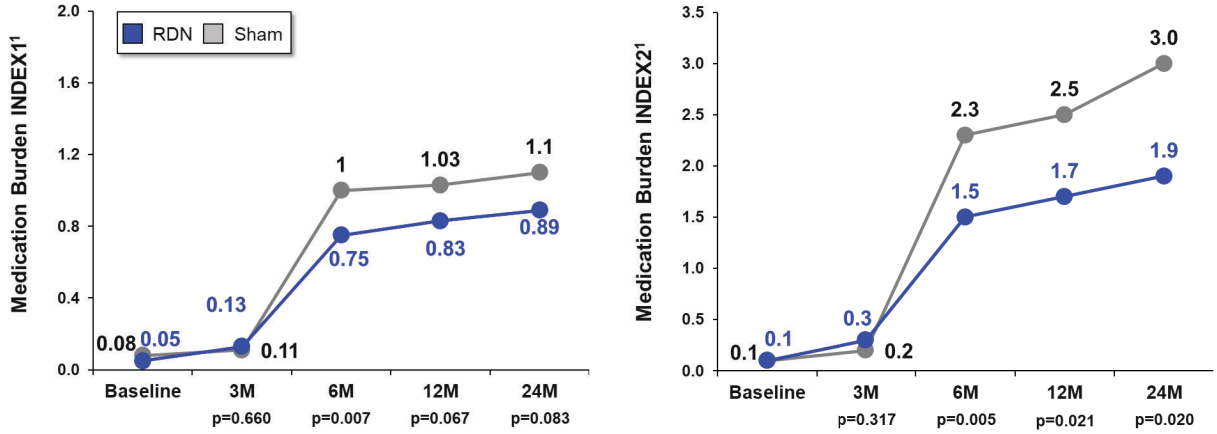
To assess treatment effectiveness durability, ambulatory and office SBP and medication burden were evaluated. In the HTN-OFF protocol, medications were to be withheld (unless escape criteria were met) through 3-month post-procedure and could be restarted after 3 months (Figure 15), with a protocol-driven medication escalation protocol used through 6 months for subjects not at SBP goal (<140 mmHg).

Figure 15 shows the office SBP and medication burden (MedIndex 1 and MedIndex 2 for subjects with available office SBP) through 24 months for the HTN-OFF MED Full Cohort. Figure 16 shows the 24-hour SBP and medication burden (MedIndex 1 and MedIndex 2) for subjects with available 24-hour SBP) through 24 months. Starting at 6 months, there was higher BP medication use in the Sham group, and the OSBP and 24 hour SBP reduction vs. baseline was greater in the Sham group.

Interpretation of BP changes between treatment groups at later timepoints is challenging because Sham subject crossover to rfRDN treatment after 6 months reduced the Sham group sample size and resulted in a loss of a randomized comparison.

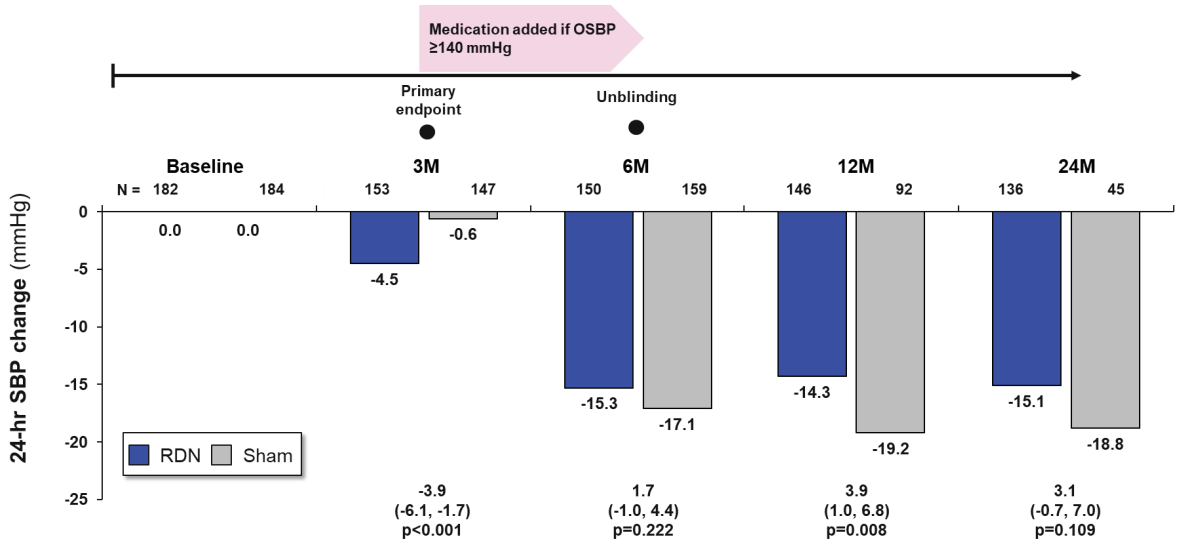


p-values not adjusted for multiplicity.
Crossovers were allowed starting at 6 months are not included in this analysis.

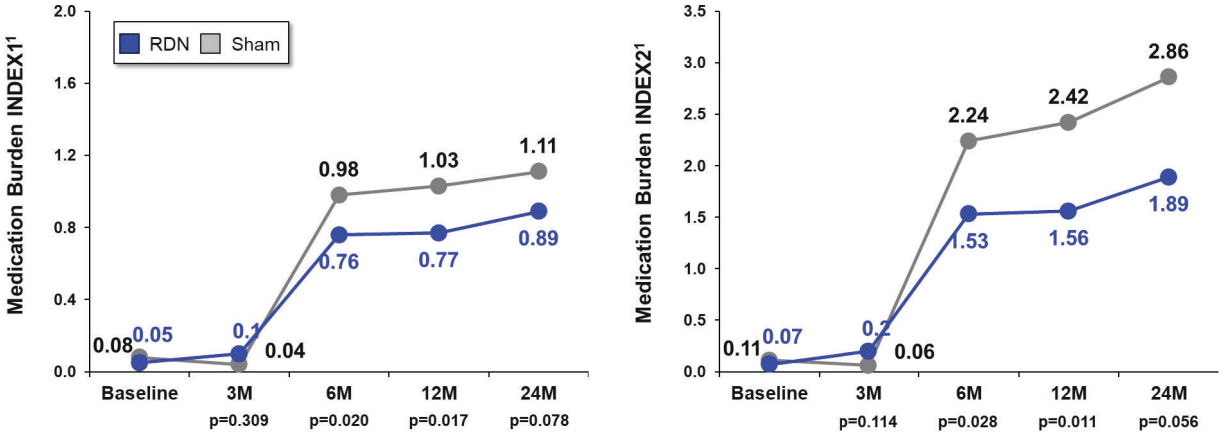


[1]Medication burden INDEX1 and INDEX2 data presented for patients with available office SBP data, and is calculated using drug testing and when unavailable, prescribed medication data.
p-values not adjusted for multiplicity.
Crossovers were allowed starting at 6 months are not included in this analysis.

Figure 15: HTN-OFF MED Full Cohort Office Systolic Blood Pressure and Medication Burden Through 24 Months



p-values not adjusted for multiplicity
Crossovers were allowed starting at 6 months are not included in this analysis.



[1]Medication burden INDEX1 and INDEX2 data presented for patients with available 24-hour SBP data, and is calculated using drug testing and when unavailable, prescribed medication data.
p-values not adjusted for multiplicity
Crossovers were allowed starting at 6 months are not included in this analysis.

Figure 16: HTN-OFF MED–24-Hour Systolic Blood Pressure and Medication Burden through 24 Months

F. HTN-ON MED Effectiveness Results

1. Powered Primary Endpoint Results

The powered primary effectiveness endpoint and the non-powered secondary effectiveness endpoint were based on difference between randomized groups (rfRDN and Sham) using the Bayesian power prior methodology.

Primary Effectiveness Endpoint (Powered): 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): Change in OSBP from baseline to 6-months post-procedure, compared between rfRDN and Sham groups

Table 23 shows the HTN-ON MED Primary Cohort Bayesian analysis for the primary and secondary effectiveness endpoints. Due to differences in the results for the Pilot and Expansion Cohorts, much of the Pilot data was discounted (power prior parameter = 0.194 for rfRDN and 0.0002 for Sham) for the 24-hour SBP primary effectiveness endpoint, meaning that little Pilot Cohort blood pressure 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 Pilot and Expansion Cohorts were generally similar such that a higher proportion of Pilot Cohort outcome information was used.

- For the primary effectiveness endpoint of 24-hour ASBP at 6 Months:
  - In the rfRDN group, there was an estimated 0.03 mmHg greater reduction in 24-hour ASBP at 6 months vs. the Sham group.
  - The 24-hour ASBP treatment difference did not meet study success criteria for superiority (posterior probability of superiority = 0.51).

- For the secondary effectiveness endpoint of OSBP at 6 Months:
  - In the rfRDN group, there was an estimated 4.1 mmHg greater reduction in OSBP at 6 months vs. the Sham group.
  - The OSBP treatment difference had posterior probability of superiority = 0.99 for rfRDN.

Table 23: HTN-ON MED Primary 24-Hour ASBP and Secondary OBP Effectiveness Results at 6 Months: Bayesian Analysis

	Power prior parameter	Prior N[b]	N	Bayesian treatment effect[a]	Posterior probability of success
24-hour ASBP Change					
rfRDN	0.194	6.999	156	-0.03 mmHg (-2.82, 2.77)	0.508
Sham	0.0002	0.007	80		
Office SBP Change					
rfRDN	>0.999	38	161	-4.095 mmHg (-7.44, -0.75)	0.992
Sham	0.156	6.2	86		

[a] Posterior mean and 95% Bayesian credible interval
[b] Effective prior sample size after discounting

Additional Bayesian sensitivity analyses were performed on the primary endpoint for the ITT population (without adjustment for medication use). Consistent with less discounting of the pilot data than in the primary Bayesian analysis, the estimated treatment effects in the Bayesian sensitivity analyses were similar to the effect estimated from the prespecified frequentist ANCOVA analysis .

Additional Primary and Secondary Effectiveness Analyses

Table 24 shows a frequentist analysis of covariance (ANCOVA) for the baseline BP adjusted treatment effect for the HTN-ON MED Pilot, Expansion, and Full Cohorts.

For 24-hour ASBP, 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. BP reduction differences were greater in the rfRDN group vs. the Sham group and were significant for all cohorts (Pilot, Expansion, and Full).

Table 24: Frequentist ANCOVA Analyses for ASBP and OSBP at 6 Months for HTN-ON MED Cohorts

ITT Population	rfRDN	Sham	ANCOVA difference[a]	ANCOVA p-value*
24Hr SBP Change				
HTN-ON MED Pilot Cohort	-9.3 ± 10.9 (36)	-1.6 ± 10.7 (36)	-7.3 (-12.2, -2.4)	0.0041
HTN-ON MED Expansion Cohort	-5.9 ± 10.6 (156)	-5.8 ± 10.0 (80)	0.0 (-2.8, 2.9)	0.9735
HTN-ON MED Expansion Cohort (1:1)	-8.2 ± 11.2 (N=13)	-7.4 ± 14.7 (N=9)	-1.3 (-12.5, 9.9)	--
HTN-ON MED Expansion Cohort (2:1)	-5.9 ± 10.6 (N=143)	-5.6 ± 9.4 (N=71)	0.0 (-2.9, 3.0)	--
HTN-ON MED Expansion Cohort (weighted average)	--	--	-0.1 (-2.9,2.7)	--
HTN-ON MED 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 MED Pilot Cohort	-9.2 ± 12.3 (38)	-2.6 ± 12.9 (40)	-6.6 (-12.3, -0.8)	0.0259
HTN-ON MED Expansion Cohort	-10.1 ± 14.3 (161)	-6.2 ± 13.2 (86)	-4.0 (-7.6, -0.4)	0.0280
HTN-ON MED Expansion Cohort (1:1)	-12.3± 10.7 (N=15)	-8.1 ± 10.9 (N=10)	-4.2 (-13.6, 5.1)	--
HTN-ON MED Expansion (2:1)	-9.9± 14.6 (N=146)	-6.0 ± 13.5 (N=76)	-4.0 (-7.9, 0.2)	--

ITT Population	rfRDN	Sham	ANCOVA difference[a]	ANCOVA p-value*
HTN-ON MED Expansion Cohort (weighted average)	--	--	-4.1 (-7.6,0.5)	--
HTN-ON MED 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)

[a] Estimated treatment effect and 95% confidence interval

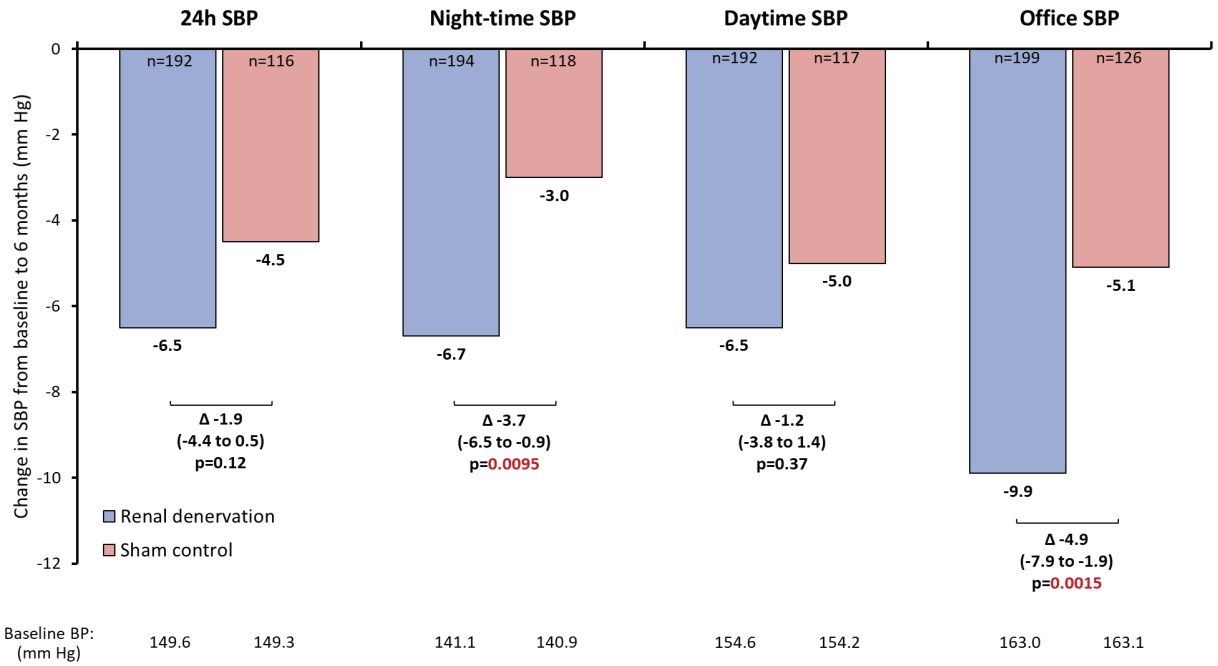
* p-values not adjusted for multiplicity, and the results of HTN-ON MED Expansion and Full cohorts not adjusted for difference randomization ratios

2. Secondary Effectiveness Results

Figure 17, Figure 18, and Figure 19 show the changes of 24-hour, daytime and nighttime ASBP, and Office SBP at 6 months for the HTN-ON MED Full, Expansion and Pilot Cohorts respectively.

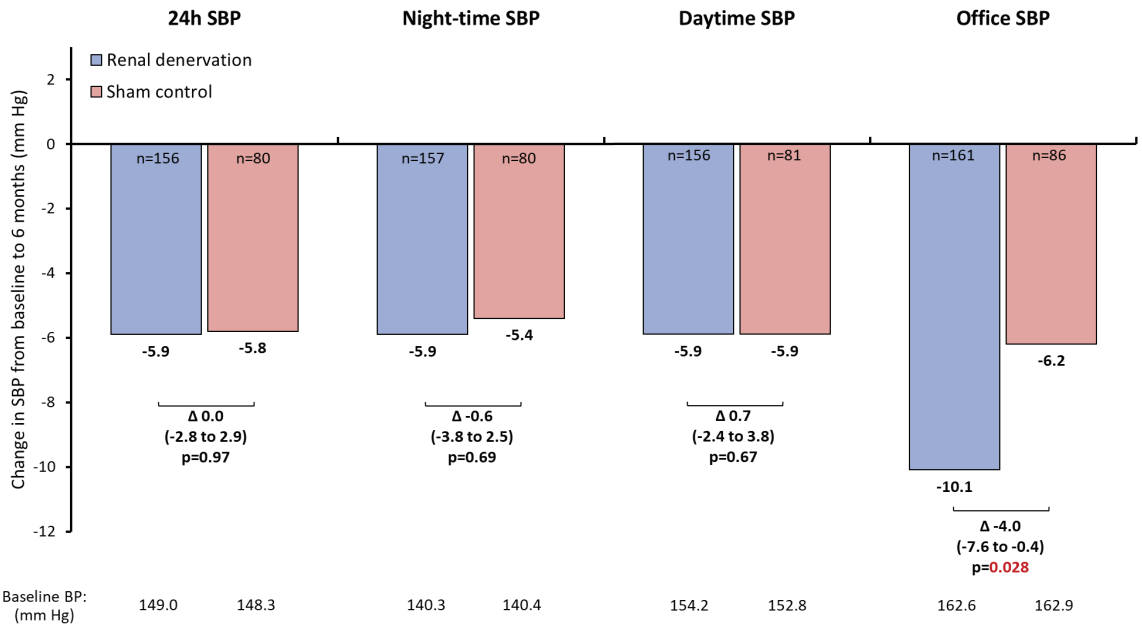
- Daytime was defined as ABPM readings between 7 am and 10 pm.
- Nighttime was defined as ABPM readings between 10 pm to 7 am.

The difference in rfRDN vs. Sham SBP reduction was greater for nighttime SBP (3.7 mmHg) vs. daytime SBP (1.2 mmHg) for the Pilot and Full cohorts.



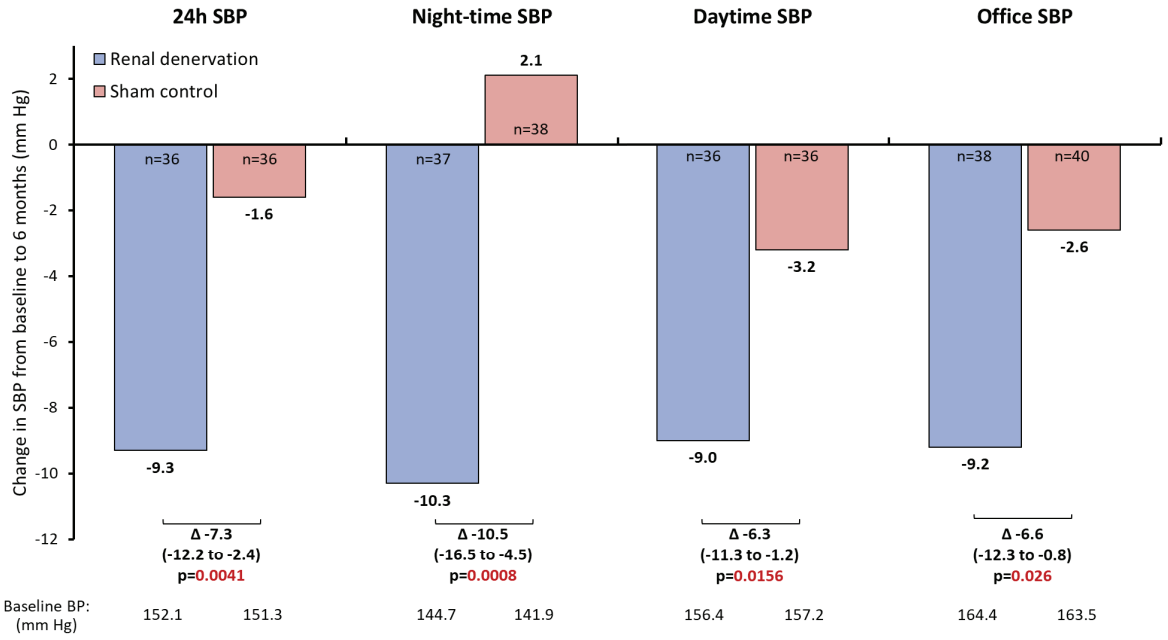
p-values not adjusted for multiplicity, and the results of HTN-ON MED Full cohort not adjusted for difference randomization ratios. SBP changes are unadjusted absolute drops from baseline. Differences and p-values determined from ANCOVA models adjusting for the baseline value

Figure 17: 24-hour, Night-time, and Daytime ASBP and Office SBP Changes at 6 Months – HTN-ON MED Full Cohort



p-values not adjusted for multiplicity, and the results of HTN-ON expansion cohort not adjusted for difference randomization ratios. SBP changes are unadjusted absolute drops from baseline. Differences and p-values determined from ANCOVA models adjusting for the baseline value

Figure 18: 24-hour, Night-time, and Daytime ASBP and Office SBP Changes at 6 Months – HTN-ON MED Expansion Cohort



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

Figure 19: 24-hour, Night-time, and Daytime ASBP and Office SBP Changes at 6 Months – HTN-ON MED Pilot Cohort

Distribution of Magnitude of SBP Reduction

Figure 20 and Figure 22 show the proportion of subjects with BP reductions in office and 24-hour SBP, respectively, ≥5, 10, 15, and 20 mmHg and patients who achieved goal SBP (<140 mmHg) at 6 months. In the HTN-ON MED study, 20% of rfRDN subjects achieved target office SBP compared with 6% of sham subjects (p=0.001). Additionally, subjects treated with rfRDN reduced their office SBP by ≥10, ≥15 and ≥20 mmHg at statistically higher rates compared to the Sham group and at numerically higher rates for SBP reductions of ≥5 mmHg.

Waterfall plots demonstrating the distribution of change in office SBP at 6-months in both the rfRDN and sham groups are presented in Figure 21.

Tiers of 24-hour ASBP reduction and the proportion of subjects achieving a SBP <140 mmHg are shown in Figure 22.

Figure 20

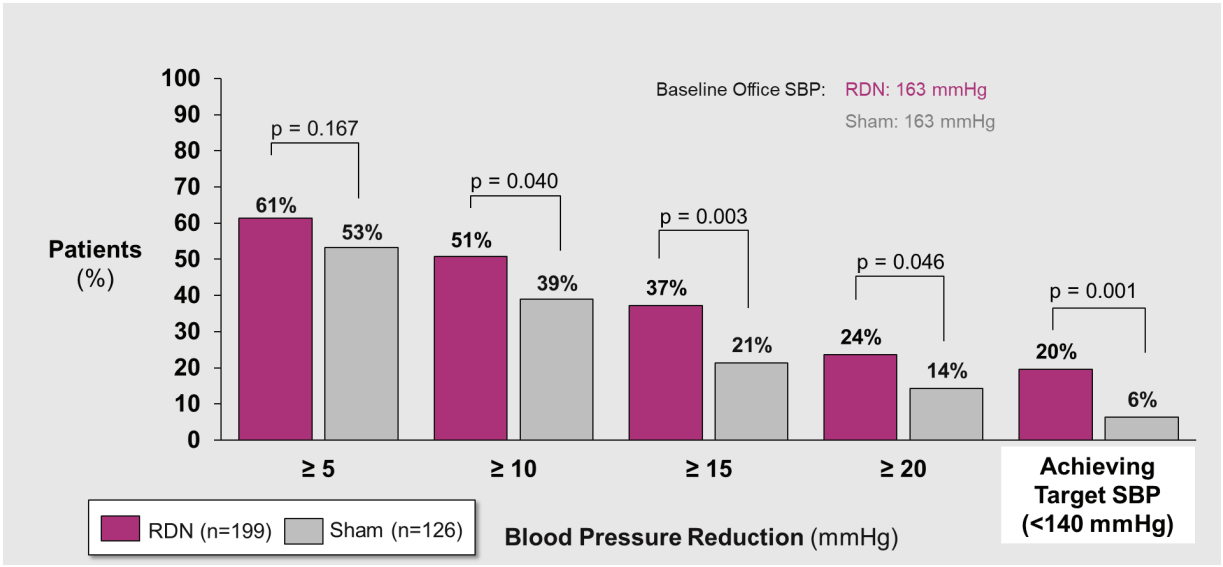
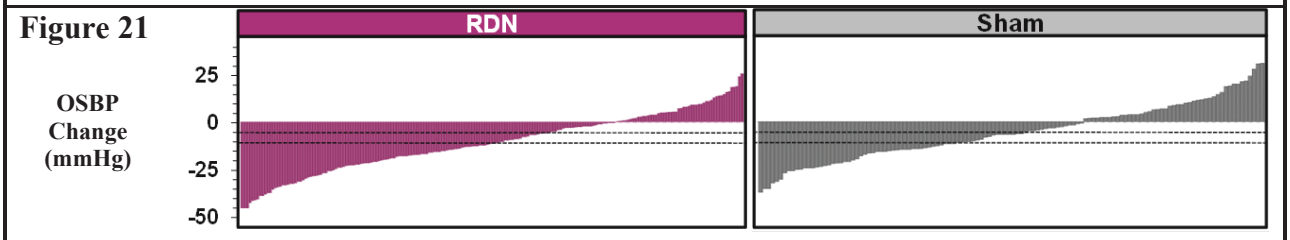


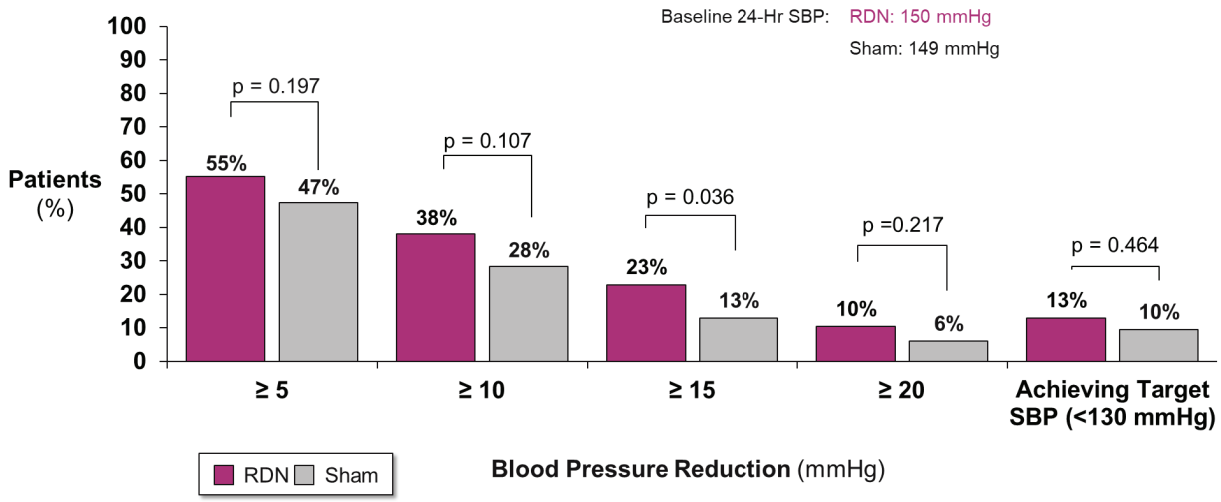
Figure 21



p-values not adjusted for multiplicity

Figure 20: HTN-ON MED Tiers of Office SBP Reduction and Achievement of Target SBP at 6 Months

Figure 21: Waterfall Plots for HTN-ON MED Full Cohort Office SBP at 6-Months



p-values not adjusted for multiplicity

Figure 22: HTN-ON MED Full Cohort Tiers of 24-Hour SBP Reduction and Achievement of Target SBP at 6-Months

Figure 23 shows box plots of the change in 24-hour SBP and Office SBP for the Full Cohort HTN-ON MED study at 6 months. For 24-hour SBP changes, the median and IQR for the rfRDN and sham groups were -7.0 mmHg (-13.22, 1.72) and -3.9 mmHg (-11.45, 1.52), respectively. For Office SBP changes, the median and IQR for the rfRDN and sham groups were -10.0 mmHg (-19.3, 0.15) and -6.0 mmHg (-13.9, 3.3) respectively.

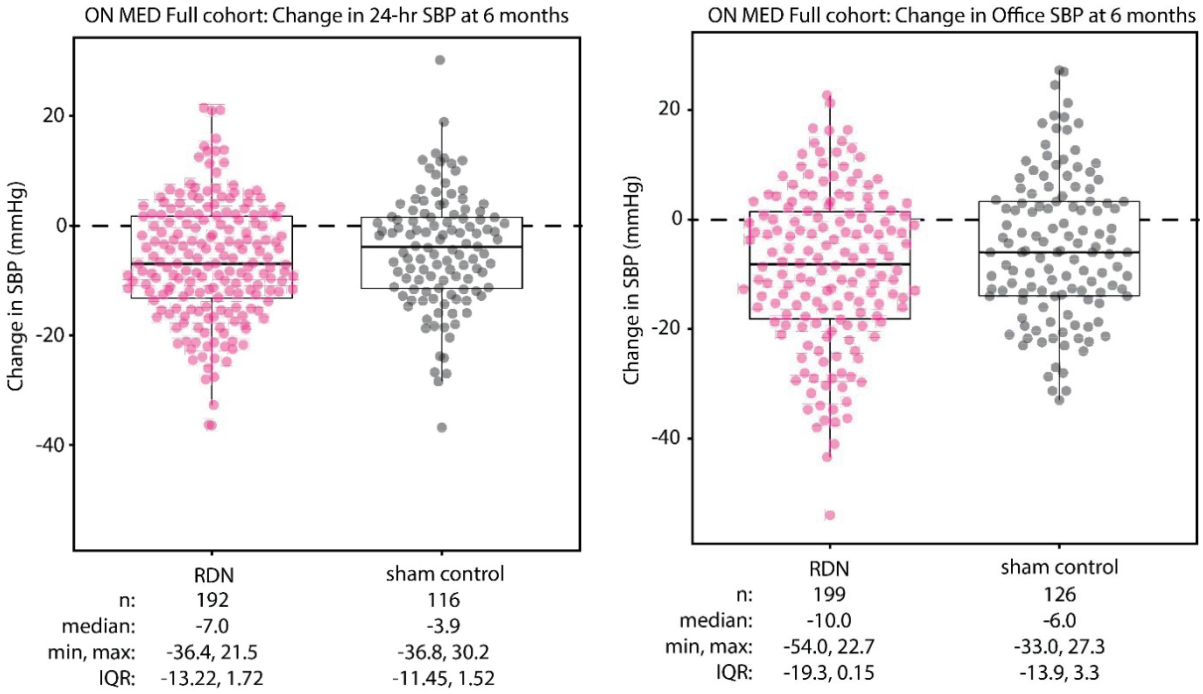


Figure 23: HTN-ON MED Full Cohort Box Plots of 24-Hour and Office Systolic Blood Pressure Change at 6-Months

The box plot shows the distribution of BP change with each individual patient observation represented as a dot. The box contains the middle 50% of the patient BP changes (between the 25th and 75th percentiles, the inter-quartile range or IQR). The median is represented by a horizontal line within that box. Observations that extend above or below the vertical lines outside the box (± 1.5*IQR) are considered to be outliers.

3. Long-Term Effectiveness Results

The HTN-ON MED study was not designed to assess the durability of blood pressure reduction, as the effect of rfRDN at later timepoints may be challenging to interpret because of the use and escalation of BP medications after 6 months, unblinding of study subjects to their treatment assignment, and crossover of some Sham subjects to rfRDN treatment (reducing the Sham group sample size). Additionally, crossover of Sham subjects to rfRDN treatment resulted in a loss of a randomized comparison.

To help assess rfRDN effectiveness durability, ambulatory and office BP and medication burden were evaluated. BP reduction durability data are not available for the HTN-ON Expansion Cohort beyond 6 months, so data beyond 6 months is limited to the HTN-ON Pilot Cohort. Figure 24 and Figure 25 show the office SBP and 24-hour ambulatory SBP, respectively, and medication burden (MedIndex 1 and MedIndex 2 in subjects with available SBP) through 36 months for the Pilot Cohort. For patients in the Sham group who crossed over and received rfRDN between the 24-month and 36-month follow-up visit, the last observations of BP measurements and medication burden were used to impute their 36-month values. Office and 24-hour ASBP in both the rfRDN and Sham groups declined after 6 months with larger reductions from baseline in the rfRDN group. Medication burden increased over the course of the study in both groups with no differences between groups.

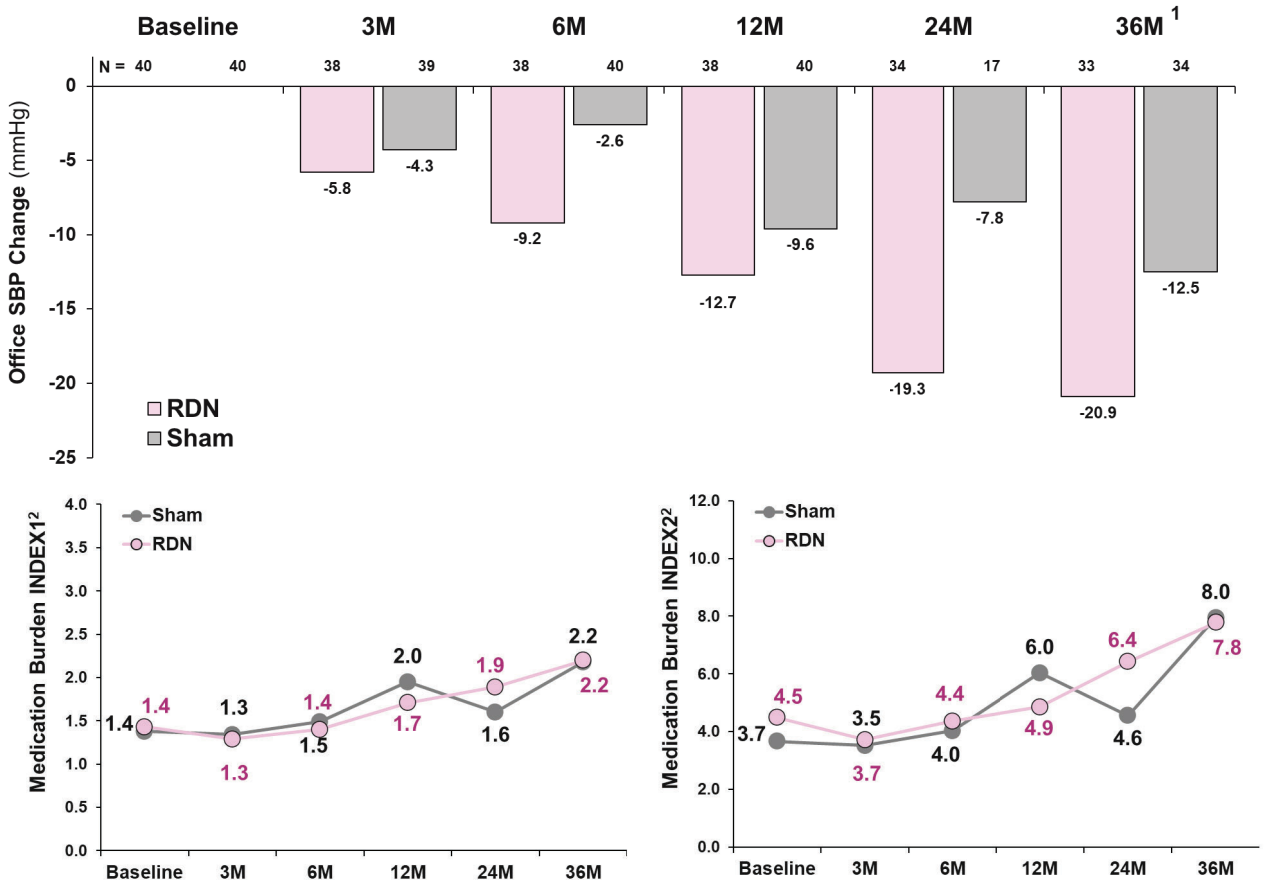


Figure 24: HTN-ON MED Pilot Cohort Office Systolic Blood Pressure and Medication Burden to 36 Months

[1] Last observations of BP measurements and medication burden used to impute 36-month values (note that the extrapolation may be biased)

[2] Medication burden INDEX1 and INDEX2 data presented for patients with available office SBP data and calculated using drug testing and when unavailable, prescribed medication data

p-values not adjusted for multiplicity

Crossovers not included in this analysis.

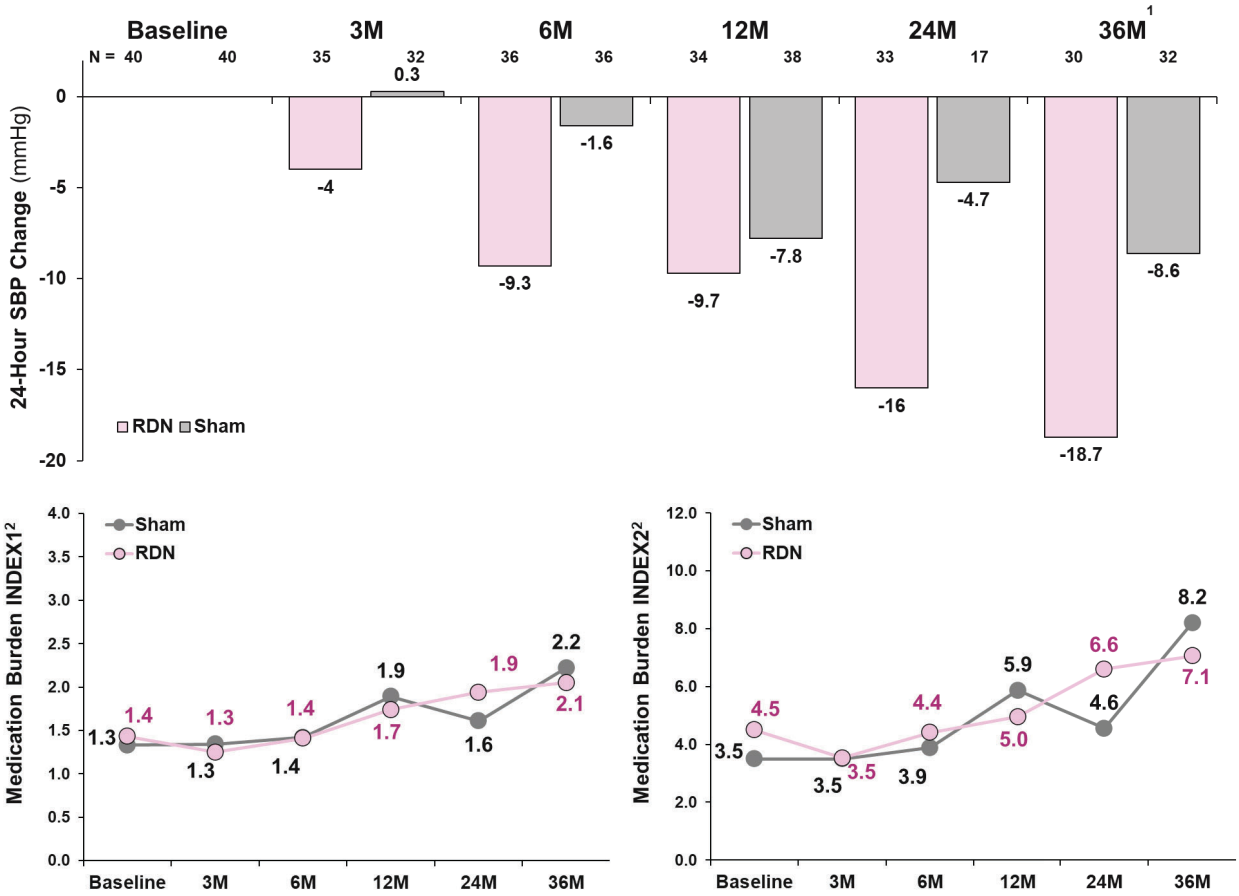


Figure 25: HTN-ON MED Pilot Cohort 24-Hour Ambulatory Systolic Blood Pressure and Medication Burden to 36 Months

[1] Last observations of BP measurements and medication burden used to impute 36-month values (note that the extrapolation may be biased)
[2] Medication burden INDEX1 INDEX2 data presented for patients with available 24-hour SBP data and calculated using drug testing and when unavailable, prescribed medication data
Crossovers not included in this analysis.
p-values not adjusted for multiplicity

G. HTN-OFF MED and HTN-ON MED Subgroup Analyses

1. Subgroup Analyses by Baseline Characteristics

Figure 26 shows 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.

Subgroup		RDN N	Sham N	24-h ambulatory systolic BP adjusted treatment difference mmHg (95% CI)	interaction p-value
Age	< 65	135	135		**0.41**
	≥ 65	18	12		
Sex	Male	104	101		**0.33**
	Female	49	46		
BMI (kg/m ^{2})	Tertile 1 (<28.2)	58	46		**0.94**
	Tertile 2 (28.2 to 32.3)	43	59		
	Tertile 3 (≥32.3)	52	42		
Diabetes type II	Yes	4	3		**0.80**
	No	149	144		
Smoking status	Current	27	22		**0.39**
	Former	41	43		
	Never	85	82		
Obstructive Sleep Apnea	Yes	13	10		**0.63**
	No	140	137		
AH med compliance at baseline and 3M	Yes	130	128		**0.96**
	No	20	11		
Geography	US	75	66		**0.40**
	Outside US	78	81		
Race (US only)	Black Americans	27	22		**0.66**
	Non-Black Americans	48	44		
Baseline eGFR (mL/min/1.73 m ^{2})	<60	6	6		**0.48**
	≥60	147	141		
Baseline aldosterone (ng/dL)	Tertile 1 (<6)	57	63		**0.92**
	Tertile 2 (6 to 10)	66	47		
	Tertile 3 (≥ 10)	49	67		
Baseline plasma renin activity (ng/mL/h)	<0.65	76	62		**0.09**
	≥0.65	66	71		
Baseline office heart rate (bpm)	Tertile 1 (<69)	54	45		**0.13**
	Tertile 2 (69 to 78)	50	55		
	Tertile 3 (≥78)	49	47		
Baseline 24 -hour SBP (mmHg)	Tertile 1 (<146.9)	56	51		**0.12**
	Tertile 2 (146.9 - 154)	45	55		
	Tertile 3 (≥154)	52	41		
Baseline office SBP (mmHg)	Tertile 1 (<158.7)	52	52		**0.89**
	Tertile 2 (158.7 - 166.7)	53	52		
	Tertile 3 (≥166.7)	48	43		

Figure 26: HTN-OFF MED Full Cohort 24-hour Ambulatory SBP Subgroup Analyses at 3 Months

Figure 27 shows subgroup analyses for the difference of 24-hour SBP at 6 months for the HTN-ON MED Full cohort. The sample size is small for many of the subgroups, and outcome differences between treatment were generally small.

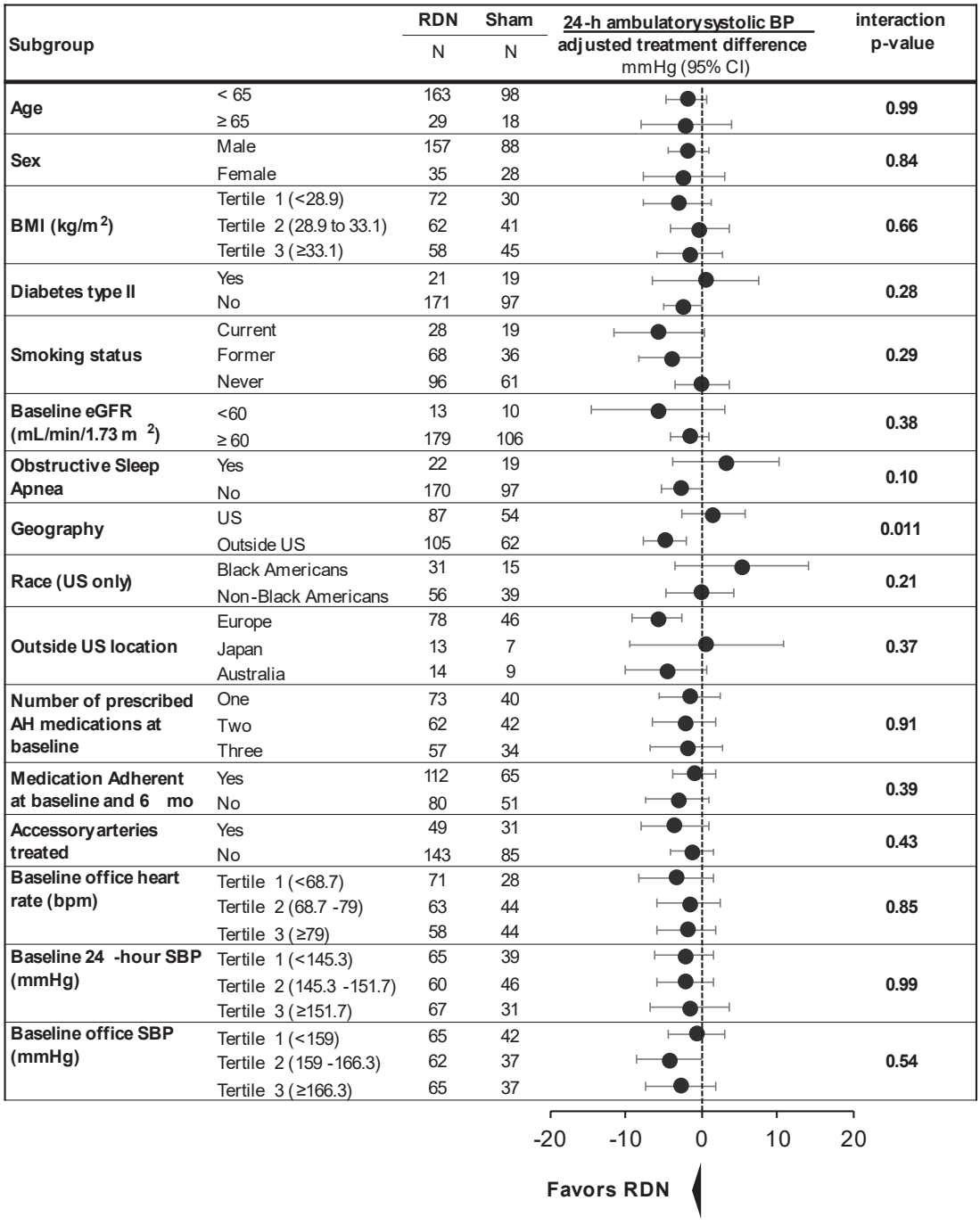


Figure 27: HTN-ON MED Full Cohort 24-hour SBP Subgroup Analyses at 6 Months

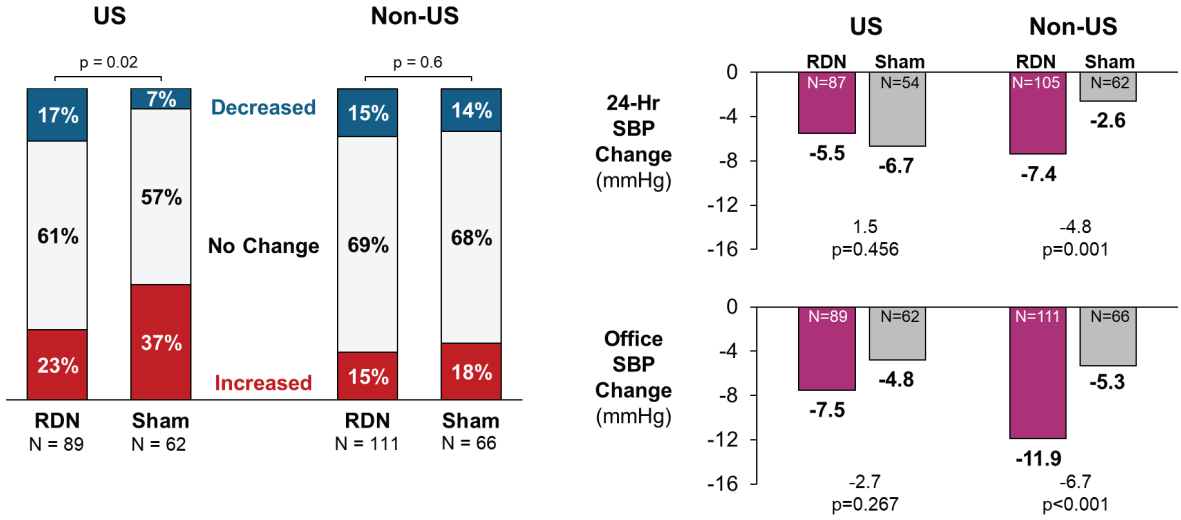
HTN-OFF MED and HTN-ON MED were not powered to assess BP responses in subgroups. However, in the HTN-ON MED study, statistically significant differences in 24-hour ASBP were noted in US vs OUS subjects, and the interaction p-value was 0.21 in African Americans vs non-African Americans, which are discussed further below.

2. US Population

In both the HTN-OFF MED and HTN-ON MED studies, pre-specified analyses were performed to evaluate the poolability of data from different groups. If the resulting tests were significant at the 0.15 level, further exploratory analyses were conducted to identify covariates that may help explain these differences. The HTN-OFF MED study, which did not have significant confounding due to medication differences between groups, showed no difference in effectiveness by geographic region (Figure 26).

In the HTN-ON MED study, there was a significant interaction observed between US sites and non-US for the primary effectiveness endpoint poolability analysis (p = 0.011, Figure 27).

Additional post-hoc analyses were performed to analyze the geographic effect. Medication changes were assessed using MedIndex 1 and MedIndex 2. Each patient was categorized by increase, decrease, or no change (results for this categorization were generally consistent for both Med Indices used). Outside the US, antihypertensive medication changes assessed via MedIndex 2 were generally similar between rfRDN and Sham (Figure 28) and there was a statistically significant 4.8 mmHg 24-hour ASBP reduction difference at 6 months in favor of rfRDN vs. Sham (Figure 28). These results illustrate a potential impact of medication differences on the HTN-ON MED study results.



p-values not adjusted for multiplicity

Figure 28: HTN-ON MED Study US and Non-US Subgroups from the Full Cohort: Medication Changes from Baseline to 6 Months and Change in SBP

3. Black American Population

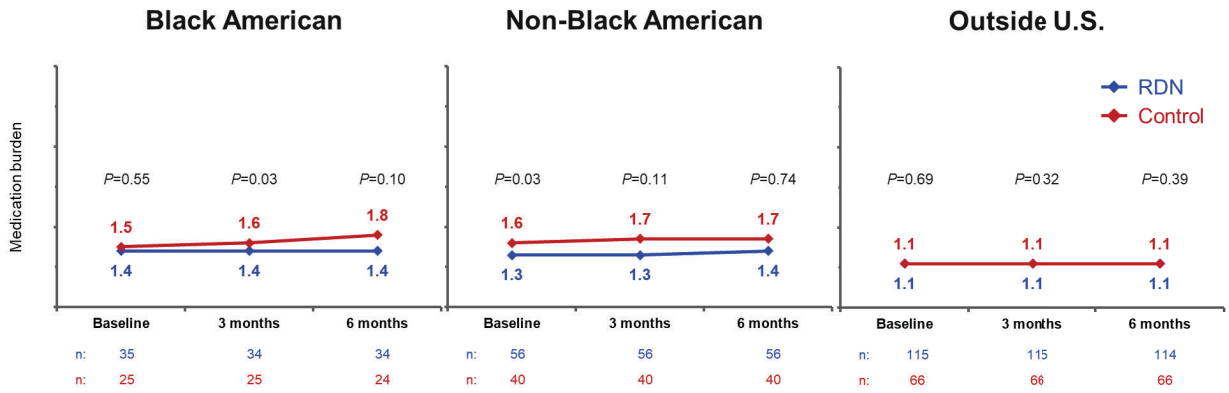
In the HTN-OFF MED study, there was no difference in blood pressure results by race (Black Americans (n=49) vs. non-Black Americans (n=92), Figure 26, interaction p-value =0.66).

In the HTN-ON MED there was a difference in the magnitude of the BP treatment effect. While this difference did not reach statistical significance (Black Americans, n=46 and non-Black Americans, n=95, Figure 27, interaction p-value = 0.21), it was examined further in the following analyses.

Figure 31 and Figure 32 show changes in prescribed BP medication use at 6 months in Black Americans and non-Black Americans:

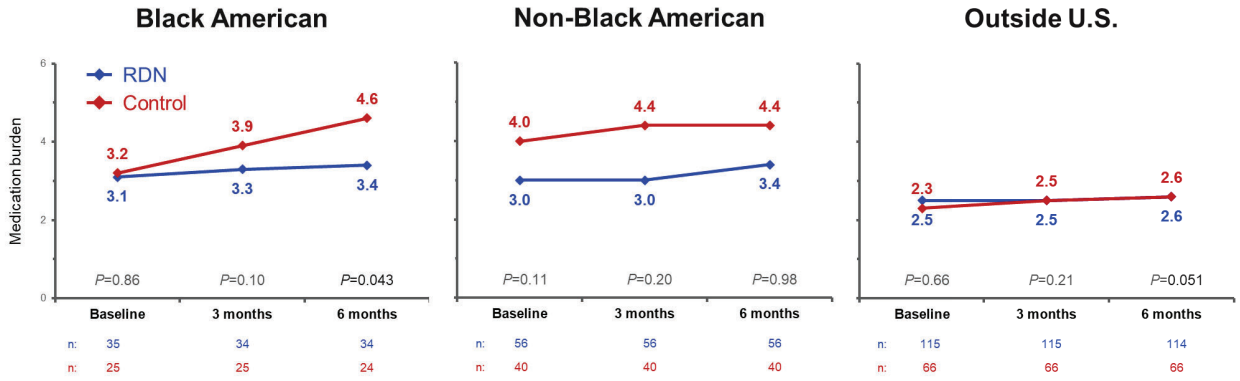
- Black Americans: The Sham group had a 0.3 MedIndex 1 increase from baseline (corresponding to an average of ~1/3 of a maximal dose of one pill.) vs. no change in the rfRDN group.
- Non-Black Americans: The Sham and rfRDN groups had a 0.1 MedIndex 1 increase from baseline.

The BP medication increase vs. baseline assessed by MedIndex 2 was more pronounced in Black Americans in the Sham group compared with the medication changes assessed with Med Index 1 method.



[1] Medication burden based on number, class and dosage, where all medication classes are considered of equivalent potency (Mahfoud 2022)
P-values at follow-up are ANCOVA adjusted
p-values not adjusted for multiplicity

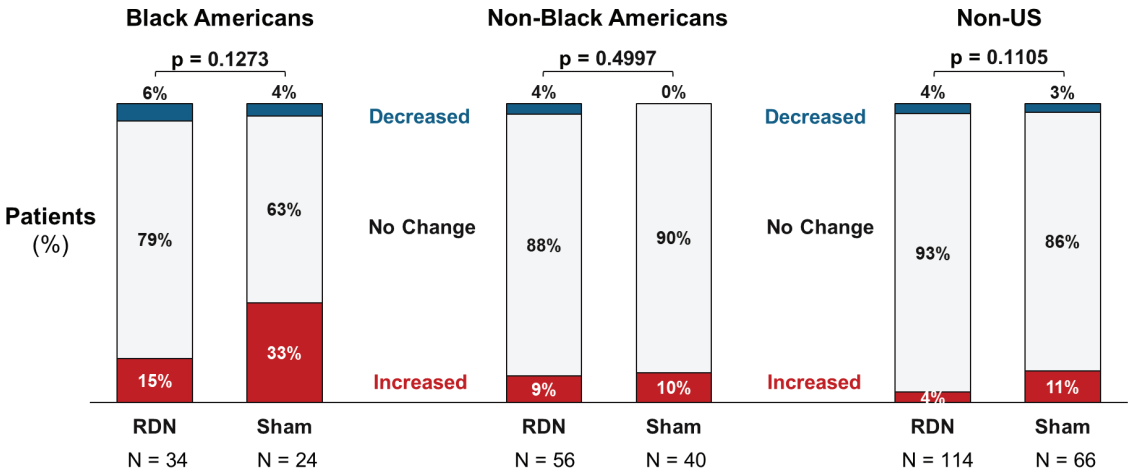
Figure 29: Prescribed BP Medication Changes (MedIndex 1) in Black Americans, Non-Black Americans, and Non-US Subjects at 6 Months – HTN-ON MED Full Cohort



[1] Medication burden based on number, class and dosage, where all medication classes are considered of equivalent potency (Mahfoud 2022)
p-values at follow-up are ANCOVA adjusted
p-values not adjusted for multiplicity

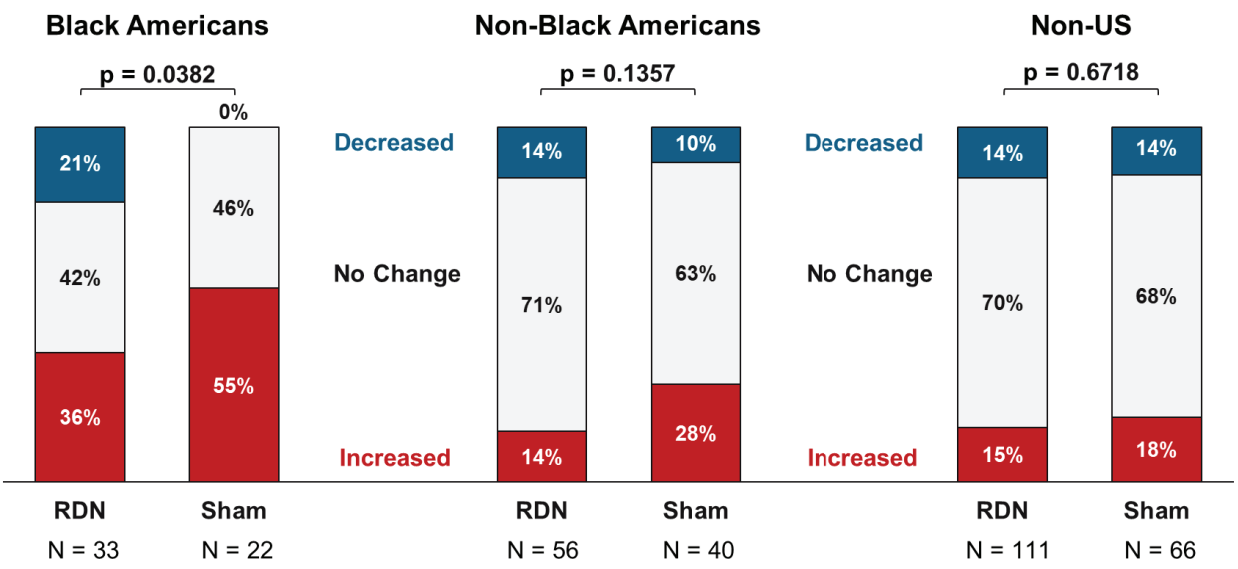
Figure 30: Prescribed BP Medication Changes (MedIndex 2) in Black Americans, Non-Black Americans, and Non-US Subjects at 6 Months – HTN-ON MED Full Cohort

Figure 33 shows HTN-ON MED prescribed medication changes based Med Index 1, and Figure 34 shows these data confirmed by drug testing. A higher proportion of Black Americans in the rfRDN and Sham group increased prescribed BP medications vs. non-Black Americans and non-US subjects. The results are similar using MedIndex 2 (not shown). The BP medication increase was most pronounced in the US Black American Sham group.



p-values not adjusted for multiplicity

Figure 31: Prescribed Medication Changes in Black Americans, Non-Black Americans, and Non-US Subjects at 6 Months – HTN-ON MED Full Cohort

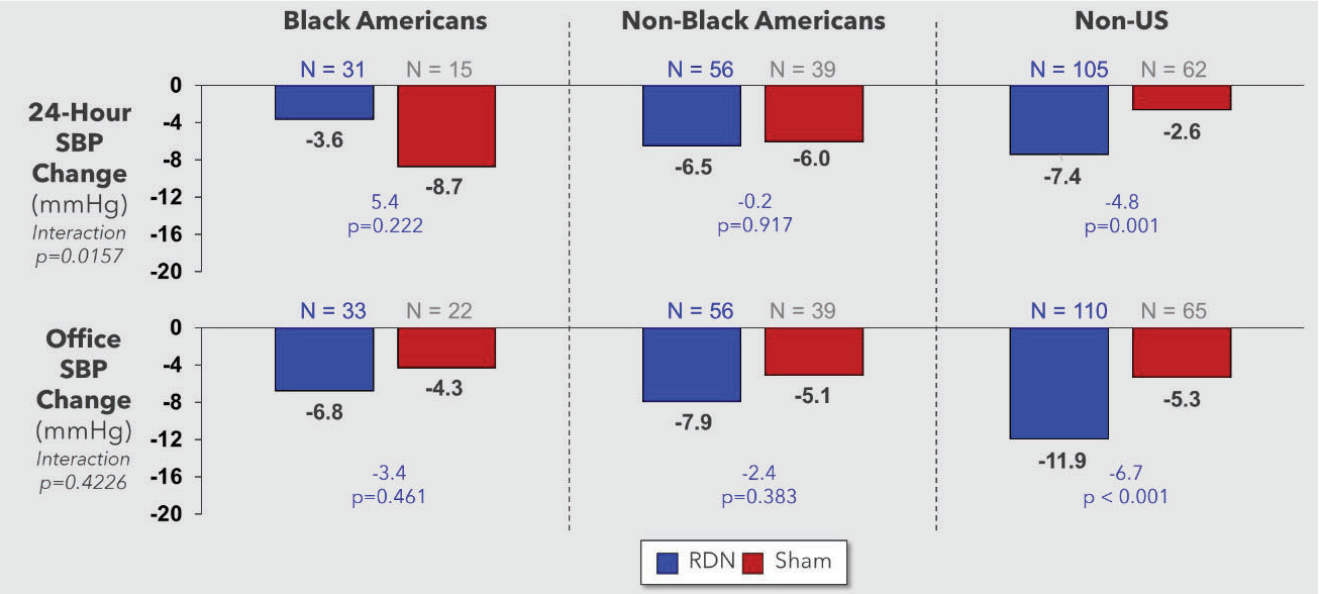


p-values not adjusted for multiplicity

Figure 32: Medication Changes Confirmed by Drug Testing in Black Americans, Non-Black Americans, and Non-US Subjects at 6 Months – HTN-ON MED 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.

The 24-hour SBP response was discordant between Black Americans (N=46) and non-Black Americans (N=95) at 6 months with a greater BP reduction observed in the Sham group in Black Americans (Figure 35). In contrast, the OSBP reduction trend in favor of rfRDN at 6-months was generally similar between Black Americans and non-Black Americans.

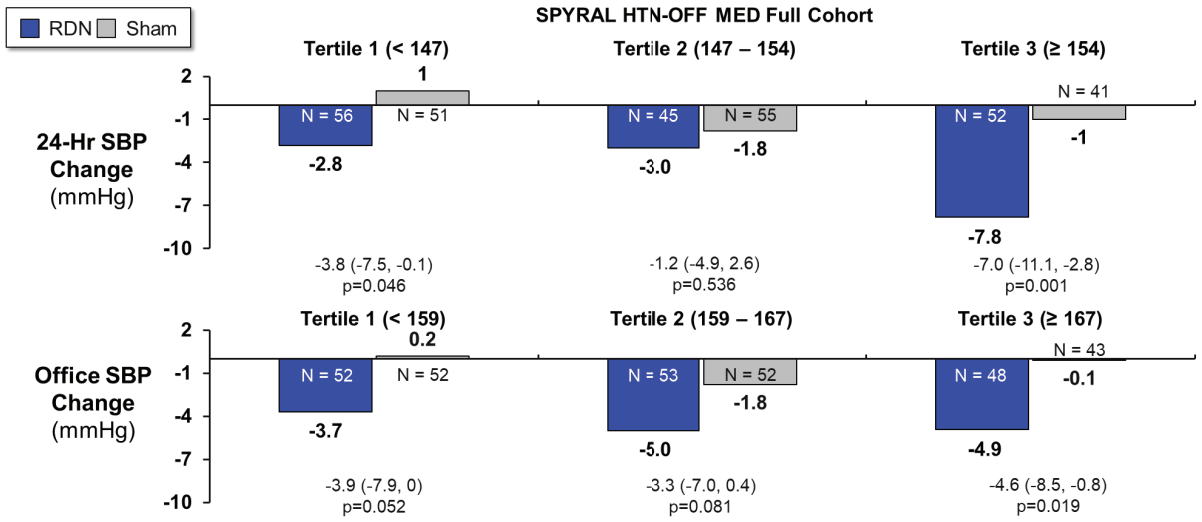


p-values not adjusted for multiplicity
SBP changes are unadjusted absolute drops from baseline. Differences and p-values are determined from ANCOVA models adjusting for the baseline value

Figure 33: 24-hour SBP Changes for Black Americans, Non-Black Americans, and Non-US Subjects at 6 Months – HTN-ON MED Full Cohort

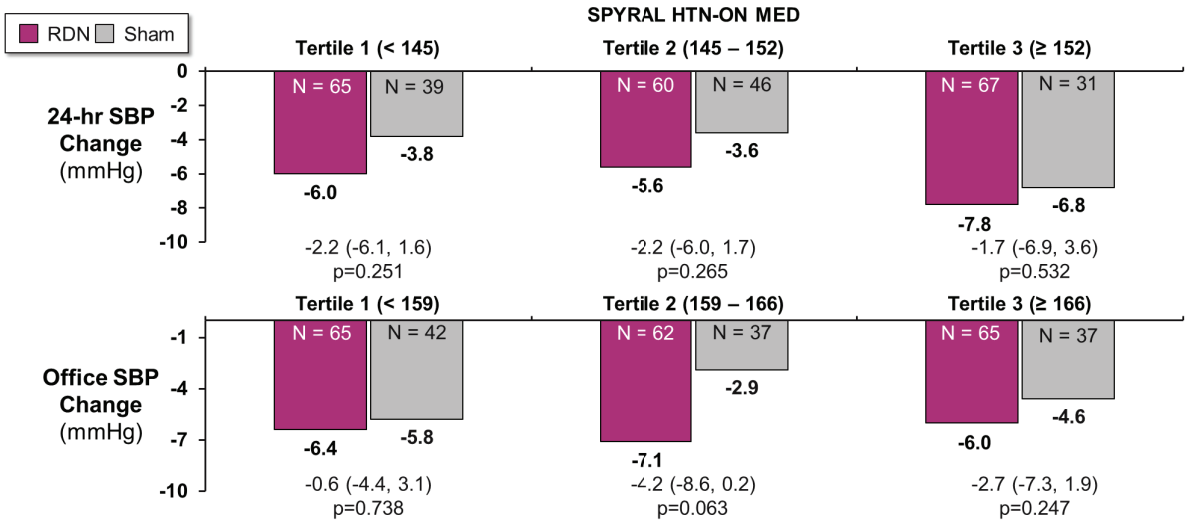
4. BP Tertiles

Figure 36 and Figure 37 show the change of 24-hour and office SBP from baseline to 3 months based on baseline 24-hour ambulatory SBP for the HTN-OFF MED and HTN-ON MED studies (Full Cohorts), respectively. General SBP reduction trends in favor of rfRDN vs. Sham were observed across SBP tertiles in both trials.



p-values not adjusted for multiplicity

Figure 34: HTN-OFF MED SBP Change from Baseline to 3 Months by Baseline 24-Hour ASBP Tertile



p-values not adjusted for multiplicity

Figure 35: HTN-ON MED SBP Change from Baseline to 6 Months by Baseline 24-Hour ASBP Tertile

H. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

I. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation.

The SPYRAL HTN-HTN-OFF MED clinical study included 322 investigators of which none were full-time or part-time employees of the sponsor and eight (8) of the investigators had disclosable financial interests and/or arrangement as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 8
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study:0

The SPYRAL HTN-ON MED clinical study included 398 investigators. of which none of the investigators were full-time or part-time employees of the sponsor and nine (9) of the investigators had disclosable financial interests and/or arrangement as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 9
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

The applicant has adequately disclosed the financial interest/arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests/arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

XI. SUMMARY OF SUPPLEMENTARY CLINICAL INFORMATION

A. 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., RDN) 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 25 shows selected subject demographics and HTN experience.

Table 25: 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%)
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 (%)

Among respondents currently on medication treatment for high BP, treatment satisfaction was relatively high, with an average score of 3.8 out of 5 (where 5 was “Extremely satisfied”), even though the average office SBP of the sample was 155 mmHg with a range of 140 to 197 mmHg. Most of the sample (84.0%) considered reducing the risk of death, heart attack, stroke, or kidney damage as one of the most important goals of treatment for hypertension. Approximately one in 5 respondents in the study would not be interested at all in an interventional treatment for hypertension when all else is equal.

Figure 38 summarizes the estimates of the mean preference weights (and 95% CIs) which are the primary endpoints describing the relative preferences for all attribute levels in the study. Attribute levels with larger preference weights are preferred to attribute levels with smaller preference weights. Thus, the results indicate that the preferences are well-ordered for the following naturally ordered treatment attributes: number of daily pills, reduction in office SBP, duration of effect, and risk of vascular injury. On average, respondents preferred the treatments in the survey to no treatment and preferred a longer duration of effect to a shorter duration of effect. Of note, respondents preferred no procedure to receiving a procedure. Interestingly, the respondents had similar preference for different levels of drug and interventional AEs.

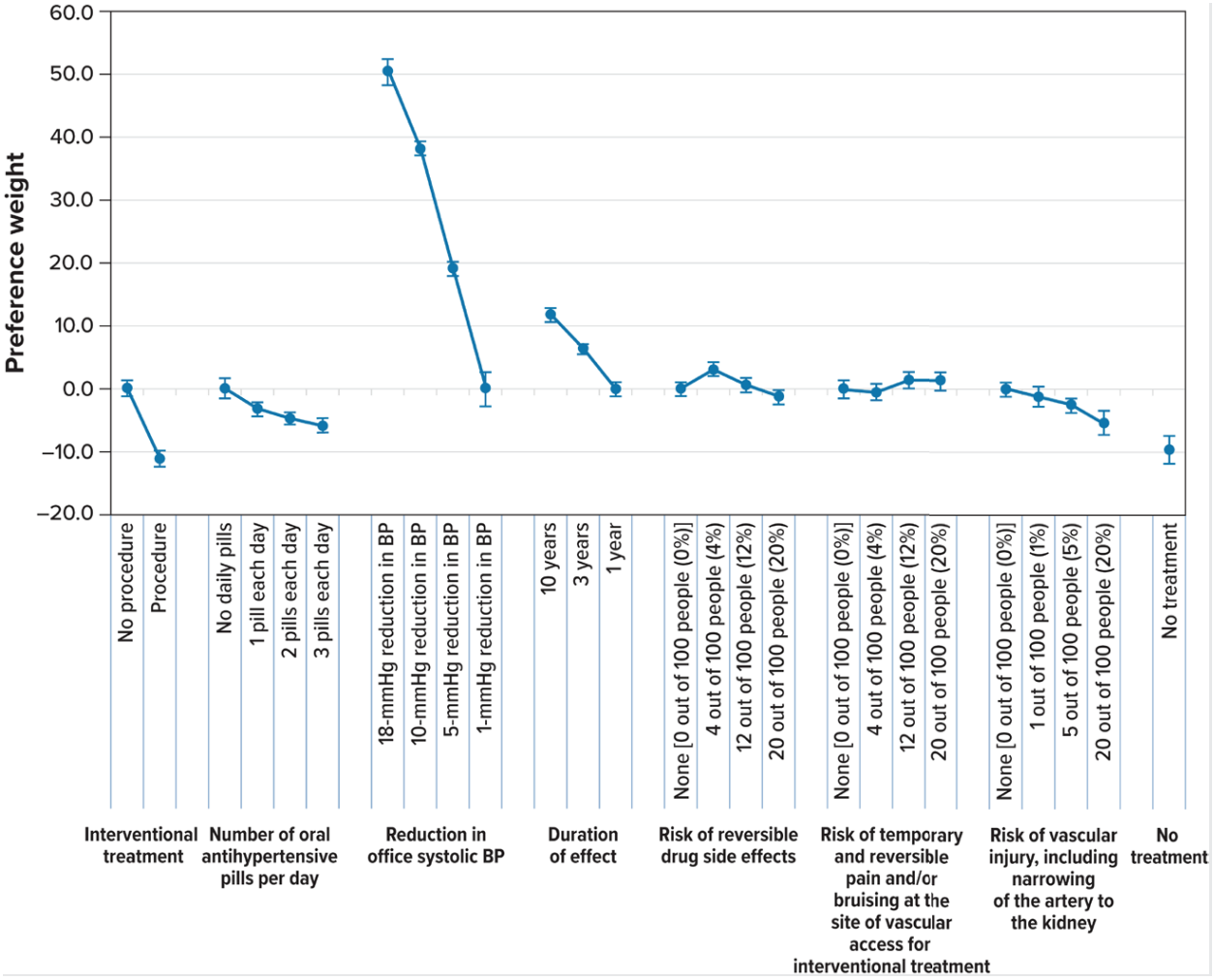
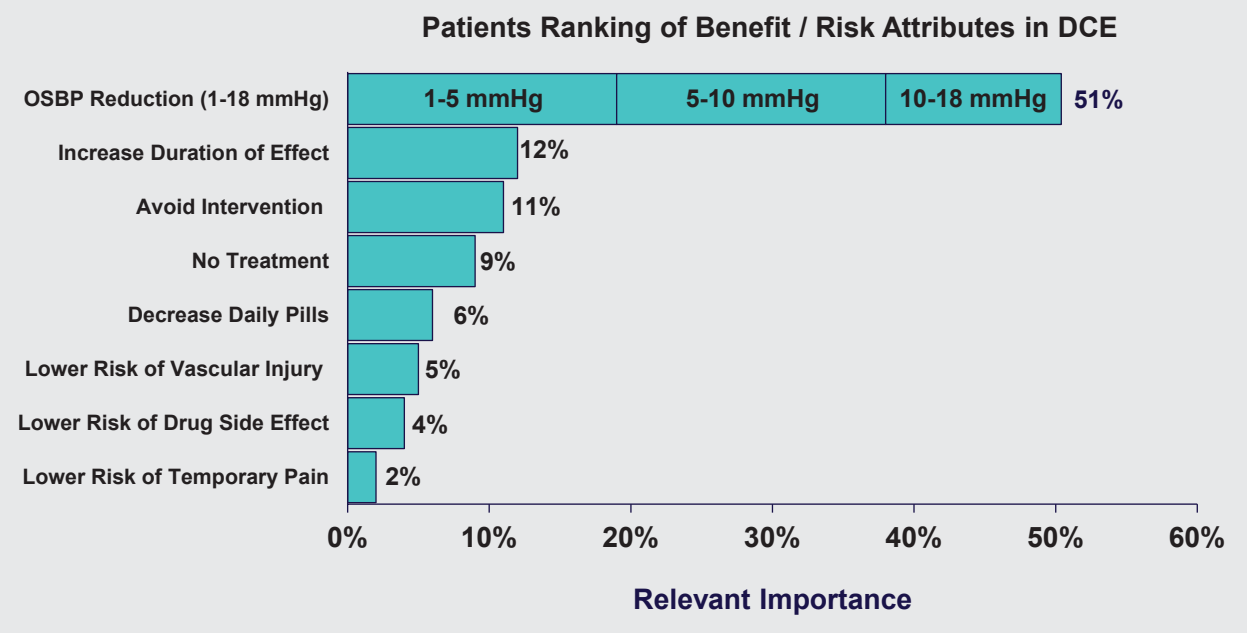


Figure 36: Preference Weights for Treatment Attributes

Most notably, patient choices in the survey revealed that BP reduction was more important than other attributes, including procedural risk. Also, the relative importance of BP reduction increased as the magnitude of BP reduction increased (Figure 39). This preference was further demonstrated using "Minimal Acceptable Benefit" (MAB) and "Maximum Acceptable Risk" (MAR) calculated using the modelled preference weights. For MAB, respondents would require that treatment reduce office SBP by any amount >0 mmHg in exchange for bearing an increase in the risks of drug-related side effects by 20% and 1.1 mmHg (95% CI: 0.6–1.6) in exchange for bearing an increase in the risks of vascular injury by 20% (assuming all other attributes were held constant). If all other attributes were equal, respondents would prefer to avoid interventional treatments for hypertension, yet only a 2.3

mmHg reduction in office SBP, on average (95% CI 1.7–2.9), was required to offset this preference.[1]

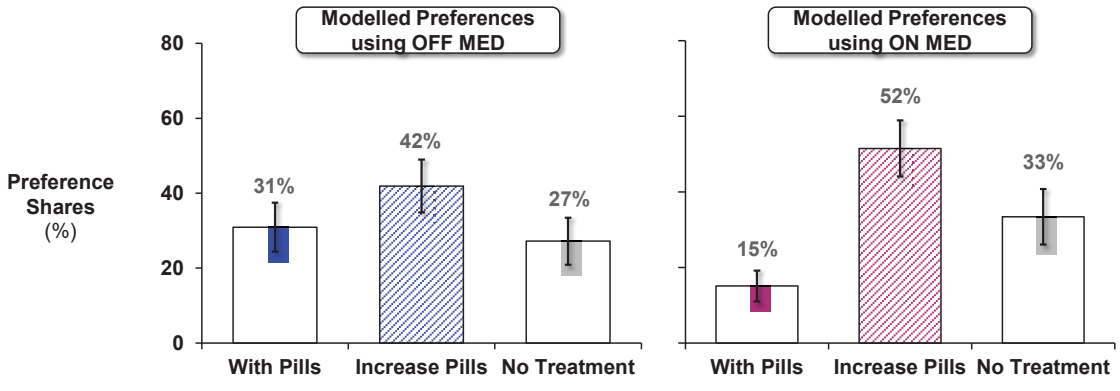


DCE: Discrete Choice Experiment; OSBP: office systolic blood pressure
Source: Kandzari 2023

Figure 37: Relevant Importance of Benefit/Risk Attributes

Application of the resultant modelled preferences to clinically observed treatment outcomes in the HTN-OFF MED Pivotal and HTN-ON MED studies suggests that 15% to 31% of patients would likely select an interventional treatment (Figure 40). This percentage increased in clinical scenarios representing an inability or unwillingness to take oral anti-hypertensive drugs or representing conditions where drug non-adherence led to reduced clinical benefit and representing increased treatment effect due to greater duration as reported with the 3-year follow-up in several RDN studies (Bhatt 2022, Mahfoud 2022, Mahfoud 2020b)

[1]Each estimate of MAB calculated should be interpreted as being in addition to a 1-mmHg reduction, which is the minimum level of office SBP reduction evaluated for this attribute." So, 2.3 is the minimum acceptable ***increase*** in benefit. Thus, the average MAB would be 3.3 mmHg reduction in OSBP



Intervention treatment	Yes	No	No treatment	Yes	No	No treatment
Change in number of oral antihypertensive pills per day	No change	Increase		No change	Increase	
Reduction in office SBP (mmHg)	6.8	5.1		4.9	5.1	
Duration of effect	1 year	1 year		1 year	1 year	
Risk of reversible drug side effects	10%	10%		10%	10%	
Risk of temporary and reversible pain and/or bruising	13%	0%		13%	0%	
Risk of vascular injury	0.3%	0%		0.3%	0%	
Average predicted likelihood of selecting treatment profile (95% CI)	30.93% (24.40, 37.45)	41.9% (34.86, 48.94)	27.18% (20.89, 33.46)	15.09% (11.02, 19.16)	51.5% (44.09, 58.92)	33.41% (26.07, 40.75)

Figure 38: Modelled Preferences Using HTN-OFF MED and HTN-ON MED Studies

The results indicated that BP reduction was the most influential driver of treatment choices and was more influential on choice than the risk of treatment-related side effects. Thus, real-world RDN candidates understand the risk-benefit trade off, and based on the DCE, 15-31% would choose an interventional procedure to help manage hypertension.

B. Global SYMPLICITY Registry (GSR)

The GSR is a prospective, multi-center, single-arm, open label registry. The GSR aims to include a patient population that resembles real-world clinical practice. The primary objective of the registry is to document the long-term safety and effectiveness of rfRDN in a real-world patient population.

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.

1. Enrolled Patients

A total of 3,077 patients, including 846 patients treated using the Symplicity Spyral catheter have been enrolled in GSR. Prior to availability of the Symplicity Spyral catheter, patients were treated with a single electrode version, the Symplicity Flex catheter. Key characteristics of the Symplicity Spyral patients are shown in Table 26.

For patients treated with the Symplicity Spyral catheter, 6-month follow-up data are available for 724 patients, 12-months follow-up data for 642 patients, 24-months follow-up data for 485 patients and 36 months follow-up data for 328 patients.

In the GSR, patient follow up is conducted as a part of routine standard of care. rfRDN procedures were performed per the commercial (non-US) Instructions for Use which indicate that ablations should occur in all vessels 3-8 mm in size. Physician discretion was utilized for the number and depth of branch vessels treated. Branch treatment was performed in 63.2% of patients. Overall, 100% of patient informed consents and 34% of patient data were monitored.

Table 26: GSR Demographics, Medical History and Risk Factors for Patients Treated with Symplicity Spyral Catheter

Characteristic	GSR Spyral
Age (Years)	59.59 ± 12.87 (n=846)
Sex (Male)	57.3 % (485/846)
BMI (kg/m^2)	30.93 ± 7.31 (n=838)
Blood pressure (mmHg)	165.83/91.19 ± 24.82/17.44 (n=792)
Heart rate (bpm)	71.46 ± 13.46 (n=761)
Renal insufficiency (eGFR < 60)	20.7% (175/845)
Sleep Apnea	21.3 % (169/795)
History of diabetes mellitus (Type 1 + Type 2) (%)	40.6 % (343/844)
Type 1 Diabetes Mellitus – insulin dependent	2.7% (23/844)
Type 2 Diabetes Mellitus – insulin independent	37.9% (320/844)
Atrial fibrillation	11.1% (93/841)
Hypercholesterolemia (%)	35.5% (299/842)
Smoking, current	11.0% (93/842)

BMI: body mass index; eGFR: estimated glomerular filtration rate; GSR: Global SYMPLICITY Registry

2. GSR Results

Safety Results

Adverse event information collection in the GSR is focused on collecting protocol-specified events only from consent up to 3 years follow-up.

Overall, the rfRDN procedure with the Medtronic Symplicity Renal denervation system was not associated with serious adverse events, and there were no unanticipated adverse device effects. No significant embolic events were reported in patients treated with the Symplicity Spyral catheter, while four significant embolic

events were reported for patients treated with the Symplicity Flex catheter. Additionally, and in line with other interventional treatments using the groin arterial access site, GSR data show a low rate of vascular complications.

GSR Efficacy Results

In data available for patients treated with the Symplicity Spyral catheter, sustained office and 24-hour SBP reductions are observed for the duration of the 3-year follow-up.

Table 27 shows the office and 24-hour SBP and DBP for the Symplicity Spyral catheter (subject of the current PMA) and the Symplicity Flex catheter. Through the 3-year follow-up period, the mean number of BP medications (4.85 at baseline, 4.87 at 6 months, 4.86 at 12 months, 4.83 at 24 months, and 4.90 at 3 years) stayed consistent.

Table 27: GSR Office SBP and DBP from Baseline to 36-months in Subjects Treated with the Symplicity Spyral

	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 N=792	-14.23 ± 25.76 N=517	-15.18 ± 26.54 N=475	-13.99 ± 27.59 N=331	-18.07 ± 26.76 N=200
Office DBP	91.19 ± 17.44 N=792	-5.52 ± 14.07 N=515	-6.42 ± 14.77 N=473	-7.67 ± 15.06 N=326	-7.79 ± 15.68 N=195

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

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on August 23, 2023, the Circulatory System Devices Panel voted 13-0-0 (yes-no-abstain) that there is reasonable assurance the device is safe, 7-6-0 that there is reasonable assurance that the device is effective, and 6-7-1 (the Panel Chair broke the tie for this question with a vote of "No") that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication. Several panelists noted that part of their positive vote was based on anticipation of a revised indication, or that they would have voted positively had the indication been revised to a patient population that reflected those enrolled in the clinical studies and completion of a robust post-approval study. Information from this advisory meeting can be found on FDA's website at the following: August 22-23, 2023: Circulatory System

Devices Panel of the Medical Devices Advisory Committee Meeting Announcement - 08/22/2023 | FDA.

B. FDA's Post-Panel Action

Despite the split panel vote at the August 23, 2023 panel meeting, the comments from several panel members made it clear that the panel believed that approval of this device with a revised indication could be appropriate and in the interest of public health. FDA worked interactively with the sponsor to revise the indications for use from what was presented at the August 23, 2023 panel meeting to the current indications for use and to develop a robust new enrollment post-approval study.

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The nonclinical and preclinical testing conducted on the Symplicity Spyral rfRDN system demonstrated that the performance characteristics of the device met the product specifications and are acceptable for clinical use. The shelf-life testing of the Symplicity Spyral catheter has established acceptable performance for a labeled shelf life of three years.

The clinical effectiveness was evaluated in the HTN-OFF MED and HTN-ON MED studies. For HTN-OFF MED where antihypertensive medications were withdrawn, the primary effectiveness endpoint of 24-hour ambulatory SBP reduction from baseline to 3 months post-procedure favored rfRDN subjects vs. Sham by 3.9 mmHg using a Bayesian Analysis (posterior probably of success 0.9996). The powered secondary endpoint of office SBP reduction from baseline to 3 months favored rfRDN subjects vs. Sham by 6.5 mmHg using a Bayesian Analysis (posterior probably of success 1.000). Generally similar results were obtained from the Pilot, Expansion, and Full (combined) Cohorts using a frequentist analysis. Additional analyses showed a greater proportion of patients with reductions of ≥5, 10, 15, and 20 mmHg in the rfRDN treatment group, and a greater proportion of rfRDN subjects reached target SBP at 3 months. Following medication escalation to reach target BP implemented after 3 months, the SBP reduction between the rfRDN and Sham groups were similar. Given the differences in BP medication use, unblinding at 6 months, and crossover of Sham subjects to rfRDN treatment, it is difficult to draw conclusions about long-term effectiveness other than to note that BP reductions from baseline persisted for both rfRDN and Sham groups through 24 months.

For the HTN-ON MED study in which patients were to be maintained on stable antihypertensive medications, the primary effectiveness endpoint of 24-hour ambulatory SBP reduction from baseline to 6 months post-procedure was not met, with rfRDN-treated subjects showing only a 0.03 mmHg greater reduction than Sham using a Bayesian Analysis (posterior probably of success 0.508). The secondary endpoint using office SBP reduction from baseline to 6 months favored the rfRDN group vs. Sham by 4.1 mmHg using a Bayesian Analysis (posterior probably of success 0.992). Frequentist analyses showed discordant results between the Pilot (7.3 mmHg 24-hour ASBP reduction favoring rfRDN) and Expansion cohorts (no difference in 24-hour ASBP between groups), with a 1.9 mmHg

ASBP reduction favoring rfRDN for the Full Cohort. Additional analyses of the Full Cohort showed a numerically greater proportion of rfRDN-treated patients with reductions of ≥5, 10, 15, and 20 mmHg, and a greater proportion of rfRDN subjects reached target SBP at 6 months, though the differences were small and discordant between the Pilot and Expansion Cohorts. Longer-term data were not available for the Expansion Cohort, but after 6 months, the SBP reduction continued to favor rfRDN in the Pilot Cohort. Given the differences in BP reduction results between the Pilot and Expansion Cohorts, BP medication changes, unblinding, and crossover from Sham to rfRDN, it is difficult to draw conclusions about long-term effectiveness other than to note that BP reductions from baseline persisted for both rfRDN and Sham Pilot groups through 36 months in the Pilot Cohort.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies, as well as data collected in the clinical studies conducted to support PMA approval as described above.

The primary safety endpoint was the incidence of major adverse events at 1 month post-procedure and new renal artery stenosis evaluated at 6 months for the first 253 consecutive patients treated with rfRDN in the HTN-OFF MED and HTN-ON MED studies. The primary safety endpoint rate was 0.4% with a one-sided upper 95% confidence interval of 1.9%. The 7.1% performance goal was met ($p < 0.001$). In addition, a post-hoc safety analysis on all rfRDN-treated subjects pooled from both studies using the same safety event definitions also resulted in a rate of 0.4% (one-sided upper 95% CI 1.2%, $p < 0.001$). The majority of events were non-serious and typical of catheter-based arterial procedures such as vascular access site complications. In an additional analysis of subjects who underwent renal artery imaging using CTA, MRA, or angiography, a conservative estimate of >50% diameter renal artery stenosis was determined to be between 2.9% and 3.9%. However, there was no evidence of renal injury, clinically significant renal artery stenosis (>70% diameter stenosis), or renal arterial events requiring intervention. rfRDN did not negatively affect renal function.

C. Benefit-Risk Determination

The probable risks of the device are based on data collected in the randomized controlled clinical studies conducted to support PMA approval as described above. Overall, the risks are low and similar to other catheter-based procedures.

The probable benefits of the device are based on data collected in the randomized controlled clinical studies conducted to support PMA approval as described above. The data from the HTN-OFF MED study, where BP medication does not confound the results, show that a probable benefit of the Symplicity Spyral rfRDN system is a reduction in blood pressure in adult patients with hypertension. On average, this reduction was 3.9 mmHg (ASBP) and 6.5 mmHg (OSBP) greater than a sham control. Since blood pressure is a validated surrogate endpoint for cardiovascular events and operates as a continuous variable risk factor, this reduction is clinically significant and

would be expected to be associated with a reduced risk of cardiovascular and renal events.

There are additional factors to be considered in determining probable risks and benefits for the Symplicity Spyral rfRDN system included. Despite available treatments, hypertension remains uncontrolled in greater than 50% of patients and additional therapies are of value. Further, patient preference information shows a desire for a device-based treatment in some patients with hypertension.

1. Patient Perspective

   Medtronic's patient preference study described in section XI demonstrated that up to 31% of patients are willing to accept alternative BP therapies, like rfRDN, based on the clinical risks and benefits associated with an interventional procedure.

In conclusion, given the available nonclinical, preclinical and clinical data, including patient perspectives collected via the Medtronic Patient Preference study, the probable benefits for the Symplicity Spyral Renal Denervation (rfRDN) system outweigh the potential risks.

Despite some uncertainty regarding the durability of rfRDN treatment and difficulty drawing conclusions when medication and other factors confound the results, the observed low risks of rfRDN combined with the effectiveness shown in HTN-OFF MED support that the probable benefits outweigh the probable risks for the Symplicity Spyral rfRDN system.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The conclusion is based on the results from the clinical trials discussed above, which show that renal artery denervation with the Symplicity Spyral rfRDN system results in reduction of BP with a low rate of procedural and device-related risks when used in accordance with the labeling and Instructions for Use.

XIV. CDRH DECISION

CDRH issued an approval order on 11/17/2023. The final clinical conditions of approval cited in the approval order are described below.

1. *SPYRAL HTN-OFF MED and HTN-ON MED: Continued Follow-up Studies.* These studies are prospective, multi-center, sham-controlled clinical trials (G150036) that treated a total of 366 subjects in HTN-OFF MED at 41 investigational sites and 337 subjects in HTN-ON MED at 42 investigational sites. The studies should be conducted per protocol revisions October 22, 2020 (HTN-OFF MED) and September 10, 2020 (HTN-ON MED). The studies will evaluate the long-term safety and effectiveness of the Symplicity Spyral Renal Denervation System. All 128 remaining

subjects across both studies will continue to be followed through 3 years post-procedure.

Follow-up at the timepoints will include the following assessments: office and ambulatory blood pressure; renal imaging; and adverse events.

2. *SPYRAL AFFIRM Post-approval Study (PAS): New-Enrollment Registry Study*. The SPYRAL AFFIRM PAS is a prospective, multi-center, single arm, study. The PAS (protocol provided interactively on October 6, 2023) will enroll 1300 subjects (including at least 700 US subjects) at 100 global sites with greater than 50% US sites to evaluate the real-world performance of the Symplicity Spyral Renal Denervation System indicated to reduce blood pressure as an adjunctive treatment in patients with hypertension in whom lifestyle modifications and antihypertensive medications do not adequately control blood pressure.

   A maximum of 1300 subjects will be enrolled at up to 100 sites with a target study population of at least 300 evaluable female, 200 evaluable Black American, 100 evaluable Hispanic, 75 evaluable with chronic kidney disease (eGFR<60), 150 evaluable elderly (≥65 years), and 50 evaluable subjects with diabetes type II at the 6-month post-procedure follow-up visit. In addition, Asian subjects will also be evaluated.

   Follow up visits/assessments will be completed at 1, 3, 6, 12, 24, and 36 months post-procedure.

   The primary effectiveness endpoints will include change in mean office systolic blood pressure from baseline to 6 months with a performance goal of 6 mmHg.

   Key secondary and observational effectiveness endpoints to be evaluated are:
   - Change in 24-hour/home/office systolic/diastolic blood pressure
   - Change in antihypertensive medications (e.g., number, dose, type)
   - Percentage with specific home/office/24-hour systolic blood pressure reductions (e.g., 5, 10, 15 mmHg)
   - Percentage of patients with controlled 24-hour/home/office systolic blood pressure

   Adverse events resulting in the following:
   - 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
   - New renal artery stenosis >70%
   - Major bleeding according to TIMI definition

- Renal Artery Reintervention
- Myocardial Infarction (MI):
- Stroke

The primary effectiveness analysis will be compared to a performance goal of 6 mmHg in the US cohort of the AFFIRM study. The hypothesis testing will be based on a one-sample t-test. Additional subgroup analyses will be conducted for the primary effectiveness endpoint. Secondary endpoints will be summarized with descriptive statistics. Categorical variables, including binary variables, will be presented with the count and percentage of patients in each category. Continuous variables will be presented with means, standard deviations, median, first and third quartiles, minimum and maximum values.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for Use: See product labeling

Hazard to Health from Use of the Product: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the product labeling

Post-approval Requirements and Restrictions: See Approval Order

XVI. REFERENCES

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