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

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

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

- 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

- Recent, long-term data from the SPYRAL HTN-ON MED Pilot trial showed significant BP lowering out to 3 years

- To further explore outcomes with RDN in the presence of antihypertensive medications, an international sham-controlled RCT was performed

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1 Blood Pressure Lowering Treatment Trialists’ Collaboration. Lancet. 2021
3 Kandzari D, et al. Lancet. 2018
SPYRAL HTN-ON MED Study Design
Randomized, Sham-Controlled Trial at 42 Sites Worldwide

**SCREENING**

**INCLUSION CRITERIA:**
- Office SBP ≥150 to <180
- Stable on 1, 2, or 3 meds for 6 weeks:
  - Thiazide diuretic
  - ACE/ARB
  - Beta blocker

**VISIT 1**
- Office SBP
- SBP ≥150 to <180
- DBP ≥90

**VISIT 2**
- Drug testing
- Office BP
- SBP ≥150 to <180
- DBP ≥90
- 24-hr ABPM
  - SBP ≥140 to <170

Screen failure if: OSBP ≥180 or DBP <90

**PILOT Cohort**
- N=80 patients

**EXPANSION Cohort**
- N=257 patients

**FULL Cohort: N = 337 randomized patients**

**TREATMENT**

**SHAM CONTROL + medications**

1M
- Office BP

3M
- Office BP
- ABPM
- Drug testing

6M

12-36M

**RENAI DENERVATION + medications**

1M

3M

6M

Primary endpoint

12-36M

Escape criteria met if: OSBP ≥180, or <115 with symptoms, or safety concern

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

NCT02439775.
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

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\(^1\) 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)
1780 Patients enrolled and assessed for eligibility

1496 Patients at screening visit 1

772 Patients at screening visit 2

337 Patients randomized

RDN group
N = 206 patients (ITT)

Sham control group
N = 131 patients (ITT)

6-month follow-up

24-hour ABPM n = 192/206 (93%)

Office BP n = 199/206 (97%)

24-hour ABPM n = 116/131 (89%)

Office BP n = 126/131 (96%)

284 patients did not meet all eligibility criteria

724 excluded:
- 610 with office BP out of range
- 8 with ABPM out of range
- 2 with ineligible renal anatomy
- 104 miscellaneous

435 excluded:
- 161 with office BP out of range
- 207 with ABPM out of range
- 24 with ineligible renal anatomy
- 43 miscellaneous

13 (10%) escapes

12 (6%) escapes

SPYRAL HTN-ON MED
Patient Flowchart
Full Cohort
# Baseline Characteristics

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

*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

<table>
<thead>
<tr>
<th></th>
<th>RDN (N = 206)</th>
<th>Sham Control (N = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean ± SD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Office measurements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Office Systolic BP (mm Hg)</td>
<td>163.0 ± 7.7</td>
<td>163.1 ± 7.9</td>
</tr>
<tr>
<td>Office Diastolic BP (mm Hg)</td>
<td>101.2 ± 7.0</td>
<td>101.5 ± 7.3</td>
</tr>
<tr>
<td><strong>24-hour ambulatory measurements</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean 24-hr Systolic BP (mm Hg)</td>
<td>149.6 ± 7.0</td>
<td>149.3 ± 7.0</td>
</tr>
<tr>
<td>Mean 24-hr Diastolic BP (mm Hg)</td>
<td>96.6 ± 7.6</td>
<td>95.7 ± 7.7</td>
</tr>
</tbody>
</table>

*P* = Not significant for differences in all baseline measurements
## SPYRAL HTN-ON MED

### Baseline Medications

<table>
<thead>
<tr>
<th>Mean ± SD or %</th>
<th>RDN (N = 206)</th>
<th>Sham Control (N = 131)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of anti-hypertensive medication</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>1.9 ± 0.8</td>
<td>1.9 ± 0.8</td>
</tr>
<tr>
<td>Medication Burden¹</td>
<td>2.8 ± 2.5</td>
<td>3.0 ± 2.6</td>
</tr>
<tr>
<td><strong>Prescribed medication classes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>38.8</td>
<td>35.9</td>
</tr>
<tr>
<td>2</td>
<td>32.5</td>
<td>35.9</td>
</tr>
<tr>
<td>3</td>
<td>28.2</td>
<td>27.5</td>
</tr>
<tr>
<td><strong>Medication class</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thiazide diuretic</td>
<td>40.8</td>
<td>43.5</td>
</tr>
<tr>
<td>Calcium channel blocker</td>
<td>53.4</td>
<td>55.7</td>
</tr>
<tr>
<td>ACE-I/ARB</td>
<td>76.7</td>
<td>75.6</td>
</tr>
<tr>
<td>Beta blocker</td>
<td>18.0</td>
<td>18.3</td>
</tr>
</tbody>
</table>

*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)
## Procedural Details

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

\(^1\) 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**

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

¹ Renal artery stenosis evaluated by duplex ultrasound and confirmed by angiogram
Pooled SPYRAL HTN-OFF & ON MED
Primary Safety Endpoint

<table>
<thead>
<tr>
<th>Safety Outcomes at 1 Month</th>
<th>RDN (N = 253)$^1$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Adverse Events</strong></td>
<td>0.4% (1)</td>
</tr>
<tr>
<td>All-cause death</td>
<td>0</td>
</tr>
<tr>
<td>End Stage Renal Disease</td>
<td>0</td>
</tr>
<tr>
<td>Significant embolic event resulting in end-organ damage</td>
<td>0</td>
</tr>
<tr>
<td>Renal artery perforation requiring re-intervention</td>
<td>0</td>
</tr>
<tr>
<td>Renal artery dissection requiring re-intervention</td>
<td>0</td>
</tr>
<tr>
<td>Vascular complications (requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion)</td>
<td>0.4% (1)</td>
</tr>
<tr>
<td>Hospitalization for hypertensive crisis/emergency</td>
<td>0</td>
</tr>
<tr>
<td>New renal artery stenosis &gt;70%$^2$</td>
<td>0</td>
</tr>
</tbody>
</table>

$^1$ 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

![Safety Outcomes at 1 Month Graph](attachment:image.png)
Antihypertensive Medication Use

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

**Number of Medications**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 Month</th>
<th>6 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>1.9</td>
<td>2.0</td>
<td>2.1</td>
</tr>
<tr>
<td>RDN</td>
<td>1.9</td>
<td>1.9</td>
<td>1.9</td>
</tr>
</tbody>
</table>

*P*=0.78, *P*=0.01, *P*=0.01

**Medication Burden**

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

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>3 Month</th>
<th>6 Month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>3.0</td>
<td>3.3</td>
<td>3.5</td>
</tr>
<tr>
<td>RDN</td>
<td>2.8</td>
<td>2.8</td>
<td>2.9</td>
</tr>
</tbody>
</table>

*P*=0.34, *P*=0.01, *P*=0.04

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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)

<table>
<thead>
<tr>
<th>Blood Pressure Change (mmHg)</th>
<th>RDN (N=192)</th>
<th>Sham (N=116)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>24-hr Systolic ABPM</strong></td>
<td>-6.5</td>
<td>-4.5</td>
<td>0.12</td>
</tr>
<tr>
<td><strong>24-hr Diastolic ABPM</strong></td>
<td>-4.4</td>
<td>-3.4</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Office Systolic BP</strong></td>
<td>-9.9</td>
<td>-5.1</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Office Diastolic BP</strong></td>
<td>-5.2</td>
<td>-3.3</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*P-values are ANCOVA adjusted*
Blood Pressure Changes at 6 Months
By Enrollment Cohort

**ON MED Full Cohort**

- **24-hr Systolic ABPM**
  - RDN: -6.5 mmHg
  - Sham: -4.5 mmHg
  - Δ: -2.0 mmHg
  - P = 0.12

- **Office Systolic BP**
  - RDN: -9.9 mmHg
  - Sham: -5.1 mmHg
  - Δ: -4.9 mmHg
  - P = 0.001

**ON MED Pilot**

- **24-hr Systolic ABPM**
  - RDN: -9.3 mmHg
  - Sham: -1.6 mmHg
  - Δ: -7.7 mmHg
  - P = 0.004

- **Office Systolic BP**
  - RDN: -9.2 mmHg
  - Sham: -2.6 mmHg
  - Δ: -6.6 mmHg
  - P = 0.03

**ON MED Expansion**

- **24-hr Systolic ABPM**
  - RDN: -5.9 mmHg
  - Sham: -5.8 mmHg
  - Δ: -0.1 mmHg
  - P = 0.97

- **Office Systolic BP**
  - RDN: -10.1 mmHg
  - Sham: -6.2 mmHg
  - Δ: -4.0 mmHg
  - P = 0.03

*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

<table>
<thead>
<tr>
<th>SPYRAL HTN - ON MED</th>
<th>Treatment Difference (mmHg) 95% Bayesian Credible Interval</th>
<th>% Borrowed from RDN arm prior</th>
<th>% Borrowed from Sham arm prior</th>
<th>Posterior probability of superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT Analysis</td>
<td>-0.03 (-2.82, 2.77)</td>
<td>19.4%</td>
<td>&lt;1%</td>
<td>0.508</td>
</tr>
</tbody>
</table>

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

Patient Arrives (before 10:30am)
Witnessed pill intake
Drug testing
Office BP measurement

Patient Leaves
Daytime

Next day pill intake at home as prescribed (AM)

Nighttime (10pm-7am)

Daytime

Patient Returns (~24 hours later)

24-hour ABPM measurement
COVID Impact on ABPM Assessment
Office and ABPM Variances Relative to Timing of Enrollment and Follow-Up

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

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 ($P=0.69$)

Daytime Systolic ABPM ($P=0.033$)
Nighttime Systolic ABPM ($P=0.001$)
Overall 24-hr Systolic ABPM ($P=0.001$)
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

<table>
<thead>
<tr>
<th></th>
<th>Increased</th>
<th>Decreased</th>
<th>Net Change to Favor BP Reduction (increase - decrease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDN (N=38)</td>
<td>23.7</td>
<td>18.4</td>
<td>5.3</td>
</tr>
<tr>
<td>Sham (N=42)</td>
<td>22.0</td>
<td>14.6</td>
<td>7.3</td>
</tr>
</tbody>
</table>

### ON MED Expansion
Medication changes from baseline to 6 months

<table>
<thead>
<tr>
<th></th>
<th>Increased</th>
<th>Decreased</th>
<th>Net Change to Favor BP Reduction (increase - decrease)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RDN (N=168)</td>
<td>17.3</td>
<td>15.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Sham (N=89)</td>
<td>29.9</td>
<td>8.0</td>
<td>21.8</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Change</th>
<th>RDN (N=35)</th>
<th>Sham (N=25)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased</td>
<td>36.4%</td>
<td>54.6%</td>
<td>0.27</td>
</tr>
<tr>
<td>Decreased</td>
<td>21.2%</td>
<td>0.0%</td>
<td>0.03</td>
</tr>
<tr>
<td>Net Change to Favor BP Reduction</td>
<td>15.2%</td>
<td>54.6%</td>
<td>0.003</td>
</tr>
</tbody>
</table>

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

1) Δ 24-hr SBP ≥ 5 mmHg
   - RDN wins 34.8%
   - Ties 39.4%
   - Sham wins 25.8%

2) Δ Med burden
   - RDN wins 14.5%
   - Ties 17.7%
   - Sham wins 7.2%

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

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\(^1\) Kreutz et al. *Journal of Hypertension* 2021
\(^2\) Azzouzi 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

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

• 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

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

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