RENAL DENERVATION IN THE PRESENCE OF ANTI-HYPERTENSIVE MEDICATIONS: SIX-MONTH RESULTS FROM THE RANDOMIZED, BLINDED, SHAM-CONTROLLED SPYRAL HTN – ON MED TRIAL

David E. Kandzari, MD | Piedmont Heart Institute, Atlanta, USA

on behalf of the SPYRAL HTN – ON MED Trial Investigators

American Heart Association.

Disclosure

David Kandzari, MD

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below:

Affiliation/Financial Relationship	**Company**
Institutional Grant/Research Support	Abbott Vascular, Ablative Solutions, Biotronik, Boston Scientific, CSI, Medtronic CardioVascular, Orbus Neich, Teleflex
Consulting Fees/Honoraria	Abbott Vascular, Medtronic CardioVascular, CSI, Teleflex, Terumo
Major Stock Shareholder/Equity	BioStar Ventures (none related to ASI)
Royalty Income	None
Ownership/Founder	None
Intellectual Property Rights	None
Other Financial Benefit	None

UNLABELED/UNAPPROVED USES DISCLOSURE

In the United States, the use of renal denervation in hypertensive patients is limited to investigational use only.

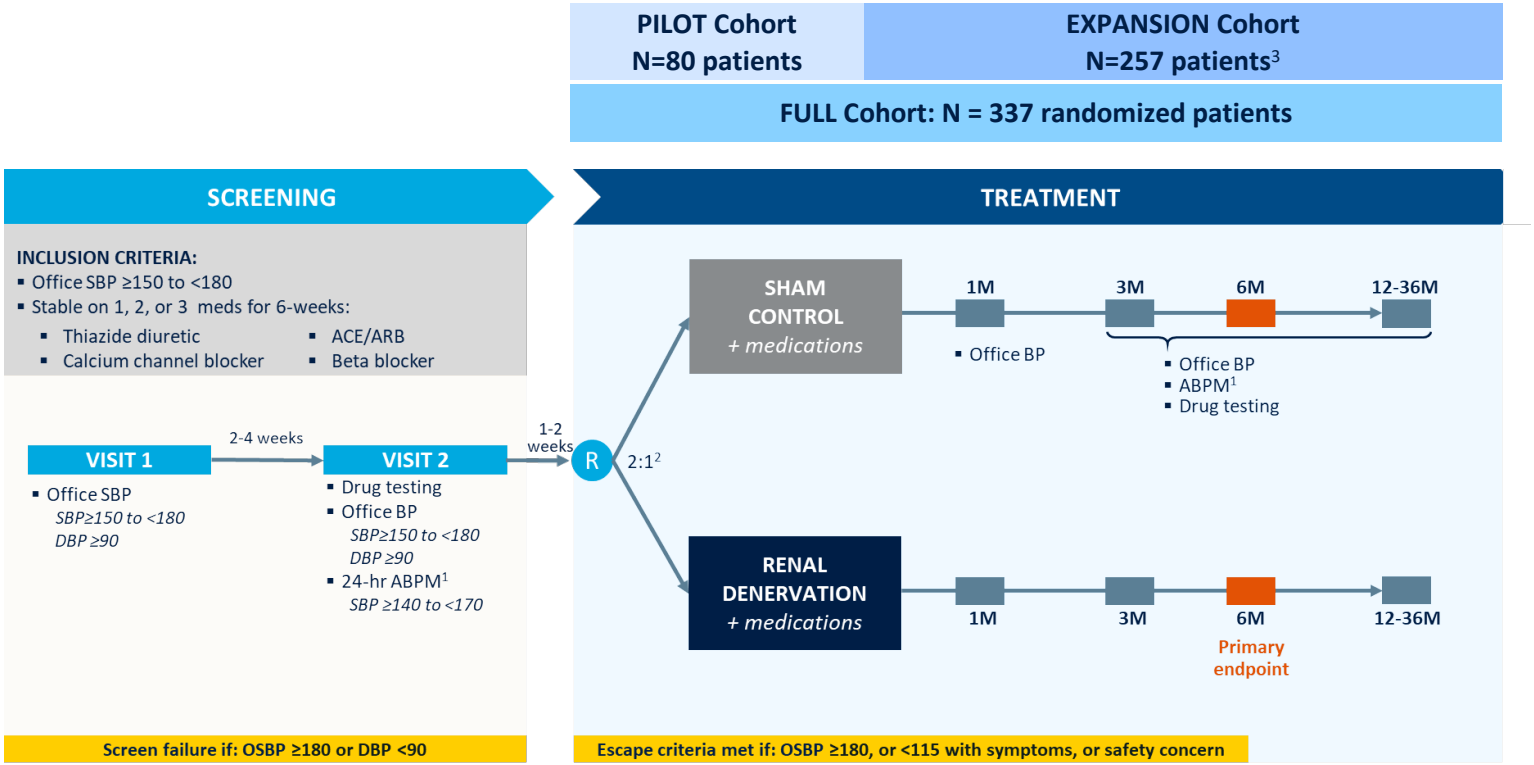
SPYRAL HTN-ON MED
Background

- Globally, over 1/3 of adults have hypertension, yet many remain uncontrolled, leading to increased risk of cardiovascular events
  - A 5-mmHg absolute reduction in Office Systolic BP leads to a 10% reduction in major CV events[1]
- Renal denervation (RDN) procedure targets the sympathetic nervous system to lower blood pressure
- The SPYRAL HTN-OFF MED Pivotal and SPYRAL HTN-ON MED Pilot trials demonstrated significant and clinically relevant blood pressure (BP) lowering after radiofrequency RDN in the absence and presence of antihypertensive medications[2,3]
- Recent, long-term data from the SPYRAL HTN-ON MED Pilot trial showed significant BP lowering out to 3 years[4]
- To further explore outcomes with RDN in the presence of antihypertensive medications, an international sham-controlled RCT was performed

[1] Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet*. 2021
[2] Böhm M, et al. *Lancet*. 2020
[3] Kandzari D, et al. *Lancet*. 2018
[4] Mahfoud F, et al. *Lancet*. 2022

SPYRAL HTN-ON MED Study Design

Randomized, Sham-Controlled Trial at 42 Sites Worldwide



NCT02439775.

Kandzari DE, et al. *Am Heart J*. 2016;171:82–91.

[1] All ABPM measurement started after witnessed drug intake

[2] Pilot cohort 1:1 randomization, Expansion cohort 2:1 after inclusion of first 106 patients

[3] Pre- and post-COVID are pre- and post-enrollment pause in pandemic

SPYRAL HTN-ON MED
Prespecified Study Endpoints

Primary EFFICACY Endpoint

Change in 24-hr Systolic ABPM at 6 months
(Bayesian analysis, 97.5% threshold for success)

Secondary EFFICACY Endpoints

Frequentist analyses at 6 months:

- **Change in 24-hr Systolic ABPM**
- **Change in Office Systolic BP**
- **Change in 24-hr Diastolic ABPM**
- **Change in Office Diastolic BP**

Win Ratio analysis[2] with ABPM and medication burden[3]

Primary SAFETY Endpoint (ON and OFF MED)[1]

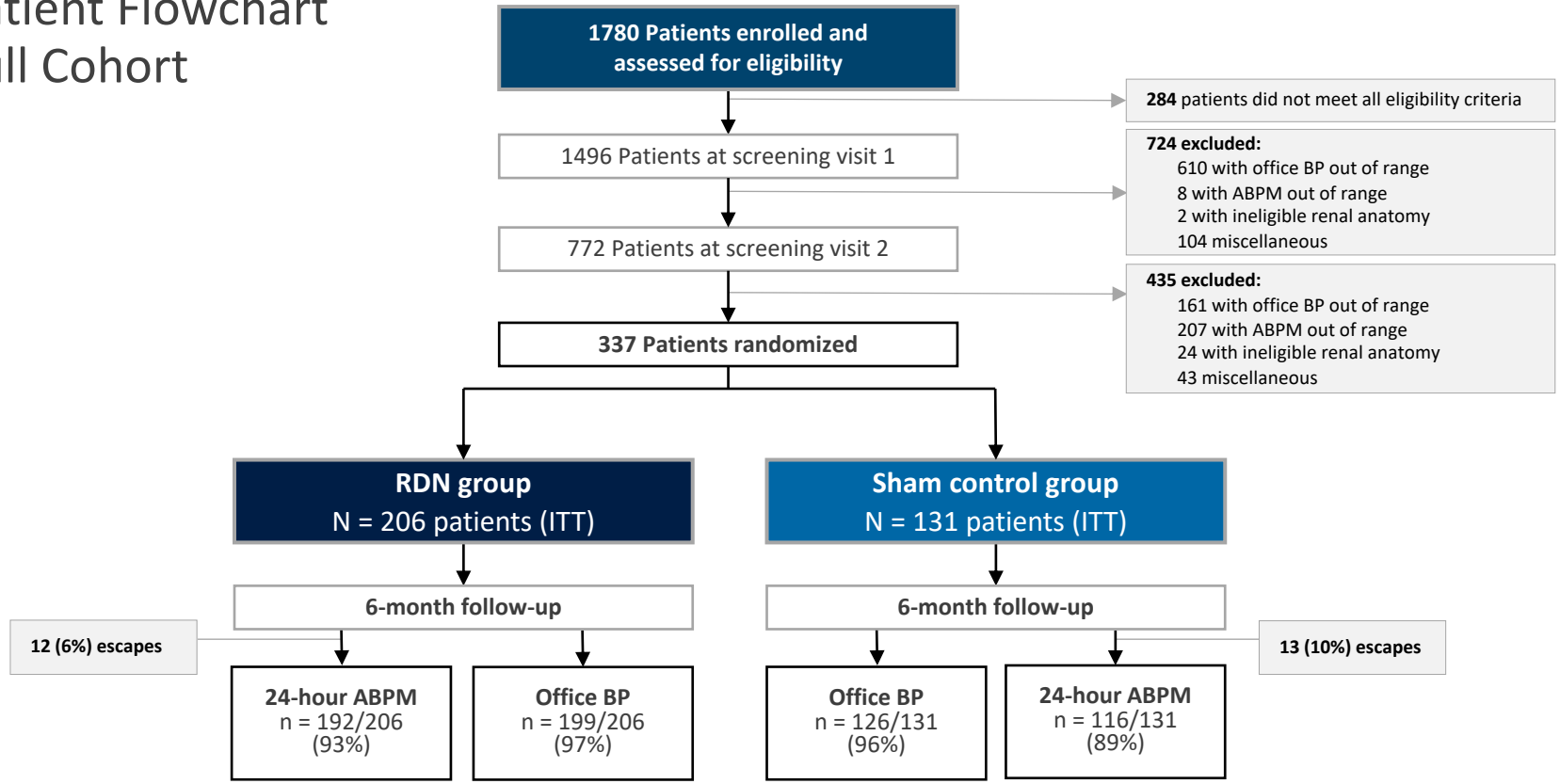
Major Adverse Events (MAE) at 1 month:
RDN compared to 7.1% performance goal

- All-cause mortality
- End stage renal disease (ESRD)
- Significant embolic event resulting in end-organ damage
- Renal artery perforation or dissection requiring intervention
- Renal artery stenosis (at 6 months)
- Vascular complications
- Hospitalization for hypertensive crisis

[1] Safety was evaluated separately for ON MED, and pooled between ON and OFF MED studies for endpoint
[2] Kandzari et al. *Eurointervention* 2021
[3] Medication burden based on number, class and dosage, where all medication classes are considered of equivalent potency (Mahfoud et al. *Lancet* 2022)

SPYRAL HTN-ON MED

Patient Flowchart
Full Cohort



SPYRAL HTN-ON MED

Baseline Characteristics

Mean ± SD or %	RDN (N = 206)	Sham Control (N = 131)
Age (years)	55.2 ± 9.0	54.6 ± 9.4
Male	81.1	78.6
BMI (kg/m^2)	31.4 ± 6.0	32.1 ± 5.2
Length of hypertension diagnosis >5 years	69.9	81.7*
Black Americans (race, % of study)	17.0	19.1
Diabetes (type 2)	10.7	17.6
Current smoker	15.5	16
Obstructive sleep apnea	11.2	17.6
History of CPAP/BiPAP use (currently using)	7.8	16.0*
History of coronary artery disease†	5.3	6.9
History of stroke / transient ischemic attack† (%)	0.5	1.5

*P< 0.05; P values not significant for differences in all other baseline characteristics unless specified
† Occurred >3 months before randomization

SPYRAL HTN-ON MED

Baseline Blood Pressure

Mean ± SD	RDN (N = 206)	Sham Control (N = 131)
Office measurements		
Office Systolic BP (mm Hg)	163.0 ± 7.7	163.1 ± 7.9
Office Diastolic BP (mm Hg)	101.2 ± 7.0	101.5 ± 7.3
24-hour ambulatory measurements		
Mean 24-hr Systolic BP (mm Hg)	149.6 ± 7.0	149.3 ± 7.0
Mean 24-hr Diastolic BP (mm Hg)	96.6 ± 7.6	95.7 ± 7.7

P = Not significant for differences in all baseline measurements

SPYRAL HTN-ON MED

Baseline Medications

Mean ± SD or %	RDN (N = 206)	Sham Control (N = 131)
Number of anti-hypertensive medication		
Mean	1.9 ± 0.8	1.9 ± 0.8
Medication Burden[1]	2.8 ± 2.5	3.0 ± 2.6
Prescribed medication classes		
1	38.8	35.9
2	32.5	35.9
3	28.2	27.5
Medication class		
Thiazide diuretic	40.8	43.5
Calcium channel blocker	53.4	55.7
ACE-I/ARB	76.7	75.6
Beta blocker	18.0	18.3

P = Not significant for differences in all baseline medications

[1] Medication burden based on number, class and dosage, where all medication classes are considered of equivalent potency (Mahfoud et al. *Lancet* 2022)

SPYRAL HTN-ON MED

Procedural Details

Mean ± SD or %	RDN (N = 204)	Sham Control (N = 130)
Main renal arteries treated / pt	2.3 ± 0.6	N/A
Branches treated / pt	5.8 ± 2.7	N/A
Total ablations / pt	47.4 ± 16.5	N/A
Main artery ablations	19.4 ± 9.5	N/A
Branch ablations	28.0 ± 14.6	N/A
Patients with accessory artery treated (%)	25.7	N/A
Catheter time (min)[1]	54.4 ± 19.2	N/A
Contrast volume used (cc)	204.2 ± 81.4	69.9 ± 35.8
Successful procedure (%)[2]	99.5	N/A

[1] Defined as time from insertion to removal of device
[2] Defined as successful delivery of any RF energy in the absence of in-hospital MAE

SPYRAL HTN-ON MED

Safety Results

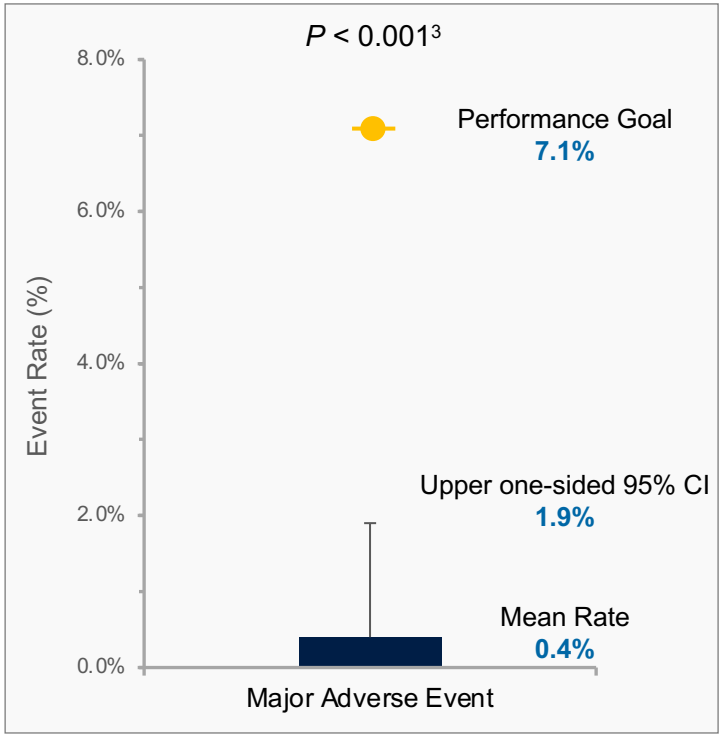
6 Month Outcomes % (n)	RDN (N = 206)	Sham Control (N = 131)
All-cause death	0	0
New MI	0	0
New-onset end-stage renal disease	0	0
Sign. embolic event resulting in end-organ damage	0	0
Renal artery perforation or dissection requiring intervention	0	0
Renal artery stenosis >70%[1]	0	0
Vascular complications (requiring surgical repair, interventional procedure, thrombin, or blood transfusion)	1 (2)	0.8 (1)
New stroke	0	0.8 (1)
Hospitalization for hypertensive crisis/emergency	0	0
Major bleeding (TIMI)	0	0
Serum creatinine elevation >50%	0	0

[1] Renal artery stenosis evaluated by duplex ultrasound and confirmed by angiogram

Pooled SPYRAL HTN-OFF & ON MED

Primary Safety Endpoint

Safety Outcomes at 1 Month % (n)	RDN (N = 253)[1]
Major Adverse Events	**0.4% (1)**
All-cause death	0
End Stage Renal Disease	0
Significant embolic event resulting in end-organ damage	0
Renal artery perforation requiring re-intervention	0
Renal artery dissection requiring re-intervention	0
Vascular complications (requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion)	0.4% (1)
Hospitalization for hypertensive crisis/emergency	0
New renal artery stenosis >70%[2]	0

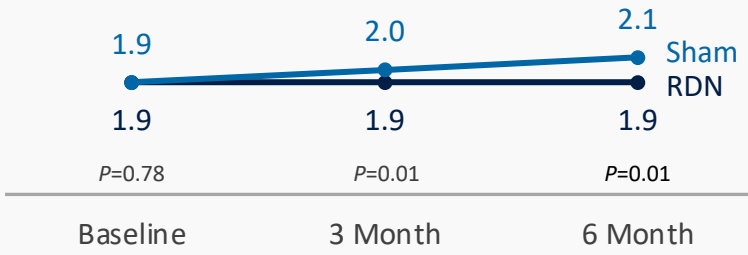


[1] All subjects treated with RDN (including Crossovers) in OFF MED and ON MED trials
[2] Major Adverse Events are measured at 1 month, except renal artery stenosis which is evaluated at 6 months by duplex ultrasound, and confirmed by angiogram
[3] *P* value based on a one-sided exact binomial test

Antihypertensive Medication Use

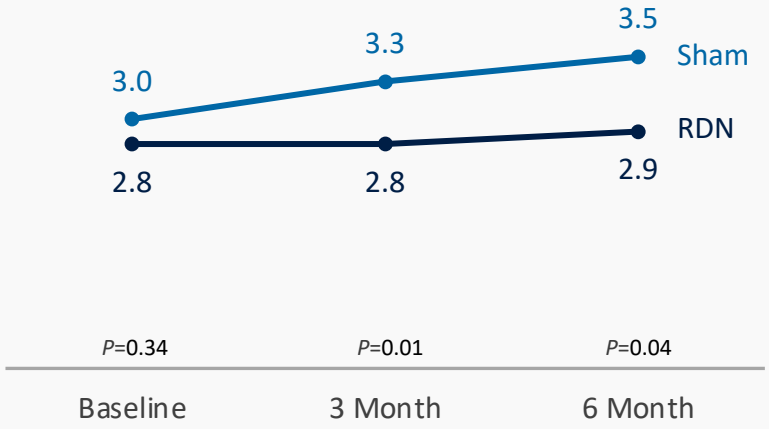
Significantly Higher Medication Number and Burden in Sham Control Over Follow-up

Number of Medications[1]



Medication Burden[1,2]

(based on number, class, and dosage of meds)



[1] Based on prescribed antihypertensive medications
[2] Medication burden based on number, class and dosage, where all medication classes are considered of equivalent potency (Mahfoud et al. *Lancet* 2022)
P-values at follow-up are ANCOVA adjusted

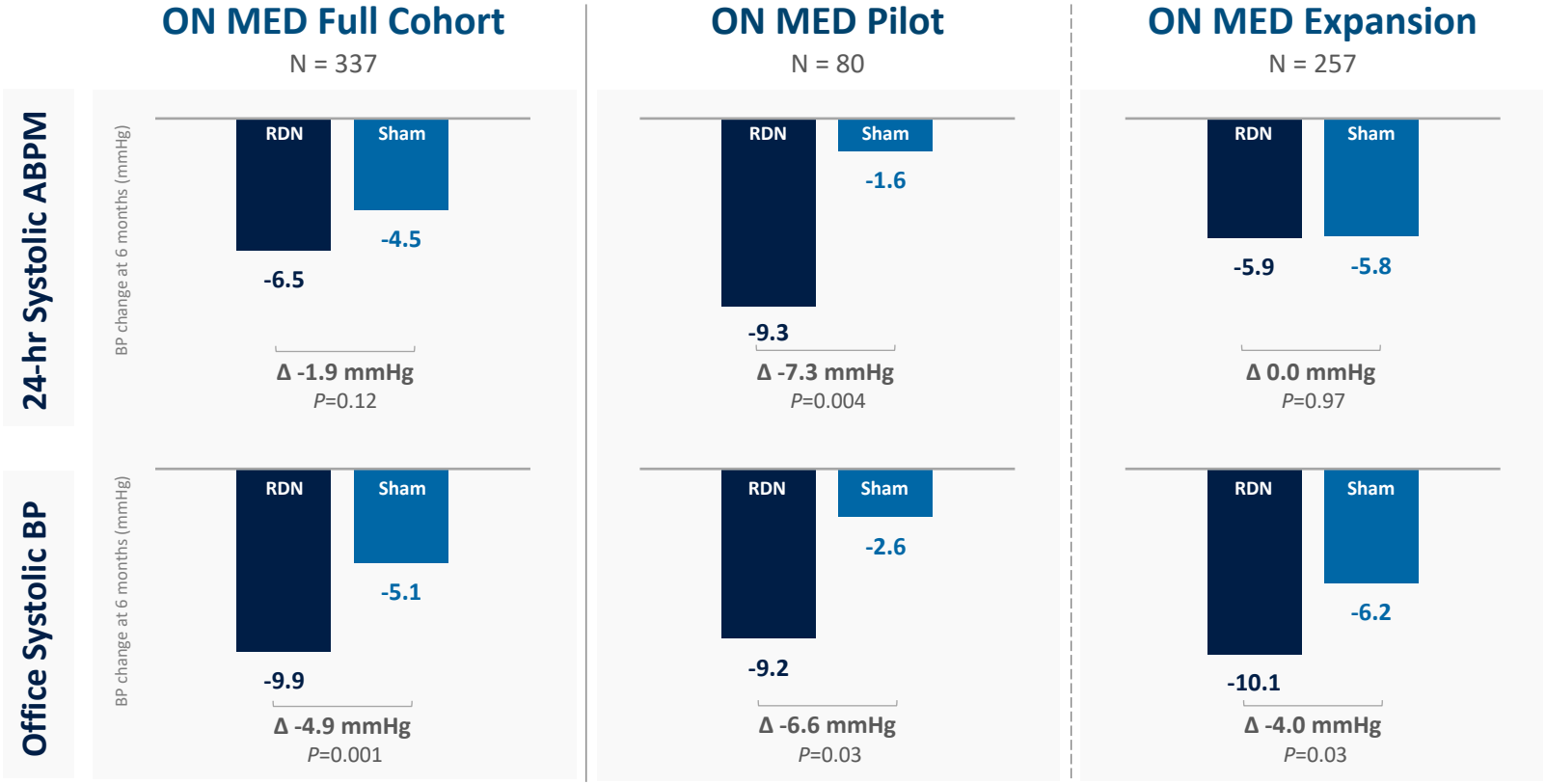
Blood Pressure Changes at 6 Months

Prespecified Efficacy Endpoints (Frequentist)

P-values are ANCOVA adjusted

Blood Pressure Changes at 6 Months

By Enrollment Cohort



P-values are ANCOVA adjusted

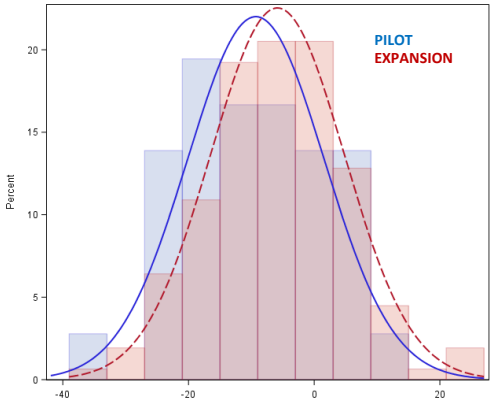
24-hr Systolic ABPM Change at 6 Months

Primary Efficacy Endpoint (Bayesian)

Due to differences in cohorts, minimal data were borrowed from the Pilot study

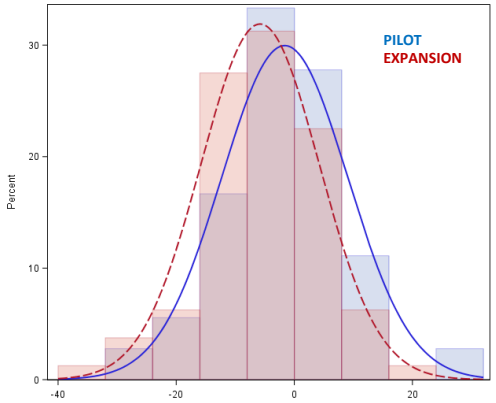
SPYRAL HTN - ON MED	Treatment Difference (mmHg) 95% Bayesian Credible Interval	% Borrowed from RDN arm prior	% Borrowed from Sham arm prior	Posterior probability of superiority
ITT Analysis	-0.03 (-2.82, 2.77)	19.4%	<1%	0.508

RDN



24-hr Systolic ABPM change at 6-mo

Sham



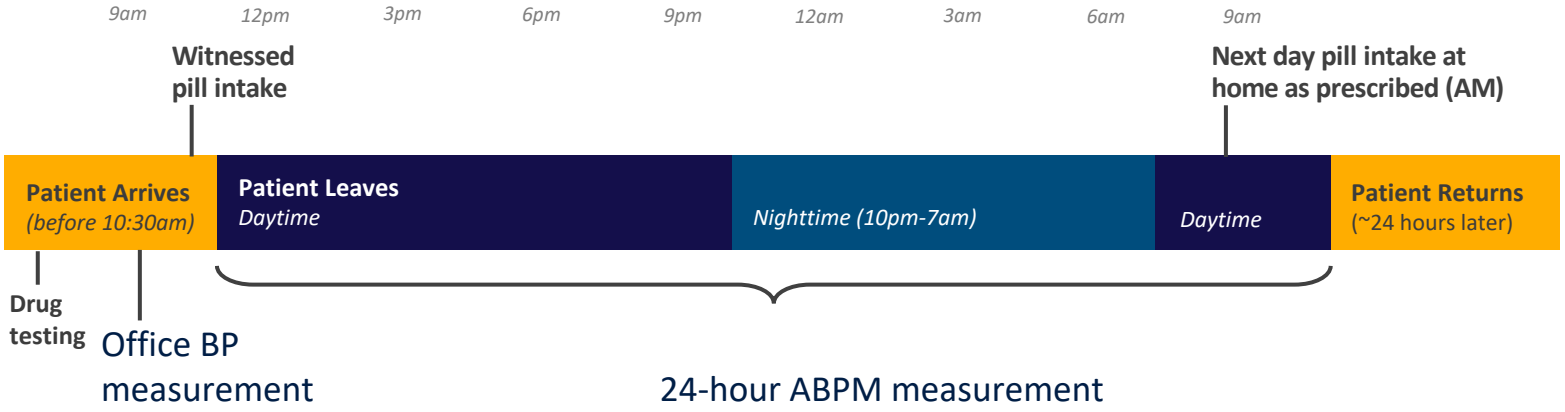
24-hr Systolic ABPM change at 6-mo

51% Probability of Superiority does not meet the Bayesian threshold for success (97.5%)

COVID Impact on ABPM Assessment

Office and ABPM Variances Relative to Timing of Enrollment and Follow-Up

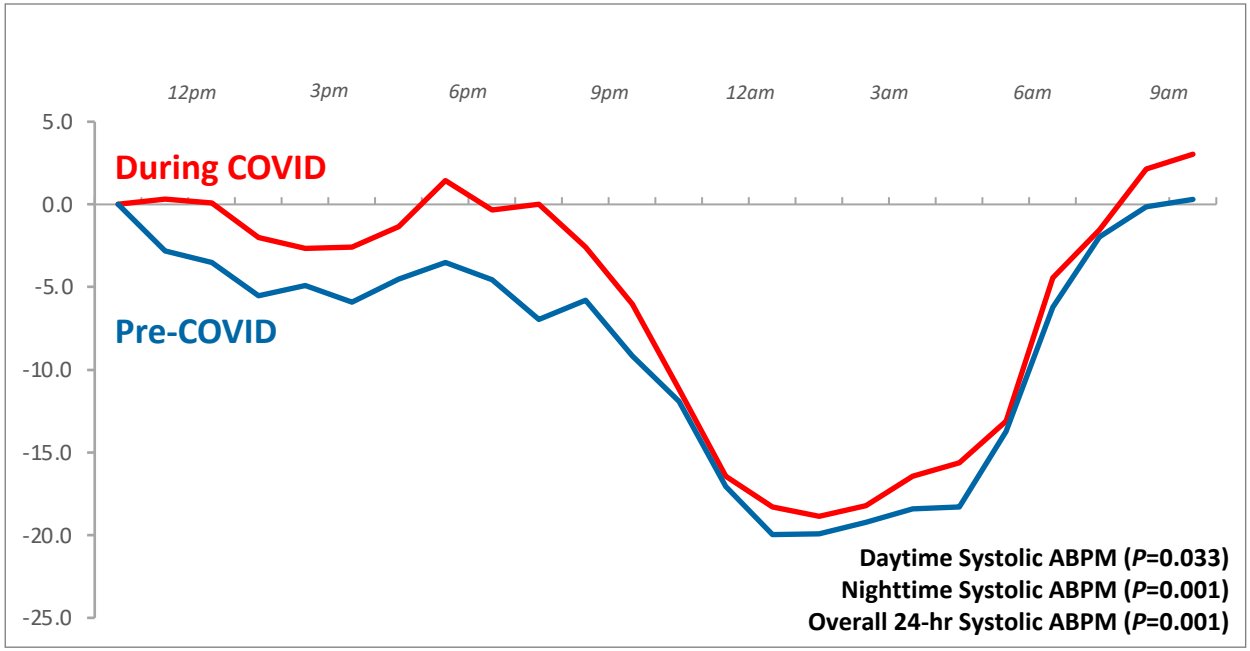
80% of Expansion Cohort follow-up occurred during COVID-19 pandemic and following brief enrollment pause



COVID Impact on ABPM Assessment

Office and ABPM Variances Relative to Timing of Enrollment and Follow-Up

Baseline Systolic ABPM Change (RDN+Sham Combined) Upon Leaving Hospital (mmHg)



Pre- and During-COVID:

- **Significant differences in baseline 24-hr SBP**
- **No significant differences in baseline Office SBP (*P*=0.69)**

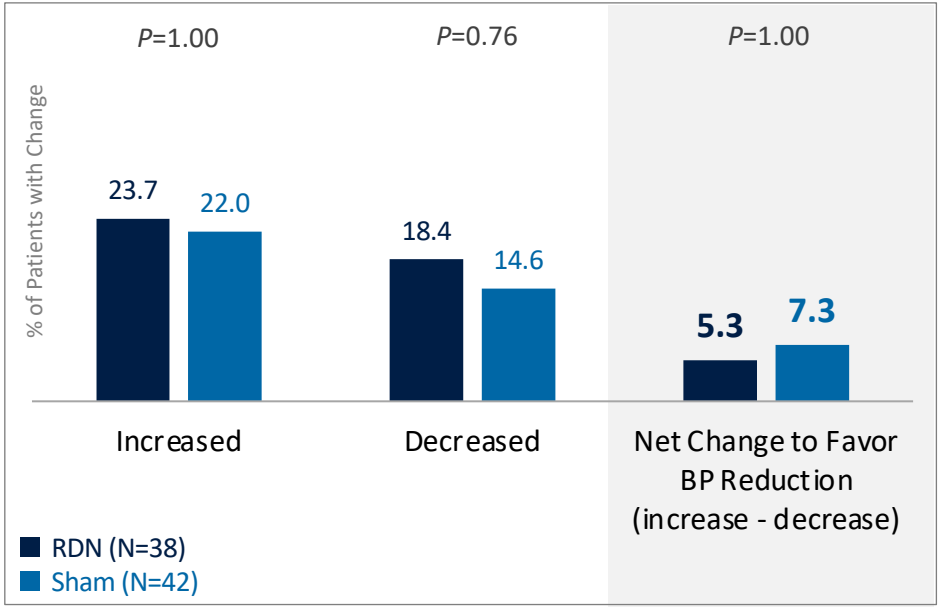
Baseline values pooled (RDN and sham control patients) before randomization; pre- and during COVID periods are pre- and post-enrollment pause in pandemic

Medication Changes Confirmed by Drug Testing

Imbalanced Medication Changes Between RDN and Sham Groups in Expansion Cohort

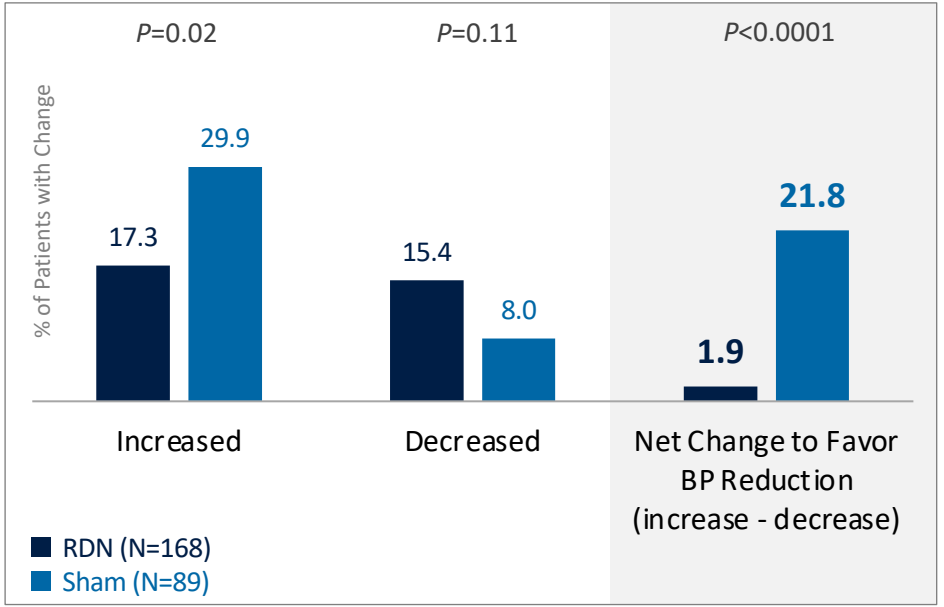
ON MED Pilot

Medication changes from baseline to 6 months



ON MED Expansion

Medication changes from baseline to 6 months



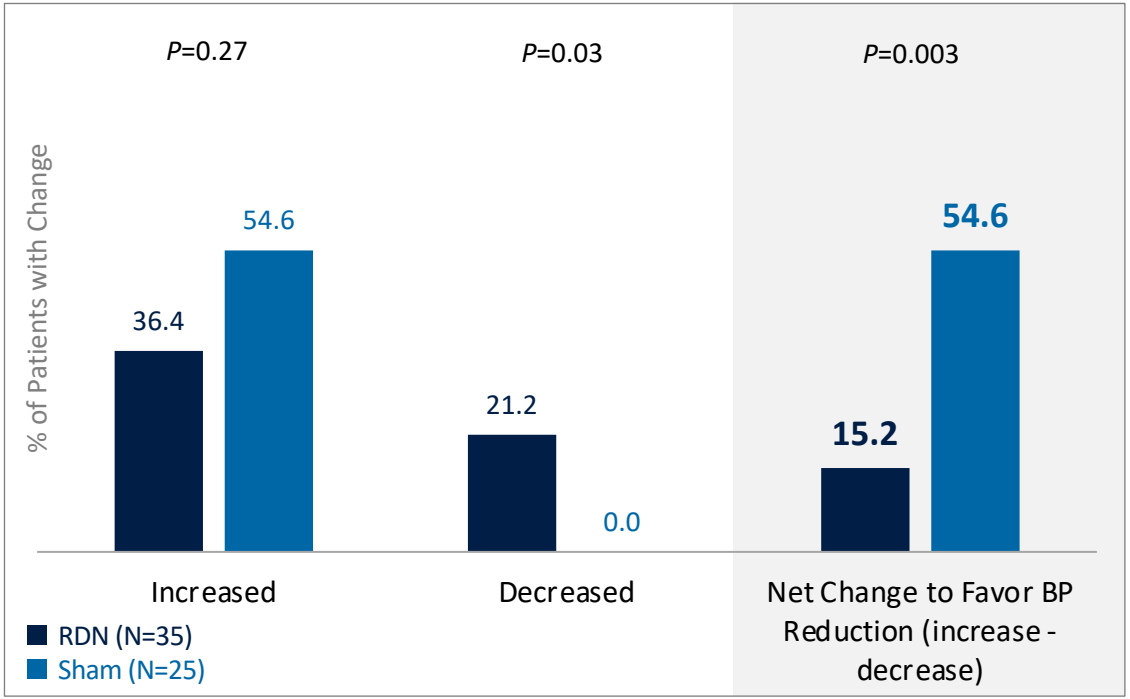
Medication burden based on number, class and dosage, where all medication classes are considered of equivalent potency (Mahfoud et al. *Lancet* 2022)

Medication Changes Confirmed by Drug Testing

Imbalanced Medication Changes Between RDN and Sham Groups

Black Americans Subgroup

Medication changes from baseline to 6 months

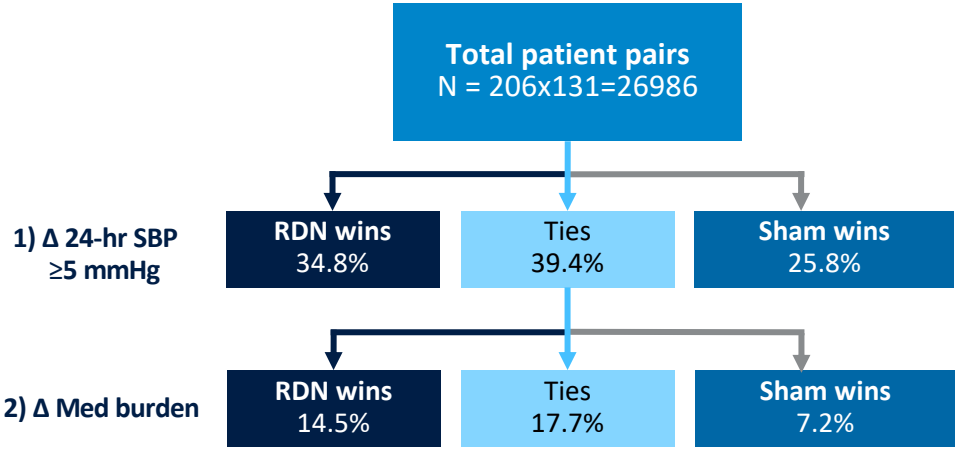


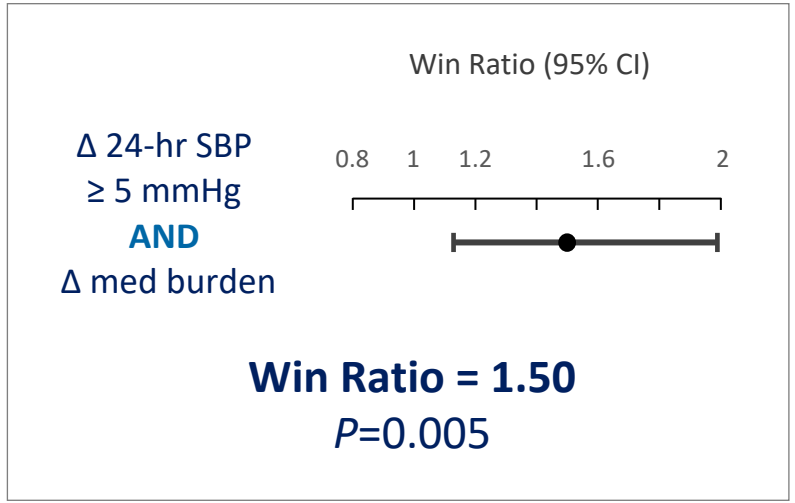
Prespecified subgroup analysis

Medication burden based on number, class and dosage, where all medication classes are considered of equivalent potency (Mahfoud et al. *Lancet* 2022)

Win Ratio Analysis

Hierarchical Analysis of ABPM and Medication Burden Reduction





Medication burden based on number, class and dosage, where all medication classes are considered of equivalent potency (Mahfoud et al. *Lancet* 2022)

SPYRAL HTN-ON MED

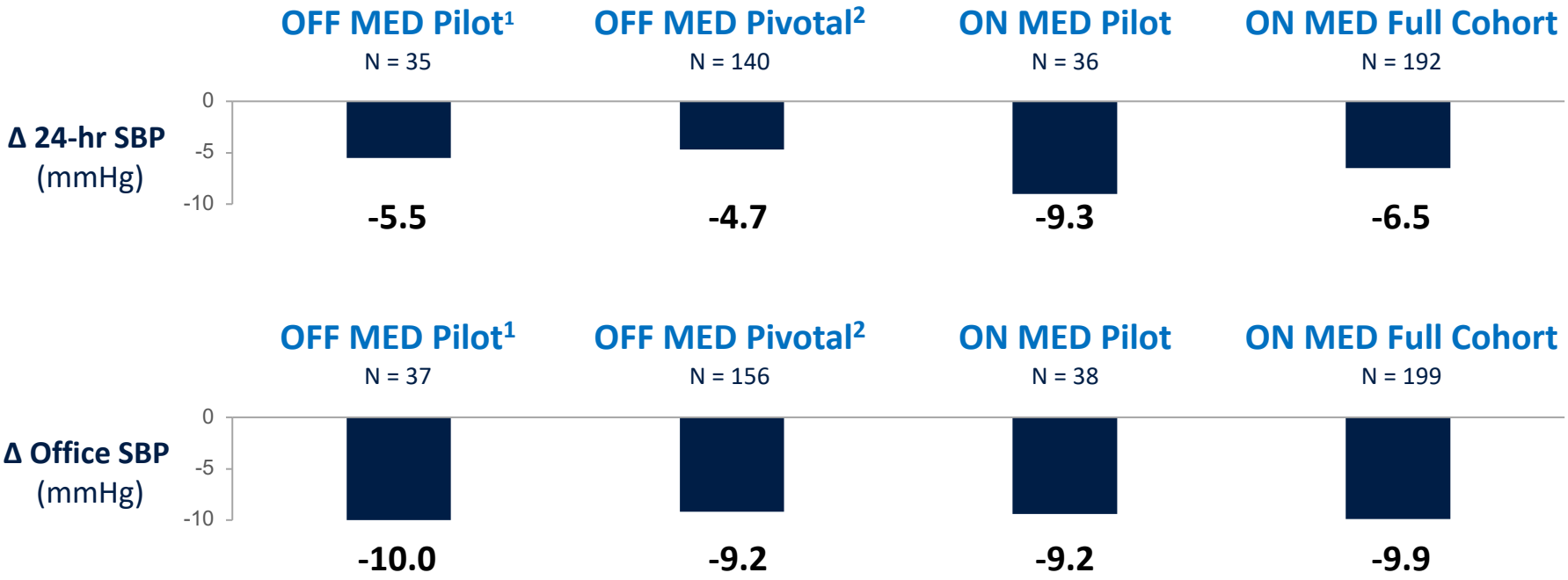
Limitations

- Substantial 24-hour ABPM outcome differences between Pilot and Expansion groups limited utilization of data between cohorts for Bayesian analysis
- Trial conduct in the context of the COVID pandemic
  - Following period of enrollment interruption during COVID pandemic, over 80% of 6-month follow-ups for Expansion cohort occurred during COVID
  - Significant differences in 24-hr ABPM patterns between pre- and during COVID populations may reflect changes in patient behavior and lifestyle during the pandemic[1,2,3]
- Significant and early changes in medication adherence identified prior to primary endpoint BP ascertainment despite protocol mandate
  - Majority of Expansion patients with medication changes did not have 24-hr ABPM performed prior to alteration of medications

[1] Kreutz et al. *Journal of Hypertension* 2021
[2] Azzouzzi et al. *Int. J. Environ. Res. Public Health* 2022
[3] Laffin et al. *Circulation* 2021

Absolute RDN Reductions in Office BP and 24-hour ABPM

Across SPYRAL HTN Clinical Program



[1] Townsend R, et al. *Lancet*. 2017
[2] Böhm M, et al. *Lancet*. 2020

All BP reductions are statistically significant and shown for the RDN group relative to their Primary Endpoint, except for ON MED Full Cohort.
SPYRAL HTN-OFF MED Pilot and Pivotal assessed at 3-months; SPYRAL HTN-ON MED Pilot and Full Cohort assessed at 6-months

SPYRAL HTN-ON MED

- Despite a significant reduction in Office BP and Win Ratio favoring RDN vs Sham, the primary efficacy endpoint was not met for 24-hr ABPM at 6 months
  - Substantial ABPM outcome differences between Pilot and Expansion groups limited utilization of data between cohorts for Bayesian analysis
  - Expansion enrollment over the COVID pandemic demonstrated differences in baseline ABPM patterns between pre- and during-COVID cohorts, in contrast to consistent baseline Office BP assessments
  - Significant differences in both medication prescription and burden were disproportionate in favor of the Sham group, and amplified in selected subgroups
  - These imbalanced medication changes impact 24-hr ABPM more than Office BP and bias ABPM towards the null given timing of both witnessed pill intake and next day morning pill intake occurring during 24-hr ABPM
- The primary safety endpoint across SPYRAL HTN trials was met with low incidence of procedural-related and clinical adverse events
- Absolute reductions in both Office BP and ABPM for RF RDN are consistent across trials

Thank You!

We thank all patients, investigators, site personnel, committee members and staff for their contribution!