U.S. FOOD & DRUG ADMINISTRATION

Premarket Approval Application (PMA) for ReCor Medical's Paradise Ultrasound Renal Denervation System

Circulatory System Devices Advisory Committee Meeting
August 22, 2023

Introduction, Background, Clinical Study Design

Paul Warren, PhD
Biomedical Engineer
Office of Cardiovascular Devices

Review Team

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Outline

- Background
- Device Description and Proposed Indications for Use
- Clinical Study Design
- Clinical Study Results
  - Safety
  - Effectiveness
  - Patient preference study
- Post-approval Study
- Conclusions

Clinical Background

- Hypertension (HTN) is a major public health problem
  - Prevalence ~45% of US adults
  - Higher rate among African Americans (57.1%) vs. Caucasians (43.6%) & Hispanics (43.7%) (NHANES, 2017-2018)[1]
- Associated with increased risk of serious conditions including[2]
  - Stroke
  - Heart disease
  - Heart failure
  - Noncardiac vascular disease
  - Renal Disease
- BP medications are the mainstay of HTN therapy, but:
  - BP medication adherence present in approximately 60% of patients[3]
  - Target BP achieved in approximately 45% of patients[4]

1. National Health and Nutrition Examination Survey Fact Sheet. *CDC*. July 2020. Available at: https://www.cdc.gov/nchs/data/factsheets/factsheet_nhanes.pdf
2. Carey RM et al. Prevention and Control of Hypertension: JACC Health Promotion Series. *J Am Coll Cardiol* 72(11). 2018.
3. Choudhry NK et al. Medication Adherence and Blood Pressure Control: A Scientific Statement From the American Heart Association. *Hypertension*. 79(1). 2022.
4. Dorans KS et al. Trends in prevalence and control of hypertension according to the 2017 ACC/AHA Guidelines. *J Am Heart Assoc* 7(11). 2018.

Defining Hypertension (1)

2017 US Societal Guideline Classification of Blood Pressure in Adults[5]

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

5. Whelton PK et al. ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: A report of the American College of Cardiology / American Heart Association task force. *Circulation* 138(17). 2018.

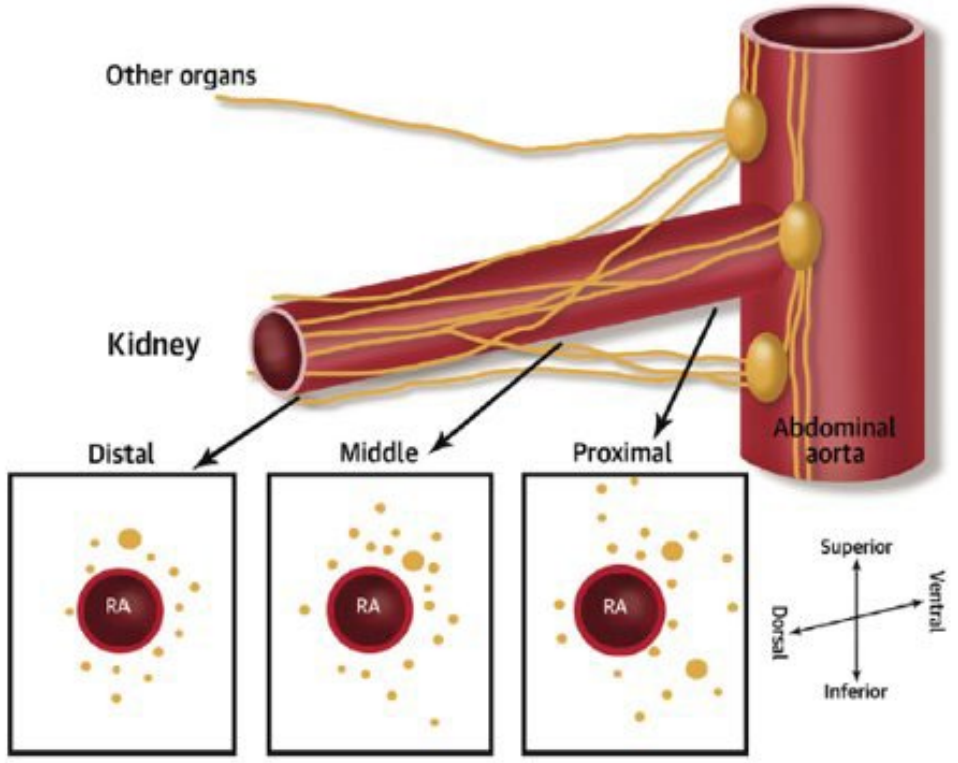
Defining Hypertension (2)

- Uncontrolled HTN: Above BP goal
  - Due to non-adherence to treatment; or
  - Despite adherence to treatment
- Resistant HTN: Above BP goal despite the use of 3 HTN medications (including a diuretic) with complementary mechanisms of action

Role of Renal Physiology in Hypertension

- Renal vasculature innervated by mainly efferent sympathetic nerves
- Stimulation of efferent nerves leading to:
  - Increased reabsorption of Na and water
  - Reduced renal blood flow and GFR (vasoconstriction)
  - Increased activity of the RAAS

Increased BP



Renal Denervation (RDN)

- An approach to reduce renal sympathetic activity by ablating the surrounding nerves
- Early single-arm clinical studies of percutaneous RDN technologies showed large decreases in BP
- However, initial sham-controlled trials did not see same degree of BP reduction, and no significant difference between RDN treatment and sham
- After denervation, some animal studies show re-innervation[6-8]
  - If re-innervation occurs in humans, sustained BP reduction could be impacted

6. Mulder J et al. Renal sensory and sympathetic nerves reinnervate the kidney in a similar time-dependent fashion after renal denervation in rats. *Am J Physiol* 304(8). 2013.
7. Booth LC et al. Reinnervation following catheter-based radio-frequency renal denervation. *Exp Physiol* 100(5). 2015.
8. Kiuchi MG et al. Renal denervation update from the International Sympathetic Nervous System Summit: JACC State-of-the-Art Review. *J Am Coll Cardiol* 73(23). 2019.

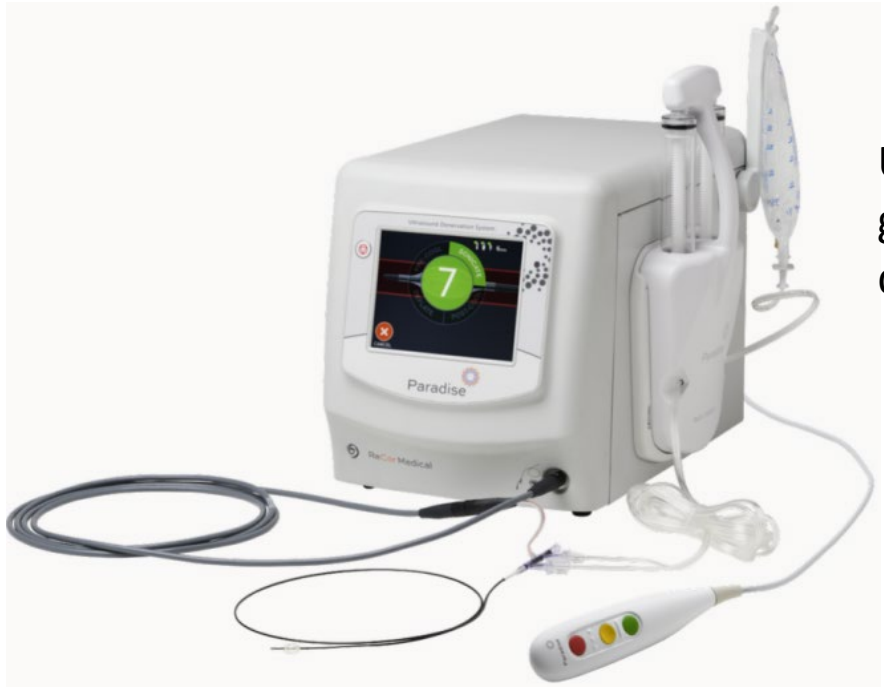
2018 FDA Advisory Committee on HTN Devices

- Discussed clinical trial designs to evaluate safety and effectiveness of devices for HTN
- Key Panel recommendations[9]
  - Sham controlled trials
  - Trial designs
    - Medication withdrawal (off-med) study
    - Standardized BP medication (on-standardized med) study
  - Ambulatory BP measurement (ABPM) used as the primary BP assessment method
  - A ≥5 mmHg difference in BP reduction between active treatment and sham as clinically significant
  - Value of patient preference information

9. 2018 FDA Advisory Committee Meeting, available at: bit.ly/3OEirtN

Paradise Ultrasound Renal Denervation (uRDN) System

Catheter tip with ultrasound transducer and balloon



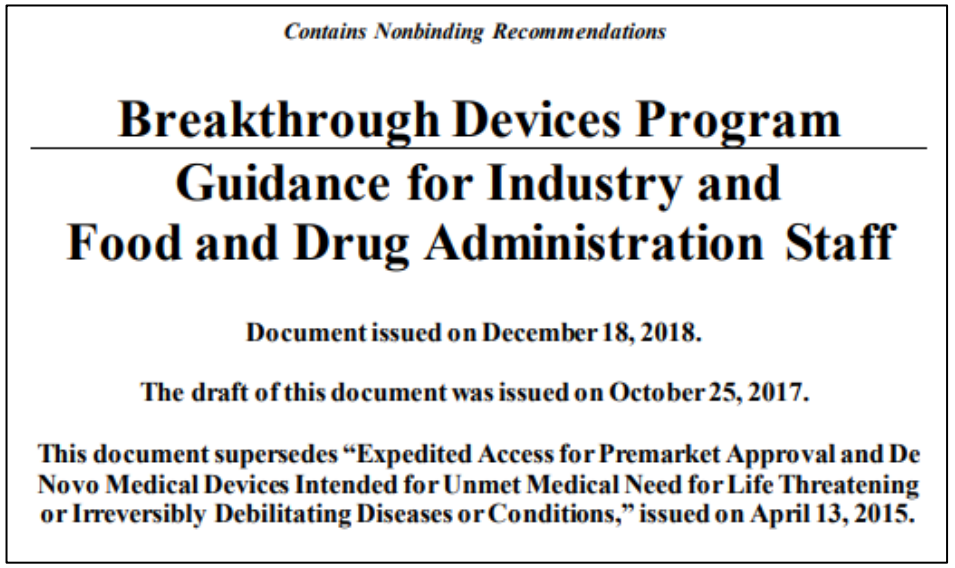
Ultrasound generator and display screen

Proposed indications for use

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

Breakthrough Devices Program

- Paradise uRDN System granted breakthrough status in Dec 2020 for patients with resistant or uncontrolled hypertension
- Breakthrough devices may provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions
- Intended to provide patients with timely access to certain devices by expediting their development, assessment, and review



Contains Nonbinding Recommendations

Breakthrough Devices Program

Guidance for Industry and Food and Drug Administration Staff

Document issued on December 18, 2018.

The draft of this document was issued on October 25, 2017.

This document supersedes "Expedited Access for Premarket Approval and De Novo Medical Devices Intended for Unmet Medical Need for Life Threatening or Irreversibly Debilitating Diseases or Conditions," issued on April 13, 2015.

Breakthrough Device Program

- **Does** allow for:
  - Interactive and timely communication with FDA
  - Prioritized submission review
  - Efficient and flexible clinical study design
  - Expedited manufacturing and quality systems review
  - Pre/Postmarket balance of data collection
- **Does not** alter/reduce the statutory requirement for premarket approval
  - A reasonable assurance of safety and effectiveness

Breakthrough Devices Program Guidance: https://www.fda.gov/media/108135/download

Pre/Postmarket Balance of Data Collection

- FDA may accept greater uncertainty for a premarket submission along with timely postmarket data collection if the uncertainty is sufficiently balanced
- Benefit/Risk considerations include:
  - Probable benefits from earlier access

    vs.
  - Probable risk of harm should postmarket data show that the device is ineffective or unsafe

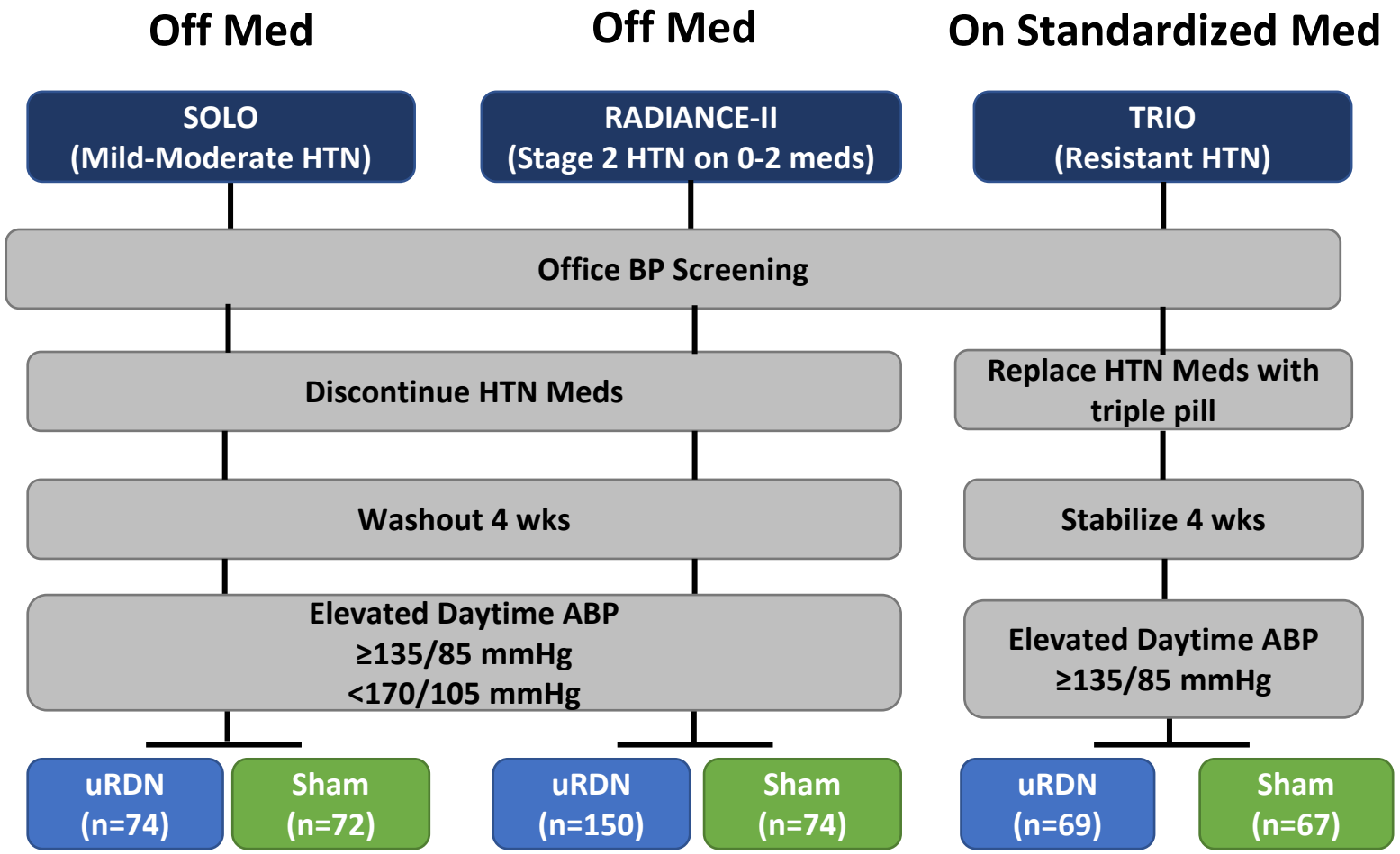
Nonclinical and Preclinical Device Evaluation

- Catheter Engineering Testing
  - Bench testing
  - Ultrasound output and delivery
- Generator Engineering Testing
  - Electrical safety
  - Software validation
  - Cybersecurity
- System Compatibility
- Biocompatibility
- Sterilization & Packaging
- Preclinical Animal Studies

No outstanding non-clinical study issues

CLINICAL STUDY DESIGN

Clinical Study Design Overview



Medication Escalation

- Between 2-6 months to goal (≤135 mmHg)

Blinding:

- SOLO and TRIO: Thru 6 months
- RADIANCE II: Thru 12 months

Sham crossover to RDN permitted:

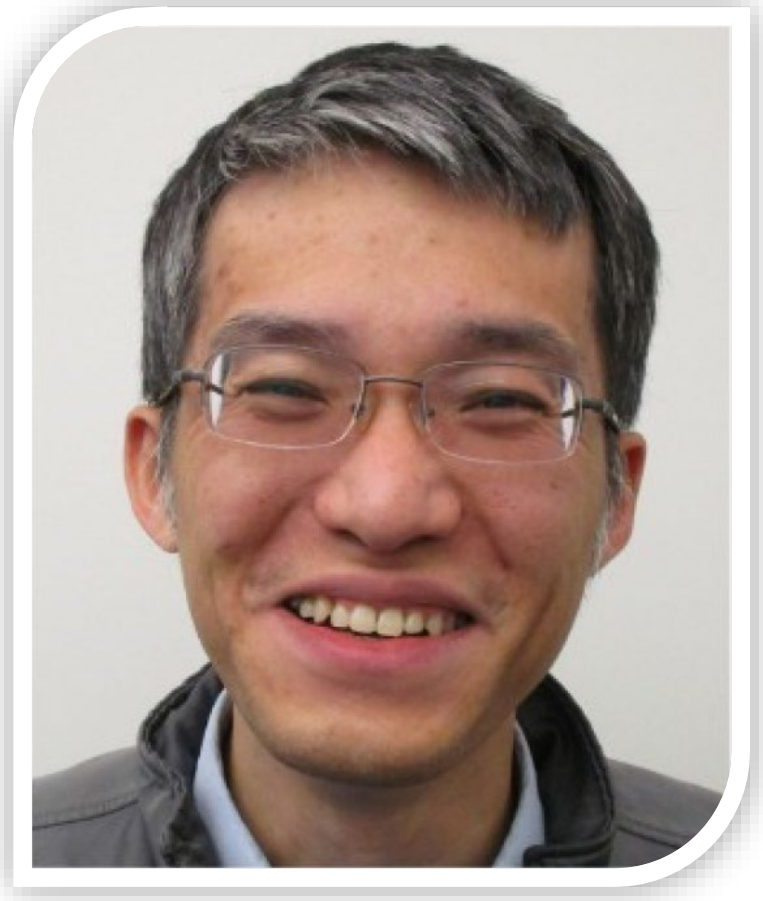
- SOLO and TRIO: At 6 months
- RADIANCE II: At 12 months

Key Enrollment Criteria

- Between 18 and 75 years old
- History of HTN
- Suitable renal anatomy

	SOLO Off-Med (Mild-to-moderate HTN)	RADIANCE-II Off-Med (Stage 2 HTN)	TRIO On-Standardized Med (Resistant HTN)
OBP	≥140/90 & <180/110 mmHg on 0, 1 or 2 meds; *or* ≤140/90 on 1 or 2 meds	≥140/90 & <180/120 mmHg on 0, 1, or 2 meds; *and* Previous or currently prescribed BP meds	≥140/90 on ≥3 meds (including a diuretic)
Daytime ABP	≥135/85 & <170/105 mmHg after washout	≥135/85 & <170/105 mmHg after washout	≥135/85 mmHg after stabilization
BP Meds	0, 1, or 2	0, 1, or 2	At least 3
Sample size	146 (1:1 randomization)	224 (2:1 randomization)	136 (1:1 randomization)

OBP/ABP = Office/ambulatory blood pressure



Statistical Analysis Plan

Wei-Chen Chen, PhD
Statistician
Office of Clinical Evidence and Analysis

Paradise uRDN Clinical Trials

Differences in statistical analysis plan

1. **SOLO & TRIO:**
   - No prespecified primary safety endpoint
   - Primary effectiveness endpoint was prespecified and tested
2. **RADIANCE-II:**
   - Primary safety endpoint was prespecified and tested
   - Primary effectiveness endpoint was prespecified and tested

Primary Safety Endpoint

Analysis Population: RADIANCE-II

- The primary safety endpoint was defined as the occurrence of at least one of major adverse events (MAE) at 30 days
  - All-cause mortality
  - New onset acute end-stage renal disease
  - Significant embolic event resulting in end-organ damage
  - Renal artery perforation requiring invasive intervention
  - Renal artery dissection requiring an invasive intervention
  - Major vascular complications
  - Hospitalization for hypertensive or hypotensive crisis
  - Hospitalization for major cardiovascular or hemodynamic-related events
  - New stroke or new MI

  or

  New renal artery stenosis (RAS), defined as a >70% diameter stenosis confirmed by CTA or MRA at 6 months

Additional analysis for pooled SOLO, TRIO, & RADIANCE-II trials

Primary Safety Evaluation

Statistical Hypothesis and Analysis

- **Safety event rate performance goal (PG) = 9.8%**, derived from literature review
- The primary safety null and alternative hypotheses are:

  H_0: $\pi \geq 9.8\%$

  H_a: $\pi < 9.8\%$

  where π is the proportion of subjects who had experienced at least one safety endpoint event.

- The upper limit of one-sided exact 95% confidence interval was used to determine endpoint success (i.e., less than PG).

Primary Effectiveness Endpoint

For each of three trials (SOLO, TRIO, RADIANCE-II), the primary effectiveness endpoint was defined as the change in daytime ASBP from baseline to two months

- Daytime: 7:00 AM – 10:00 PM

Primary Effectiveness Endpoint
Statistical Hypothesis

Hypothesis

$H_0: \beta_{txt} = 0$

$H_a: \beta_{txt} \neq 0$

where β_{txt} is the regression coefficient from the **Analysis of Covariance (ANCOVA)** model:

$$Y = \beta_0 + \beta_{txt} * X_{trt} + \beta_{bl} * X_{bl} + \text{residual}$$

and

- Y : the reduction in daytime SBP from baseline to 2 months post procedure
- β_0 : the intercept
- β_{txt} : the regression coefficient associated with the treatment effect (i.e., parameter of interest)
- X_{trt} : an indicator variable with a value of 1 for uRDN and 0 for Sham
- β_{bl} : the regression coefficient associated with the baseline daytime SBP
- X_{bl} : the baseline daytime SBP (i.e., baseline adjustment)

Primary Effectiveness Endpoint
Statistical Analysis

- Primary analysis based on Intention-to-treat (ITT) population
- The treatment effect (β_{txt}) was tested at the two-sided 0.05 alpha level
  - Mean difference between uRDN and Sham adjusting with baseline BP was reported
- Additional prespecified analysis
  - When the assumption of normality for the ANCOVA model may be in question, an **ANCOVA on the ranks** (Quade (1967)) was performed.
- Exploratory analysis
  - Median (Hodges-Lehmann estimate): Summarizes the distribution of BP reduction without adjusting for baseline BP

Primary Effectiveness Endpoint

Missing Data

Imputation

- In all three trials (SOLO, TRIO, and RADIANCE-II)
  - For subjects who met “High BP Action” escape criteria, the last BP measurement prior to medication change was used
- In SOLO and TRIO
  - For subjects missing BP values, a value of zero was used for the BP reduction
- In RADIANCE-II
  - Multiple imputation methods
  - Imputation model included age, sex, and baseline ambulatory SBP
  - Twenty (20) imputed datasets were produced and combined via Rubin’s rules for statistical inference

Secondary and Additional Effectiveness Endpoints

- Secondary endpoints
  - Change from baseline to two months
    - 24-hour SBP & DBP
    - Nighttime SBP & DBP
    - Daytime DBP
    - Office SBP & DBP
    - Home SBP and DBP
- Additional endpoints
  - Incidence of BP reduction (≥5, 10, 15, 20 mmHg)
  - Proportion with BP control (<135/85 mmHg)
  - Medication burden
    - Number of antihypertensive medication
    - Antihypertensive medication load index

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

Subgroup Analysis

Primary Effectiveness Endpoint

1) Age
2) Race
3) Sex
4) Geography: US vs EU/UK
5) Baseline daytime ASBP (<median vs. ≥median)
6) Baseline office SBP (<median vs. ≥median)
7) Baseline home SBP (<median vs. ≥median)
8) Average baseline 24-hour ABP heart rate (above and below median)
9) eGFR (<60 vs ≥60)
10) Abdominal obesity (split for male >102cm and ≤102cm; and for female >88cm and ≤88cm)
11) Number of ablations performed (Treatment Group only)
12) Presence of untreated accessory arteries (Treatment Group only)
13) Balloon size (Treatment Group only)
14) Pre/post COVID-19 enrollment

Statistical Considerations

- Gatekeeping procedure used to control overall type I error rate for secondary endpoints
  - 24-hour SBP & DBP (SOLO, TRIO, RADIANCE-II)
  - Nighttime SBP & DBP (SOLO and TRIO only)
  - Daytime DBP (RADIANCE-II only)
  - Office SBP & DBP (RADIANCE-II only)
  - Home SBP and DBP (RADIANCE-II only)
- P-values in other secondary, additional, and exploratory analyses were not adjusted for multiplicity and should be interpreted with caution.

Clinical Study Results

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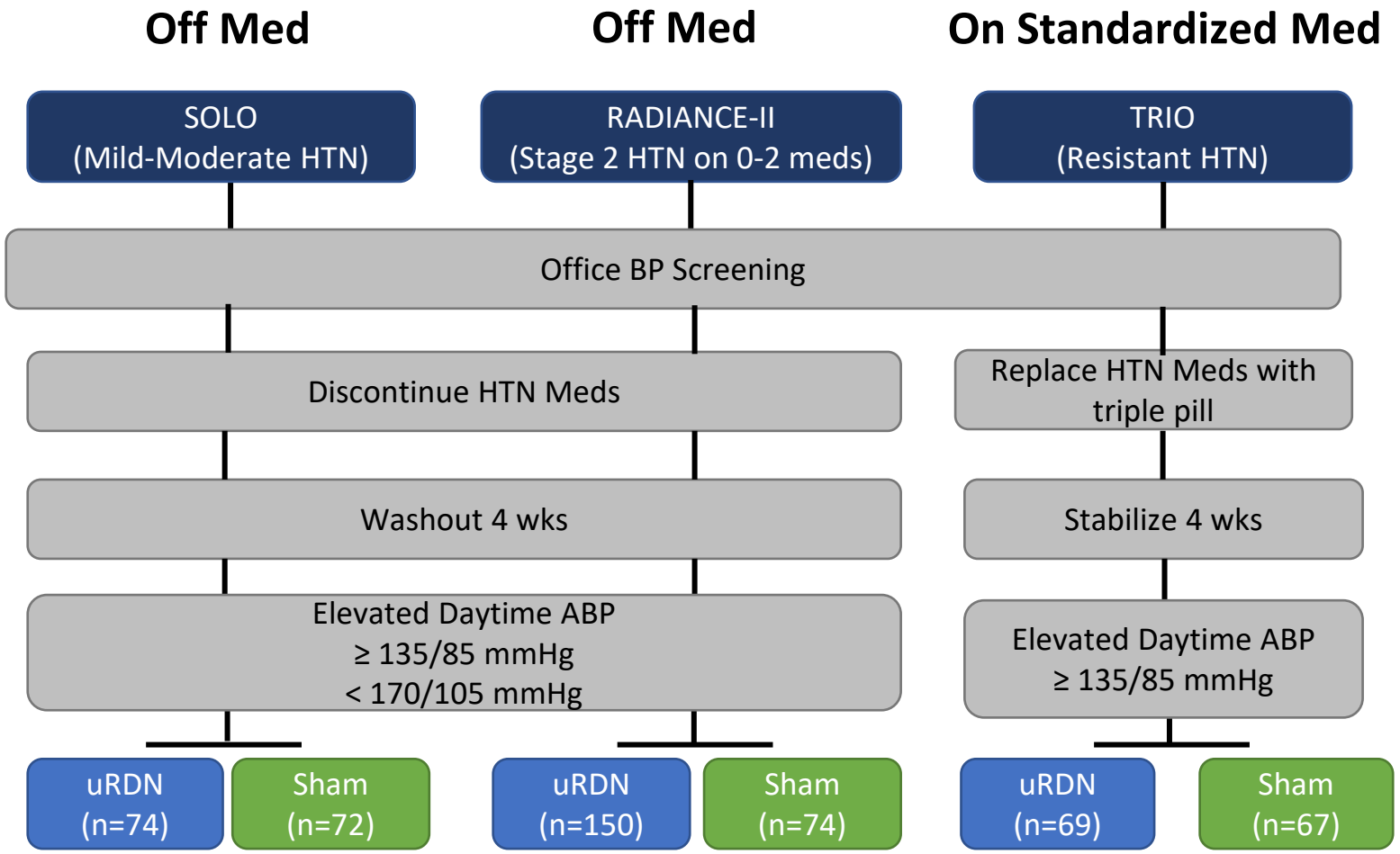
Nephrologist
Office of Gastrorenal, ObGyn, General Hospital, and Urology Devices

Clinical Study Design Overview



Medication Escalation

- **Between 2-6 months to goal (≤135 mmHg)**

Blinding:

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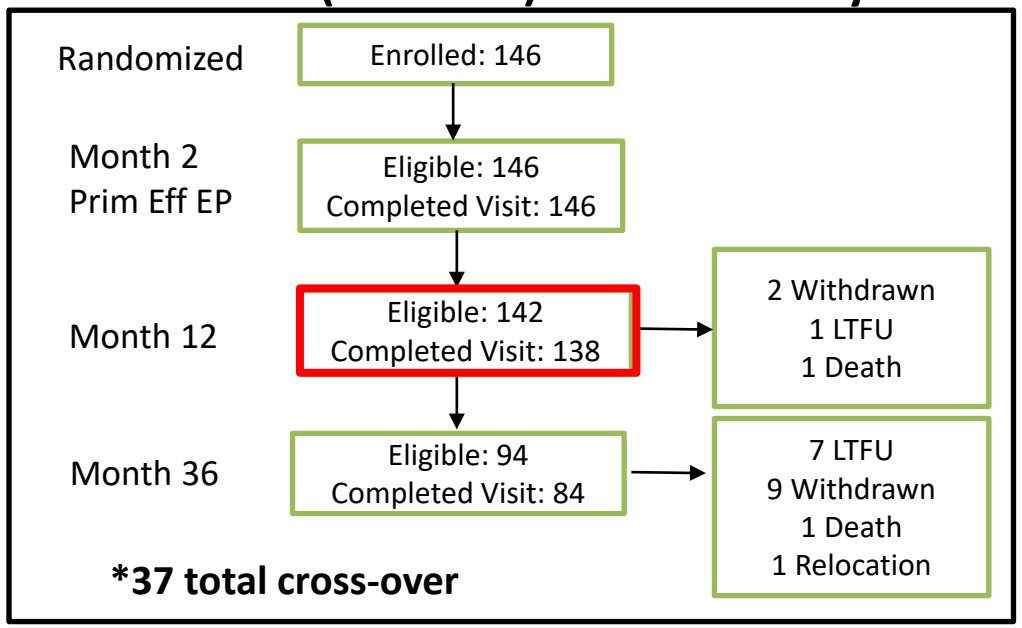
- **RADIANCE II: Thru 12 months**

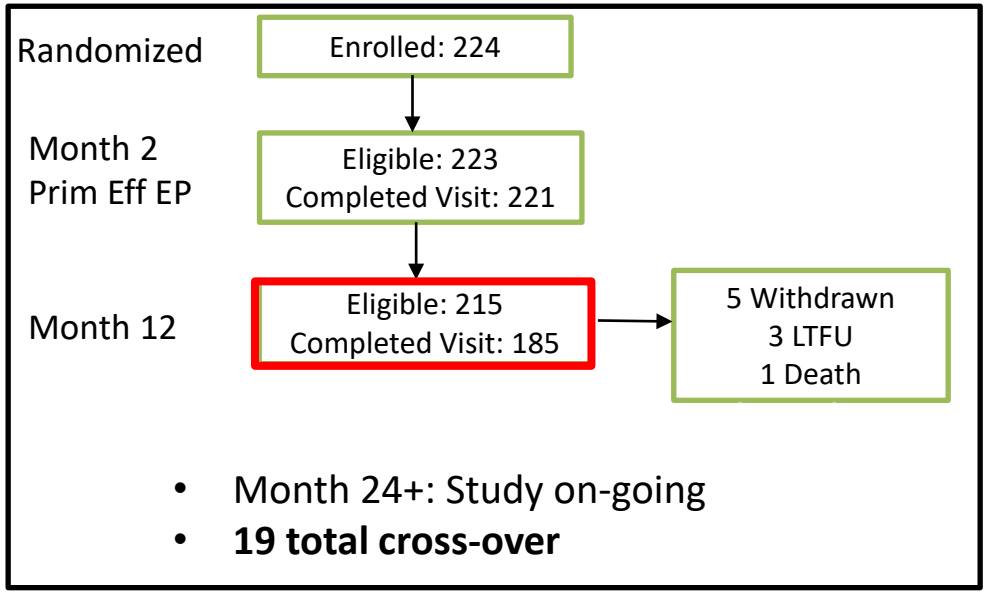
Sham crossover to RDN permitted:

- **SOLO and TRIO: At 6 months**
- **RADIANCE II: At 12 months**

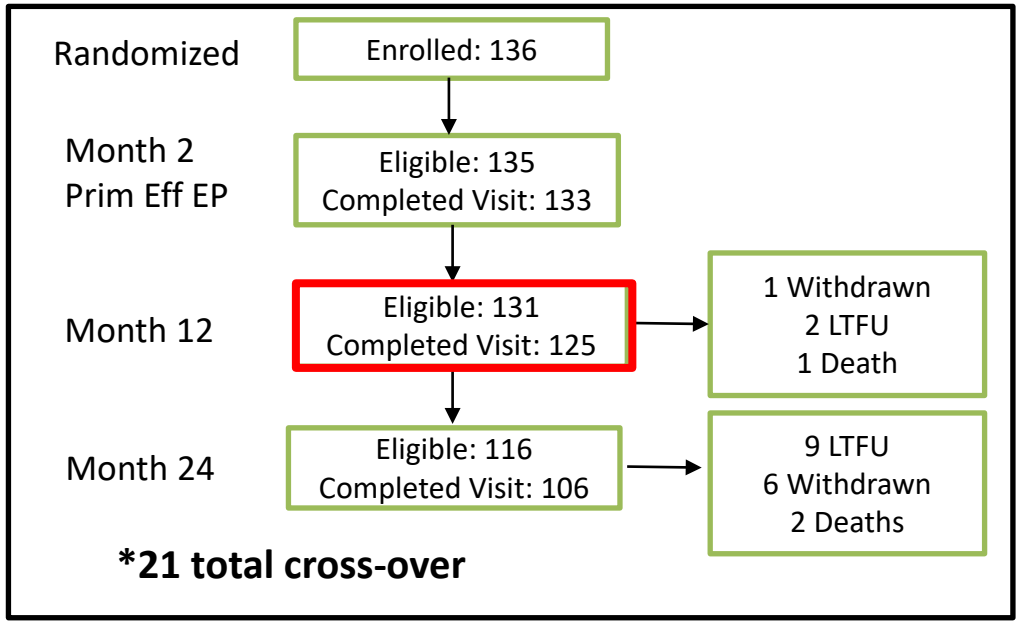
SOLO (Off-Med) Accountability



RADIANCE-II (Off-Med) Accountability



TRIO (On-Standardized Med) Accountability



Key Baseline Patient Features

	SOLO (Off-Med)		RADIANCE-II (Off-Med)		TRIO (On-Standardized Med)	
Measure	uRDN (n=74)	Sham (n=72)	uRDN (n=150)	Sham (n=74)	uRDN (n=69)	Sham (n=67)
Sex						
Male	62.2%	54.2%	68.7%	77.0%	81.2%	79.1%
Female	37.8%	45.8%	31.3%	23.0%	18.8%	20.9%
Age	54.4 ± 10.2	53.8 ± 10.0	55.1 ± 9.9	54.9 ± 7.9	52.3 ± 7.5	52.8 ± 9.1
Geography						
US	47.3%	47.2%	66.7%	62.2%	40.6%	37.3%
OUS	52.7%	52.8%	33.3%	37.8%	59.4%	62.7%
Race						
American Indian or Alaska Native	0.0%	0.0%	0.0%	0.0%	0.0%	1 (1.52%)
Asian	1.3%	0.0%	0.0%	1.3%	1.5%	1.5%
Black	16.2%	18.0%	14.0%	20.2%	20.6%	19.7%
Caucasian	81.0%	72.2%	76.0%	75.6%	66.2%	77.3%
Hispanic or Latino	1.3%	5.5%	10.0%	2.7%	7.4%	0.0%
Native Hawaiian or other Pacific Islander	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
Other/Mixed Race	0.0%	0.0%	10.0%	2.7%	4.41%	0.0%
BMI	29.9 ± 5.9	29.0 ± 5.0	30.1 ± 5.2	30.6 ± 5.2	32.8 ± 5.7	32.6 ± 5.4
Abdominal circumference (cm)	101.5 ± 14.2	98.5 ± 15.1	102.4 ± 12.3	104.3 ± 13.1	109.4 ± 15.5	109.2 ± 12.9
Office SBP (mmHg)	142.6 ± 14.7	144.6 ± 15.9	155.8 ± 11.1	154.3 ± 10.6	161.9 ± 15.5	163.6 ± 16.8
Office DBP (mmHg)	92.3 ± 10.1	93.6 ± 8.3	101.3 ± 6.7	99.1 ± 5.6	105.1 ± 11.6	103.3 ± 12.7

BP Medications at Screening

Number of BP Meds	Randomized (%)	uRDN (%)	Sham (%)
SOLO (Off-Med)			
0	19%	16%	22%
1	42%	45%	39%
2	38%	38%	38%
3	1%	1%	1%
RADIANCE II (Off-Med)			
0	34%	36%	31%
1	34%	35%	34%
2	31%	29%	34%
3	0%	0%	0%
4	0%	0%	1%
TRIO (On-Standardized Med)			
3	40%	39%	42%
4	32%	29%	36%
5	19%	23%	15%
6+	8%	9%	8%

SAFETY ENDPOINT RESULTS

Primary Safety Endpoint

Analysis Population: RADIANCE-II

- The primary safety endpoint was defined as the occurrence of at least one of major adverse events (MAE) at 30 days
  - All-cause mortality
  - New onset acute end-stage renal disease
  - Significant embolic event resulting in end-organ damage
  - Renal artery perforation requiring invasive intervention
  - Renal artery dissection requiring an invasive intervention
  - Major vascular complications
  - Hospitalization for hypertensive or hypotensive crisis
  - Hospitalization for major cardiovascular or hemodynamic-related events
  - New stroke or new MI

  or

  New renal artery stenosis (RAS), defined as a >70% diameter stenosis confirmed by CTA or MRA at 6 months

Additional analysis for pooled SOLO, TRIO, & RADIANCE-II trials

Primary Safety Results: RADIANCE-II and Pooled uRDN Subjects

	N	Rate	95% CI	Performance Goal (PG)	p-value
RADIANCE-II	150	0.0%	0 - 1.63%	9.8%	<0.0001
Pooled uRDN subjects	367	1.1%	0.3% - 2.77%		

Individual Safety Events for uRDN Subjects - Initial Treatment & Crossover

	SOLO	RADIANCE II	TRIO	Combined
N (Initial + Crossover)	109 (72 + 37)	168 (149 +19)	90 (69 +21)	367
30-day events				
All-cause mortality	0	0	2	2
Major vascular complications	0	0	2	2
Hospitalization for hypertensive or hypotensive crisis	0	0	1	1
Hospitalization for major CV or hemodynamic events	1	0	0	1
6-month RAS	0	0	0	0
Total	**1 (0.9%)**	**0**	**5 (3.3%)**	**6 (1.1%)**

Note that endpoints with 0 events are not shown here
Number of Events (% of Subjects with Events)

RADIANCE-II Renal Artery Diameter Stenosis at 6 & 12-Months by CTA/MRA

Follow-up Timepoint	Total Evaluable	1-30% Stenosis	31-50% Stenosis	51-70% Stenosis	>70% Stenosis
6 Months					
uRDN	137	1.5% (2)	0.7% (1)	0.0% (0)	0.0% (0)
Sham	58	0.0% (0)	3.4% (2)	0.0% (0)	0.0% (0)
12 Months					
uRDN	112	2.7% (3)	2.7% (3)	1.8% (2)	0.0% (0)
Sham	14	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)

Data based on core lab analysis

Renal Function (GFR) at 12 Months in SOLO

	uRDN (n = 68)			Sham (n = 67)			Baseline Adjusted	
	Baseline	12 months	Change	Baseline	12 months	Change	Mean Difference (95% CI) (RDN - Sham)[1]	p-value
eGFR	84.46 ± 16.47	83.47 ± 14.61	-0.99 ± 11.18	82.23 ± 15.79	85.63 ± 16.99	3.40 ± 11.53	-3.79 (-7.40, -0.19)	0.0391
Serum Creatinine	0.90 ± 0.18	0.90 ± 0.18	0.01 ± 0.11	0.90 ± 0.18	0.87 ± 0.17	-0.03 ± 0.10	0.04 (0.00, 0.07)	0.0326

Note not all p-values are adjusted for multiplicity.

**Data shown for SOLO study. TRIO study results show statistically similar GFR results in the RDN and Sham arms.*

EFFECTIVENESS ENDPOINT RESULTS

Primary Effectiveness Endpoint

Mean difference in change of daytime (7 AM-10 PM) ASBP between treatment and sham groups from baseline to 2 months after RDN (or Sham) procedure

- Primary analysis population: ITT cohort

Primary Effectiveness Results at 2 Months

ITT Cohort	uRDN change (mmHg)	Sham change (mmHg)	Baseline BP Adjusted Mean Treatment Effect (mmHg)[1]	p-value
Off-Med Trials				
SOLO	-8.5 ± 9.3 (74)	-2.2 ± 10.0 (72)	-6.3 (-9.4, -3.1)	0.0001
RADIANCE-II	-7.9 ± 11.6 (145)	-1.8 ± 9.5 (73)	-6.3 (-9.3, -3.2)	<.0001
On-Standardized-Med Trial				
TRIO	-9.0 ± 14.5 (69)	-4.8 ± 15.9 (67)	-4.5 (-9.6, 0.6)	0.0809

Data presented as mean ± SD (n); difference presented as mean (95% CI); p-value via a baseline adjusted ANCOVA (two-sided).

[1] Negative value favors uRDN.

Additional TRIO Results at 2 Months

ITT Cohort	uRDN change (mmHg)	Sham change (mmHg)	Unadjusted Median Treatment Effect (mmHg)[1]	p-value
On-Standardized-Med Trial				
TRIO (ANCOVA on the ranks)				0.0223
TRIO (median)	-8.0 (69)	-3.0 (67)		
TRIO (Hodges-Lehmann estimate)			-4.5	

Data presented as median (n); p-value via a baseline adjusted ANCOVA on the ranks (two-sided).
[1] Negative value favors uRDN.

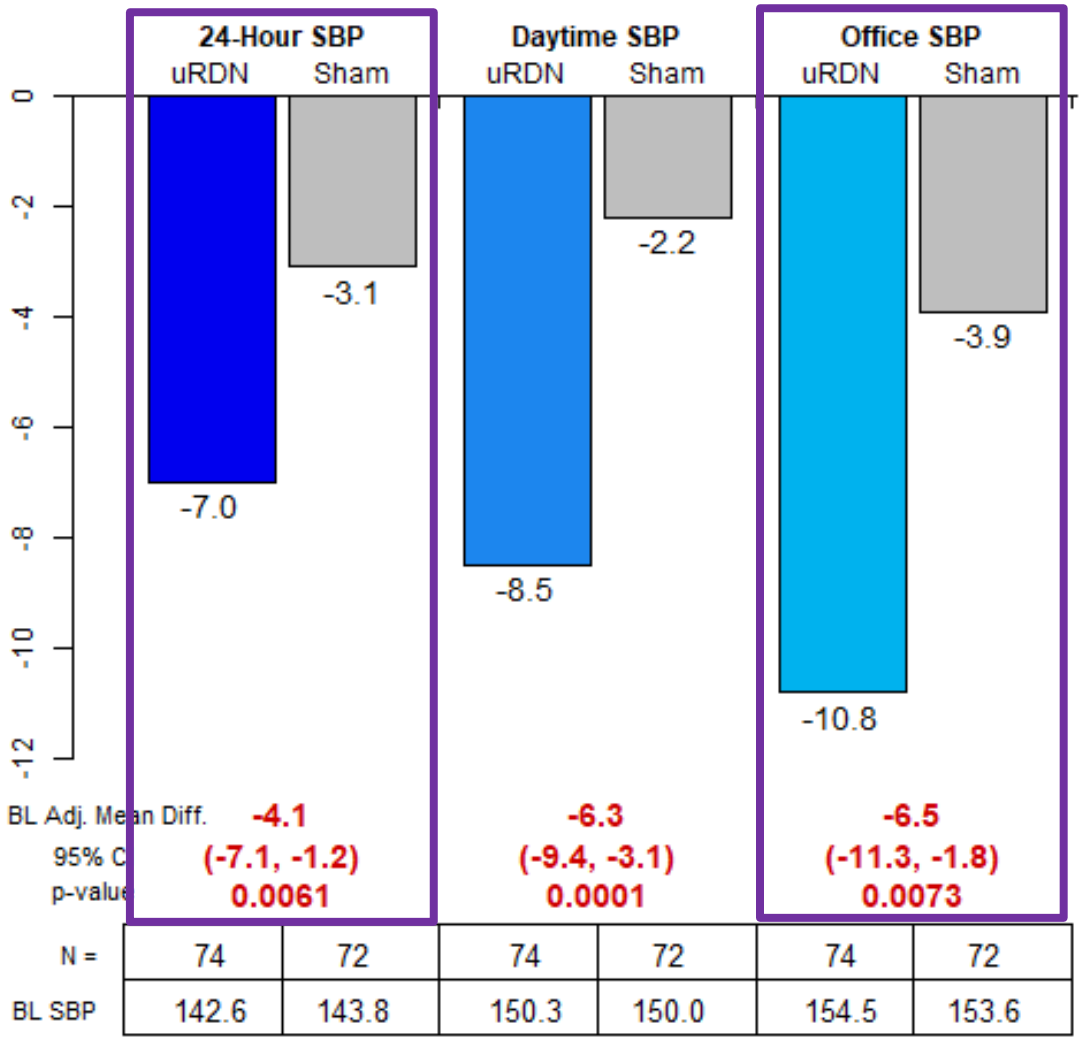
Primary and Secondary Endpoints:

Mean 24-hour SBP, Daytime SBP, and Office SBP at 2 Months

Off-Med Studies

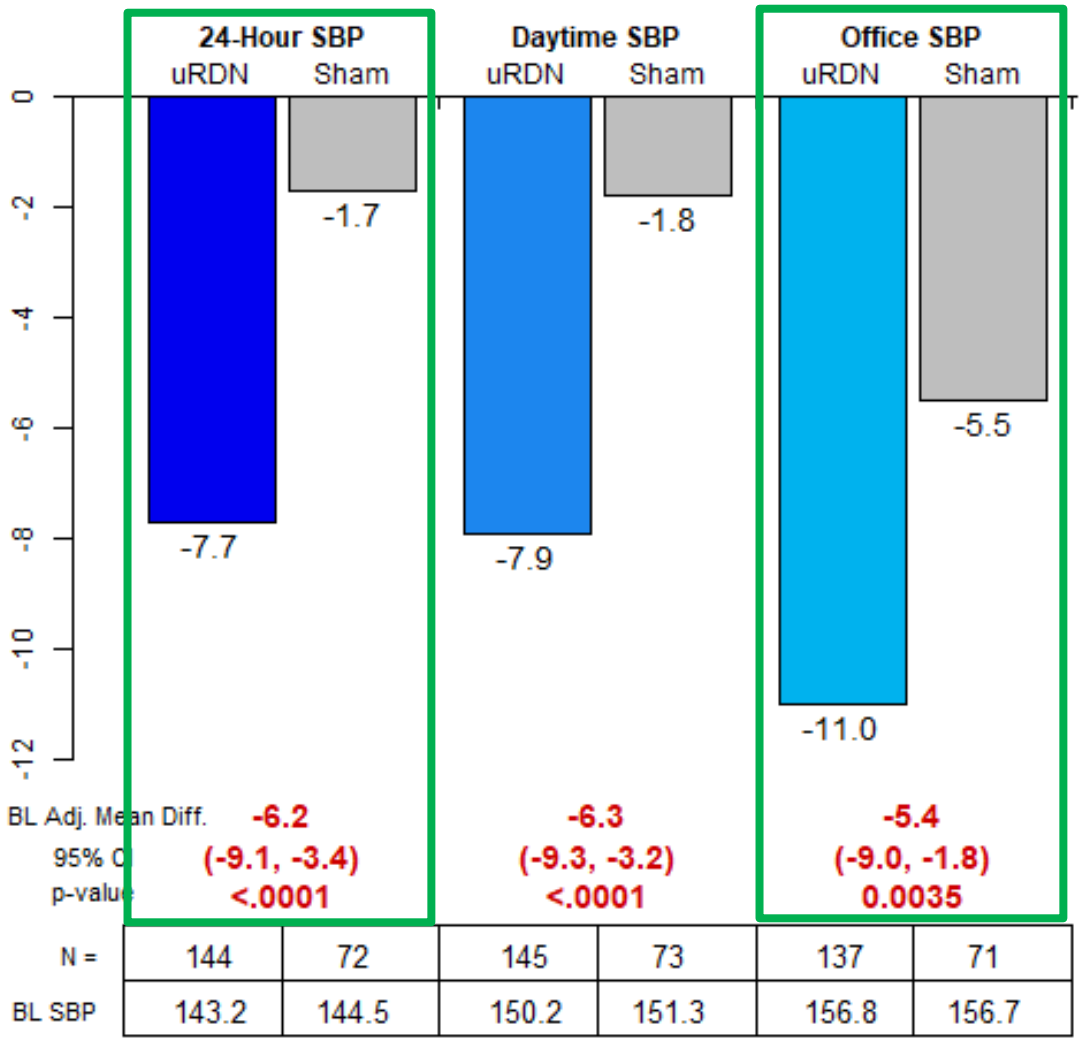
Note not all p-values are adjusted for multiplicity.

SOLO ITT



N =	74	72	74	72	74	72
BL SBP	142.6	143.8	150.3	150.0	154.5	153.6

RADIANCE-II ITT

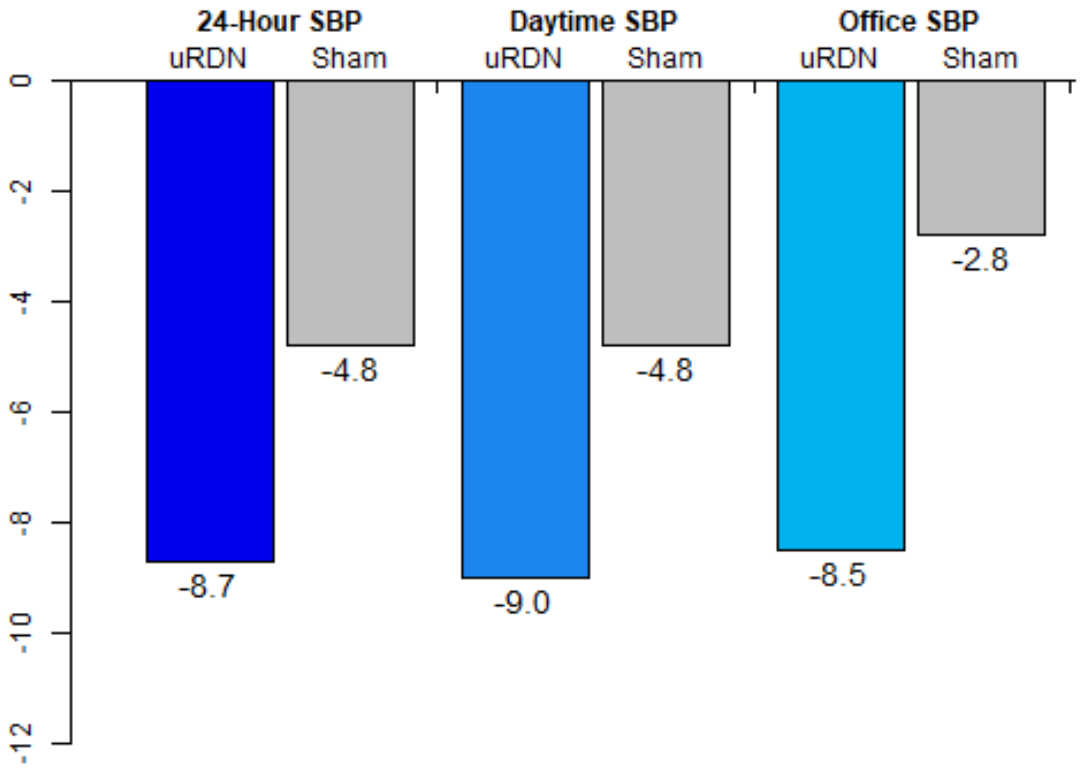


N =	144	72	145	73	137	71
BL SBP	143.2	144.5	150.2	151.3	156.8	156.7

Primary and Secondary Endpoints:
Mean 24-hour SBP, Daytime SBP, and Office SBP at 2 Months

On Standardized Med Study

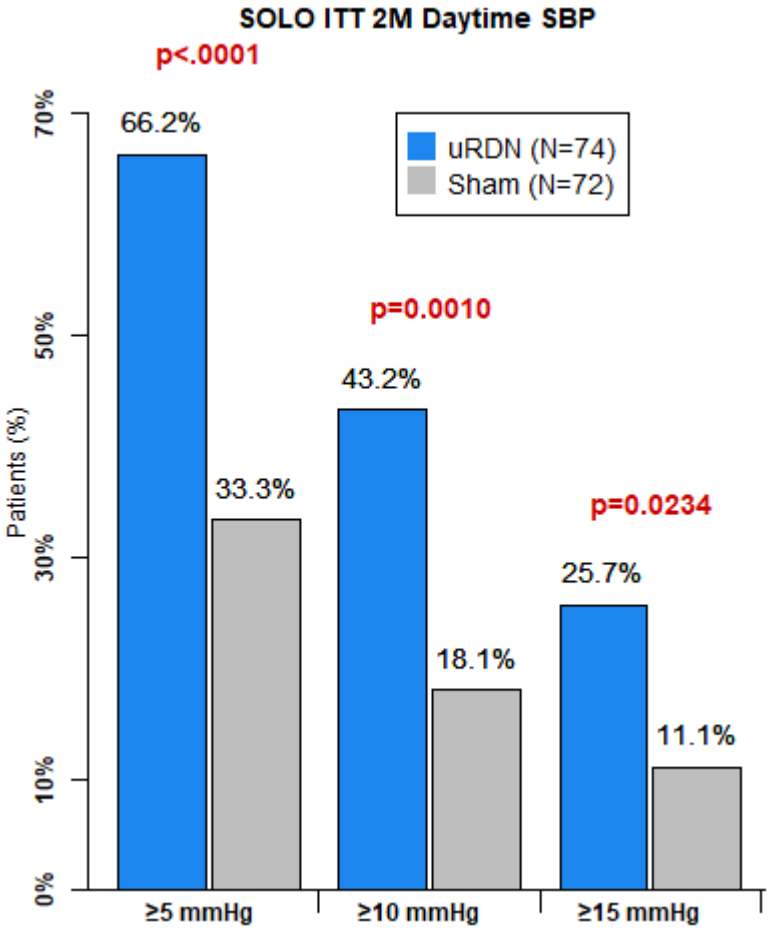
TRIO ITT

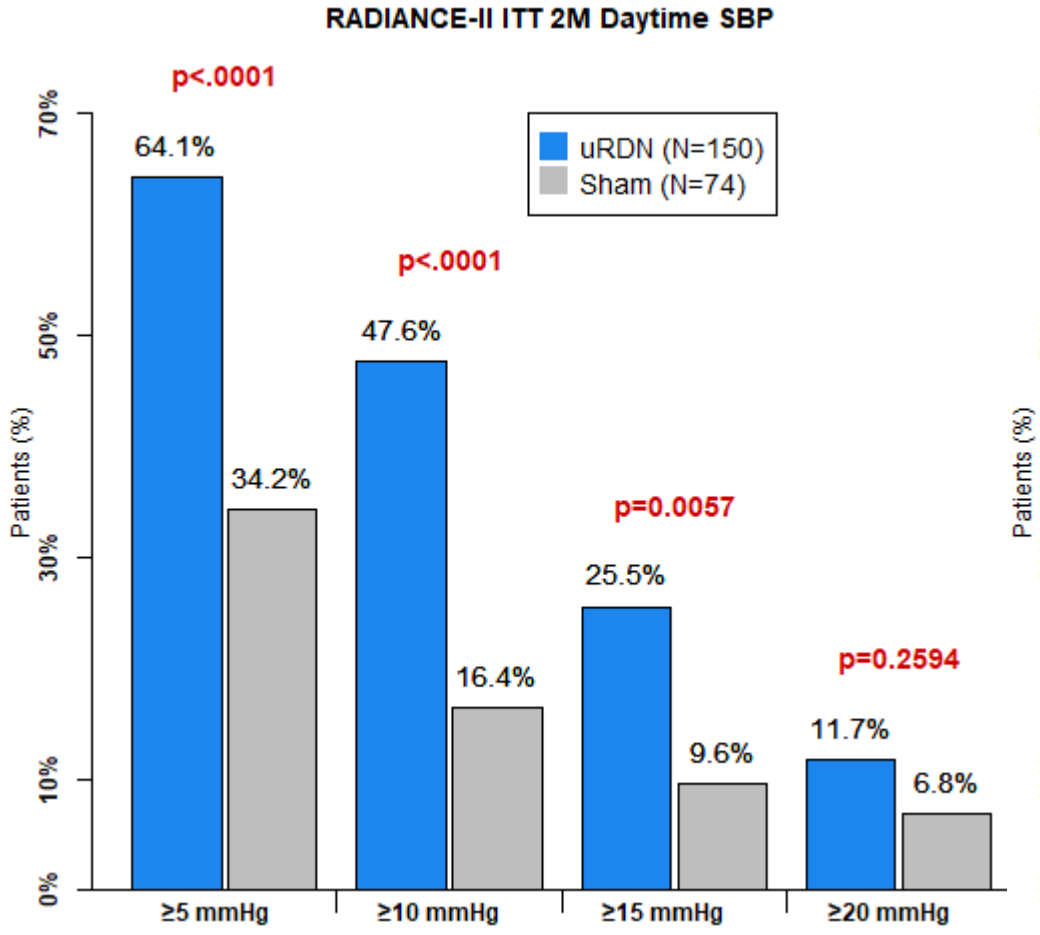


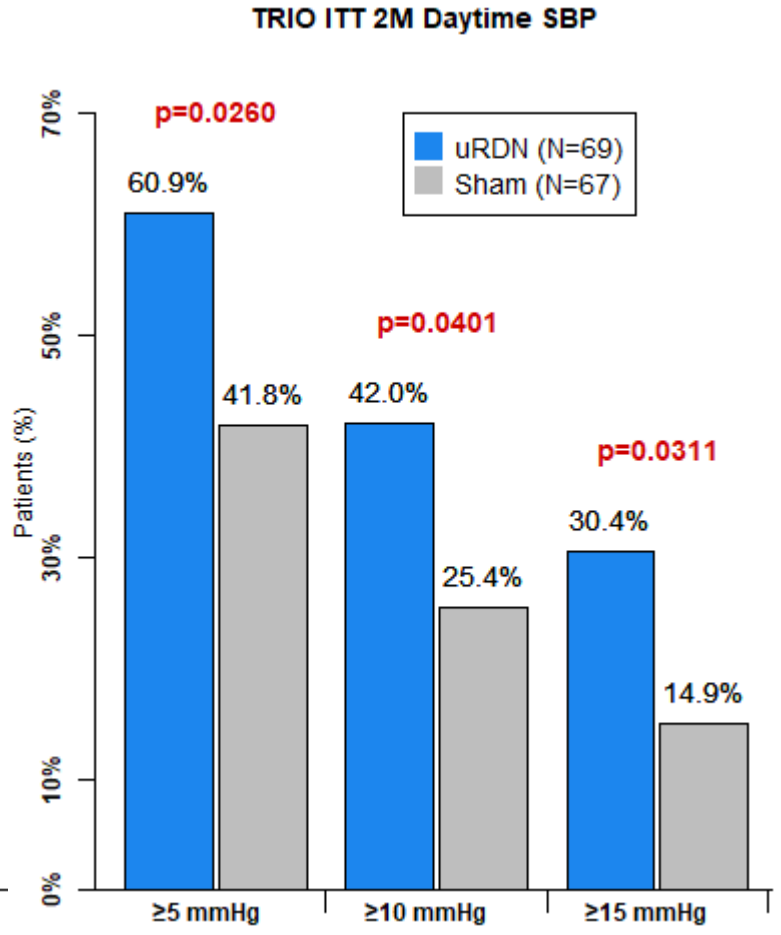
	24-Hour SBP		Daytime SBP		Office SBP	
BL Adj. Mean Diff.	-4.3		-4.5		-5.4	
95% CI	(-9.3, 0.7)		(-9.6, 0.6)		(-11.9, 1.1)	
p-value	0.0895		0.0809		0.1042	
N =	69	67	69	67	64	66
BL SBP	143.9	145.4	150.0	151.1	155.6	154.9

Note not all p-values are adjusted for multiplicity.

Proportion of Subjects with ≥5, ≥10, & ≥15 mmHg Reduction in Daytime SBP at 2 Months





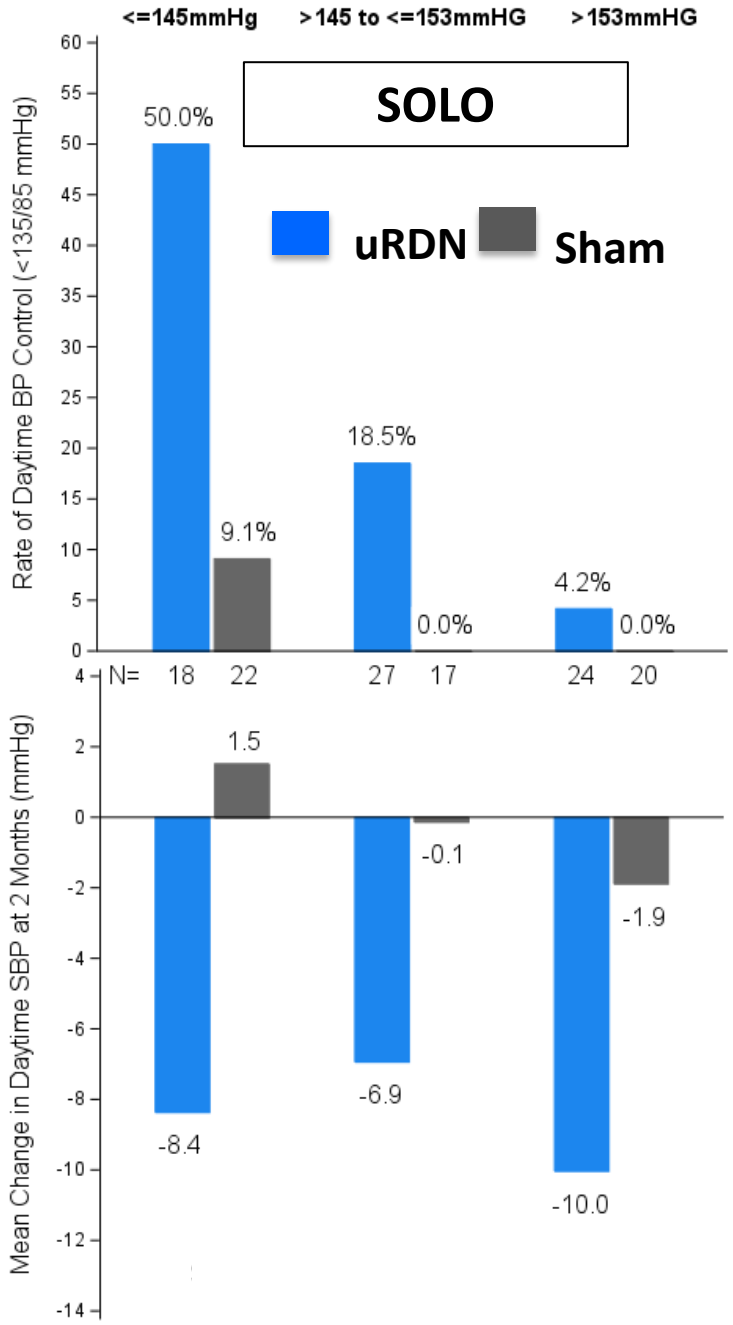


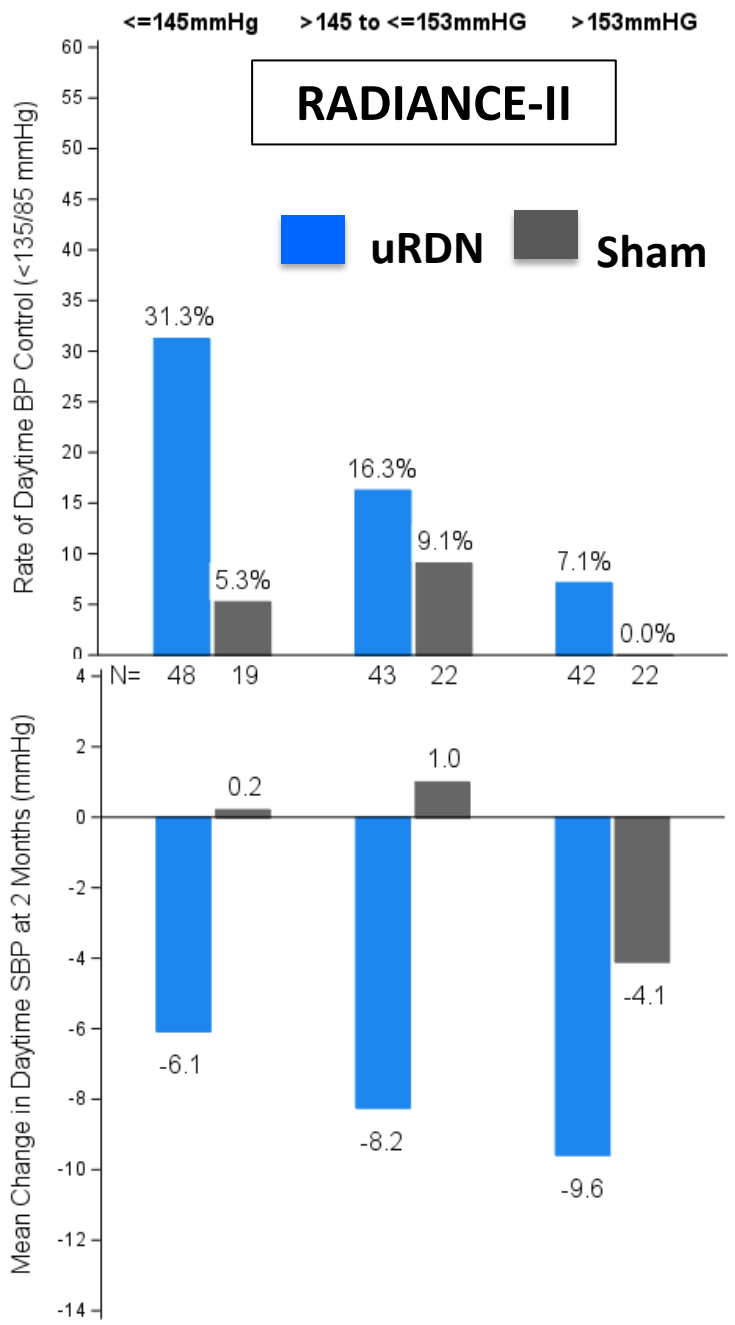
Note not all p-values are adjusted for multiplicity.

Off-Med Studies

ASBP ≤135 at 2 Months as a Function of Baseline ASBP

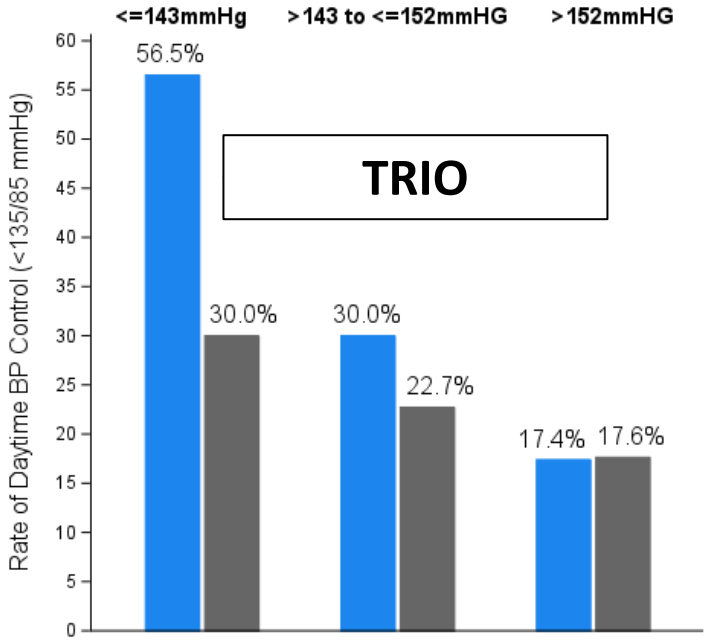
ASBP Change at 2 Months as a Function of Baseline ASBP



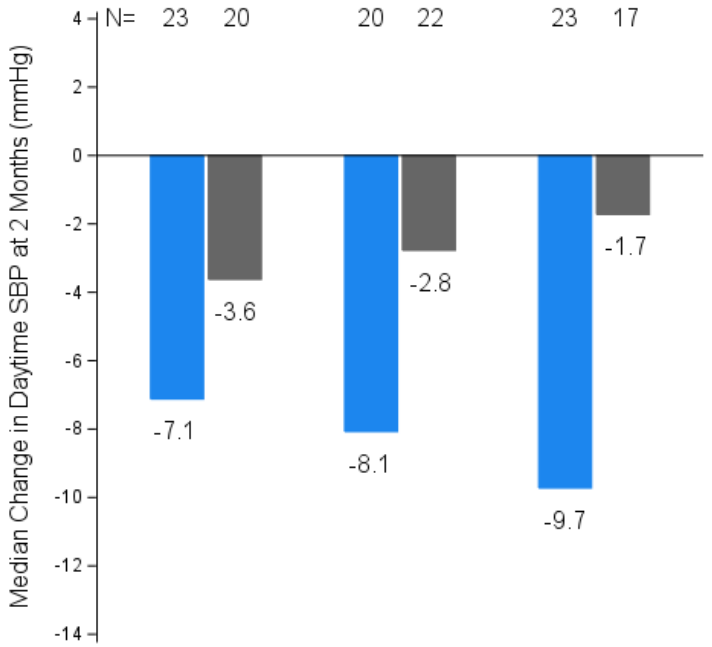


On Standardized Medication Study

ASBP ≤135 at 2 Months as a Function of Baseline ASBP



ASBP Change at 2 Months as a Function of Baseline ASBP

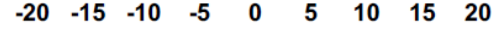


uRDN **Sham**

Off-Med Studies Subgroup Analysis at 2 Months

SOLO ITT

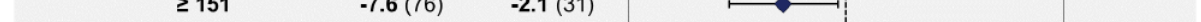
		Δ SBP at 2 Months (n)		Interaction p-value
		uRDN	Sham	
Sex	Male	-7.9 (46)	-1.7 (39)	0.659
	Female	-9.4 (28)	-2.8 (33)	
Race	Black	-7.0 (12)	-2.2 (13)	0.813
	Not Black	-8.7 (62)	-2.2 (59)	
Age	< 55	-9.8 (33)	-1.7 (35)	0.328
	≥ 55	-7.3 (41)	-2.6 (37)	
Location	US	-11.0 (35)	-2.6 (34)	0.180
	OUS	-6.2 (39)	-1.8 (38)	
Abdominal Obesity	Yes	-10.1 (41)	0.0 (44)	0.015
	No	-6.7 (32)	-5.6 (28)	
Daytime ASBP	< 150	-7.2 (39)	-1.4 (35)	0.390
	≥ 150	-9.9 (35)	-2.9 (37)	
Office SBP	< 154	-9.9 (36)	-1.9 (34)	0.340
	≥ 154	-7.1 (38)	-2.4 (38)	



Change from baseline daytime ASBP (mmHg)
Mean difference (uRDN – Sham)

RADIANCE-II ITT

		Δ SBP at 2 Months (n)		Interaction p-value
		uRDN	Sham	
Sex	Male	-8.4 (99)	-2.2 (56)	0.912
	Female	-6.7 (46)	-0.6 (17)	
Race	Black	-10.7 (20)	-2.2 (14)	0.654
	Not Black	-7.4 (125)	-1.8 (59)	
Age	< 56	-8.1 (69)	-1.0 (35)	0.253
	≥ 56	-7.7 (76)	-2.7 (38)	
Location	US	-7.6 (97)	-3.3 (45)	0.150
	OUS	-8.5 (48)	0.5 (28)	
Abdominal Obesity	Yes	-7.1 (87)	-1.2 (45)	0.583
	No	-9.0 (58)	-2.9 (28)	
Daytime ASBP	< 149	-6.6 (72)	-0.4 (33)	0.460
	≥ 149	-9.2 (73)	-3.1 (40)	
Office SBP	< 156	-9.5 (69)	-1.9 (40)	0.709
	≥ 156	-6.4 (76)	-1.8 (33)	
Home SBP	< 151	-8.4 (67)	-1.7 (41)	0.574
	≥ 151	-7.6 (76)	-2.1 (31)	
24-hr AHR	< 72	-6.0 (68)	-2.0 (40)	0.232
	≥ 72	-9.5 (77)	-1.7 (33)	



Note not all p-values are adjusted for multiplicity.

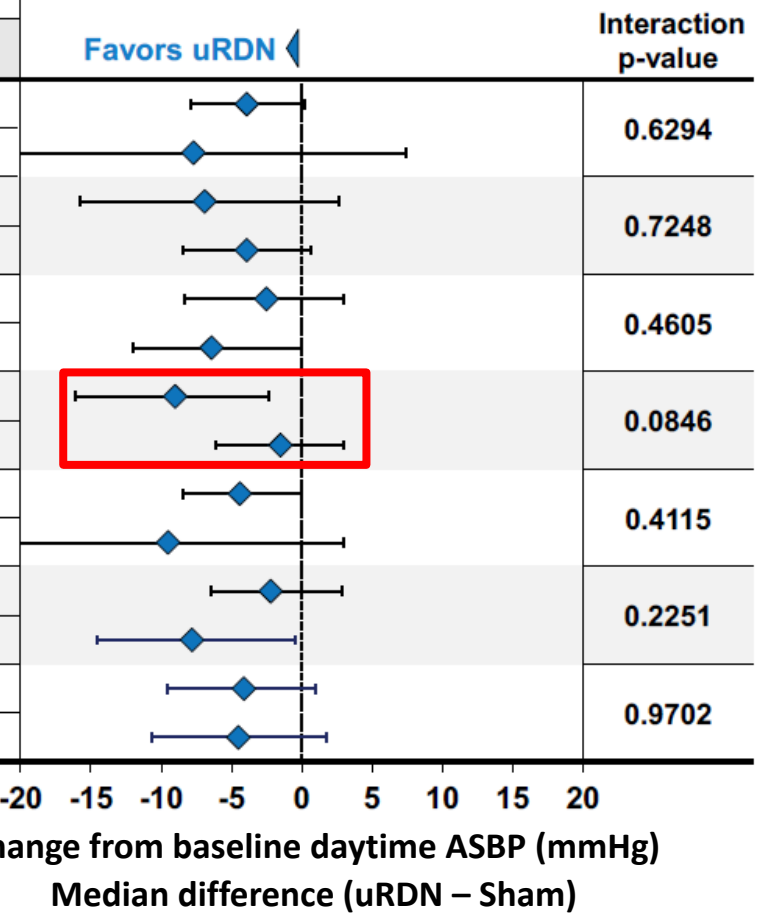
Change from baseline daytime ASBP (mmHg)
Mean difference (uRDN – Sham)

Results generally consistent across subgroups in SOLO and RADIANCE-II

On Standardized Medication Study Subgroups 2 Months

TRIO ITT

		Δ SBP at 2 Months (n)		Interaction p-value
		uRDN	Sham	
Sex	Male	-7.4 (56)	-3.3 (53)	0.6294
	Female	-15.2 (13)	-1.3 (14)	
Race	Black	-9.8 (14)	-5.0 (13)	0.7248
	Not Black	-7.4 (55)	-3.0 (54)	
Age	< Median	-8.0 (38)	-5.0 (30)	0.4605
	≥ Median	-8.0 (31)	-1.7 (37)	
Location	US	-10.5 (28)	-3.0 (25)	0.0846
	OUS	-5.9 (41)	-3.1 (42)	
Abdominal Obesity	Yes	-8.7 (54)	-3.6 (55)	0.4115
	No	-10.0 (12)	-0.3 (12)	
Daytime ASBP	< Median	-7.2 (36)	-3.6 (32)	0.2251
	≥ Median	-12.7 (33)	-1.7 (35)	
Office SBP	< Median	-7.3 (33)	-2.5 (32)	0.9702
	≥ Median	-10.1 (36)	-3.9 (35)	



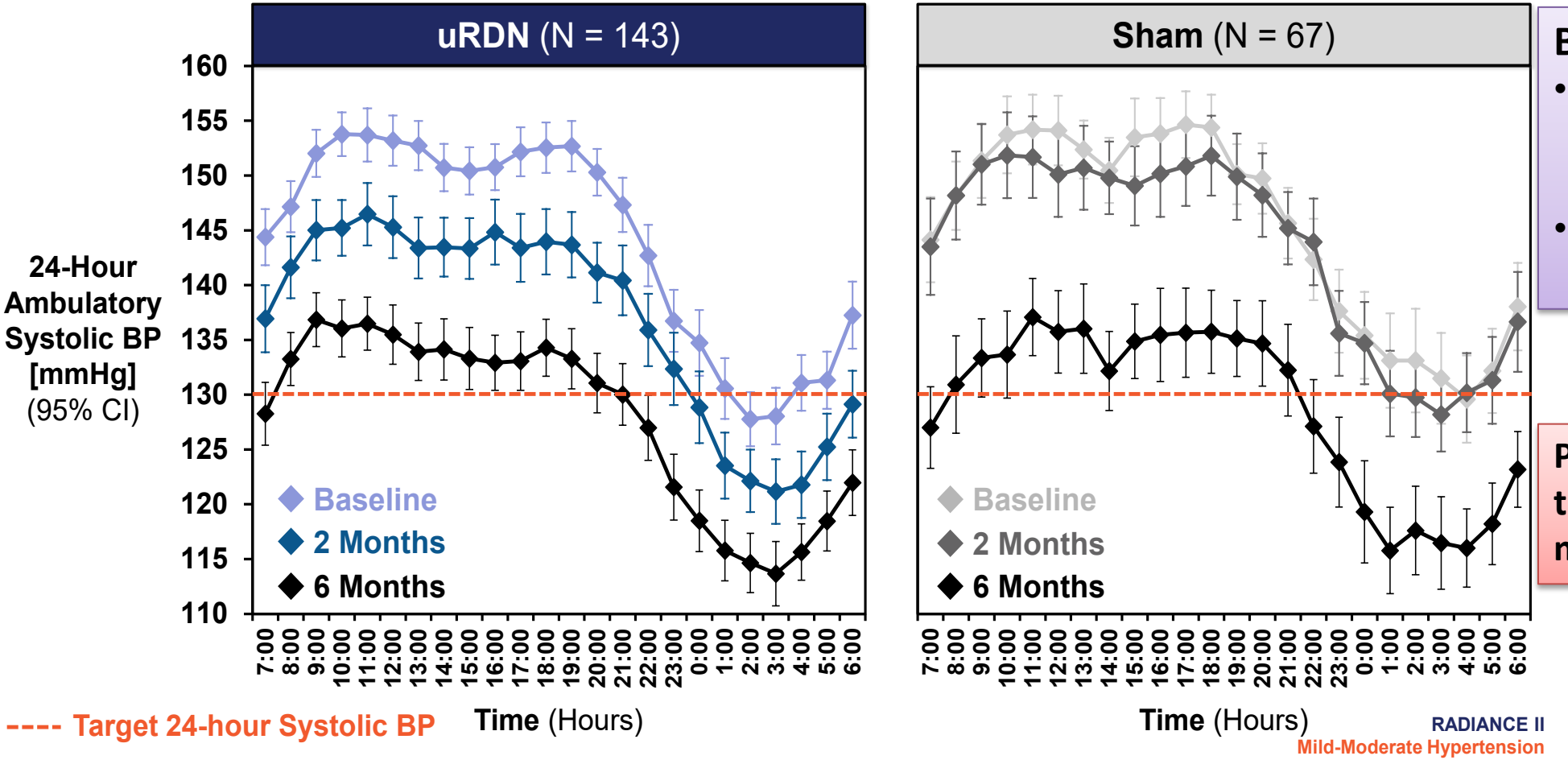
Note not all p-values are adjusted for multiplicity.

Treatment difference in favor of uRDN more pronounced in US subjects and subjects with baseline ASBP ≥ the median

DURABILITY OF BP REDUCTION

Daytime and Nighttime ASBP at Baseline, 2 Months, and 6 Months

RADIANCE-II (OFF-Med Study)



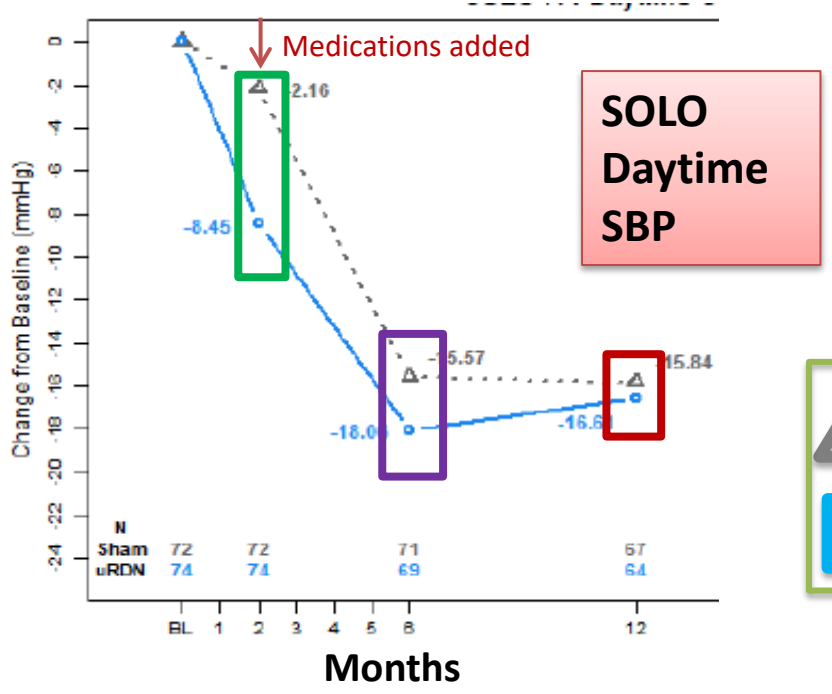
BP Meds:

- **Thru 2 months: Added for emergency only thru 2 months**
- **2-6 months: Added as needed to optimize BP**

Patients blinded to treatment group thru 6 months

Off-Med Studies

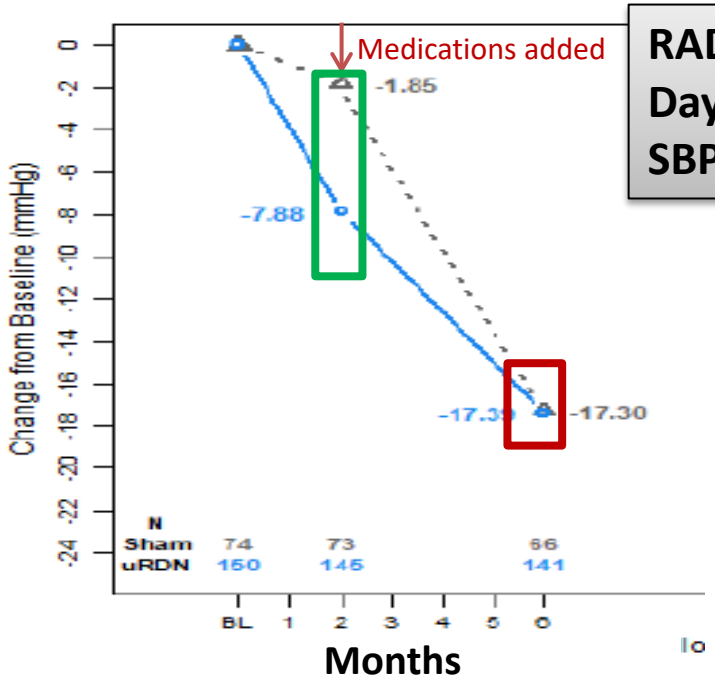
BP Δ from Baseline to Latest Available Follow-up



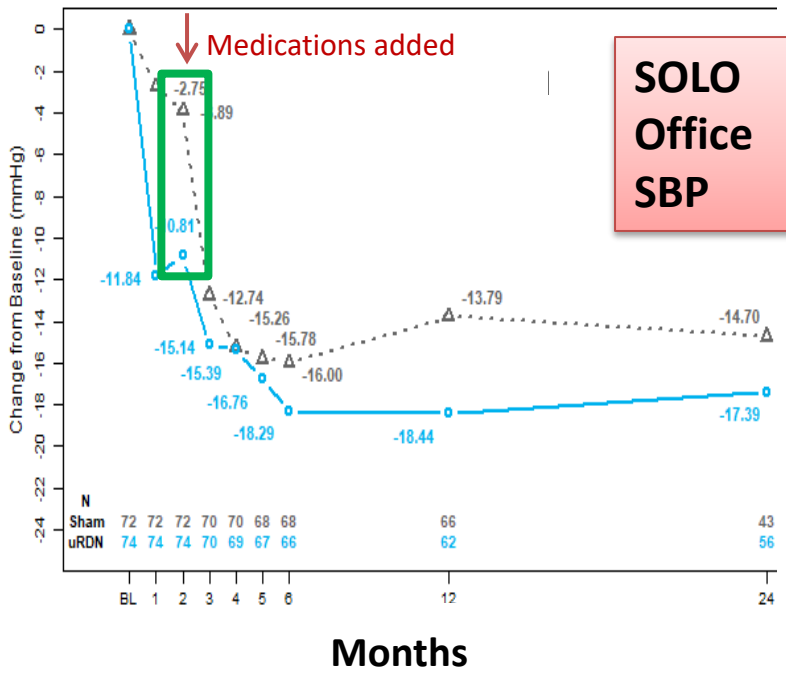
SOLO Daytime SBP

Sham

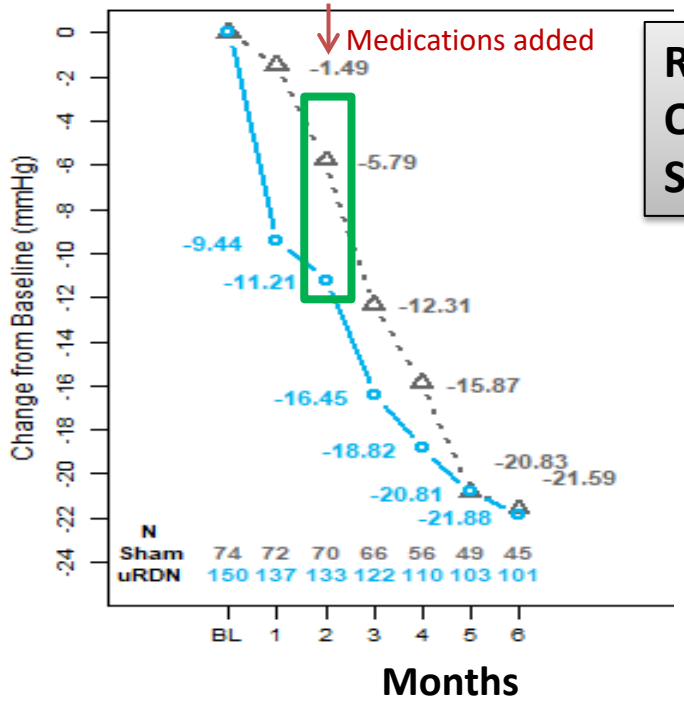
uRDN



RADIANCE-II Daytime SBP



SOLO Office SBP



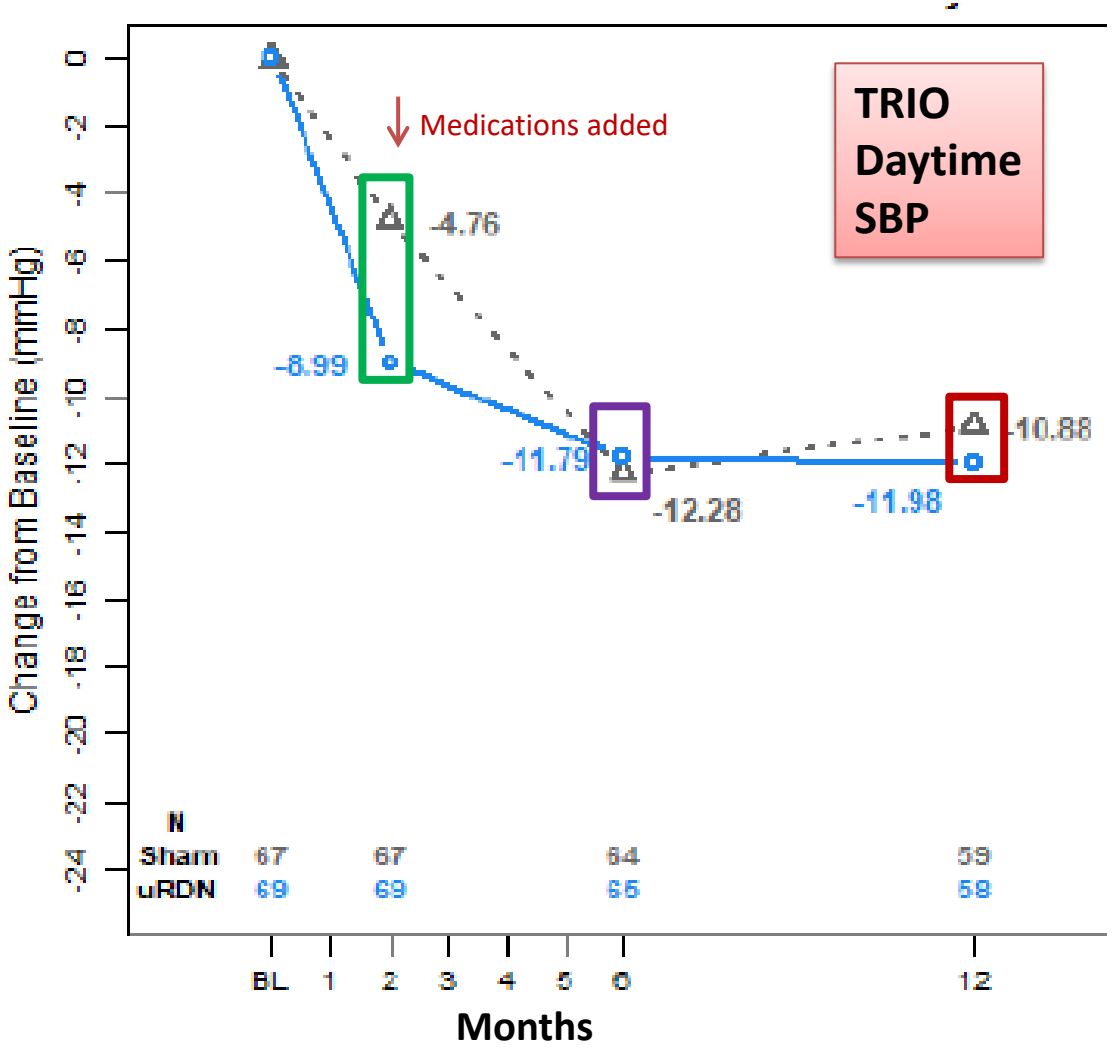
RADIANCE-II Office SBP

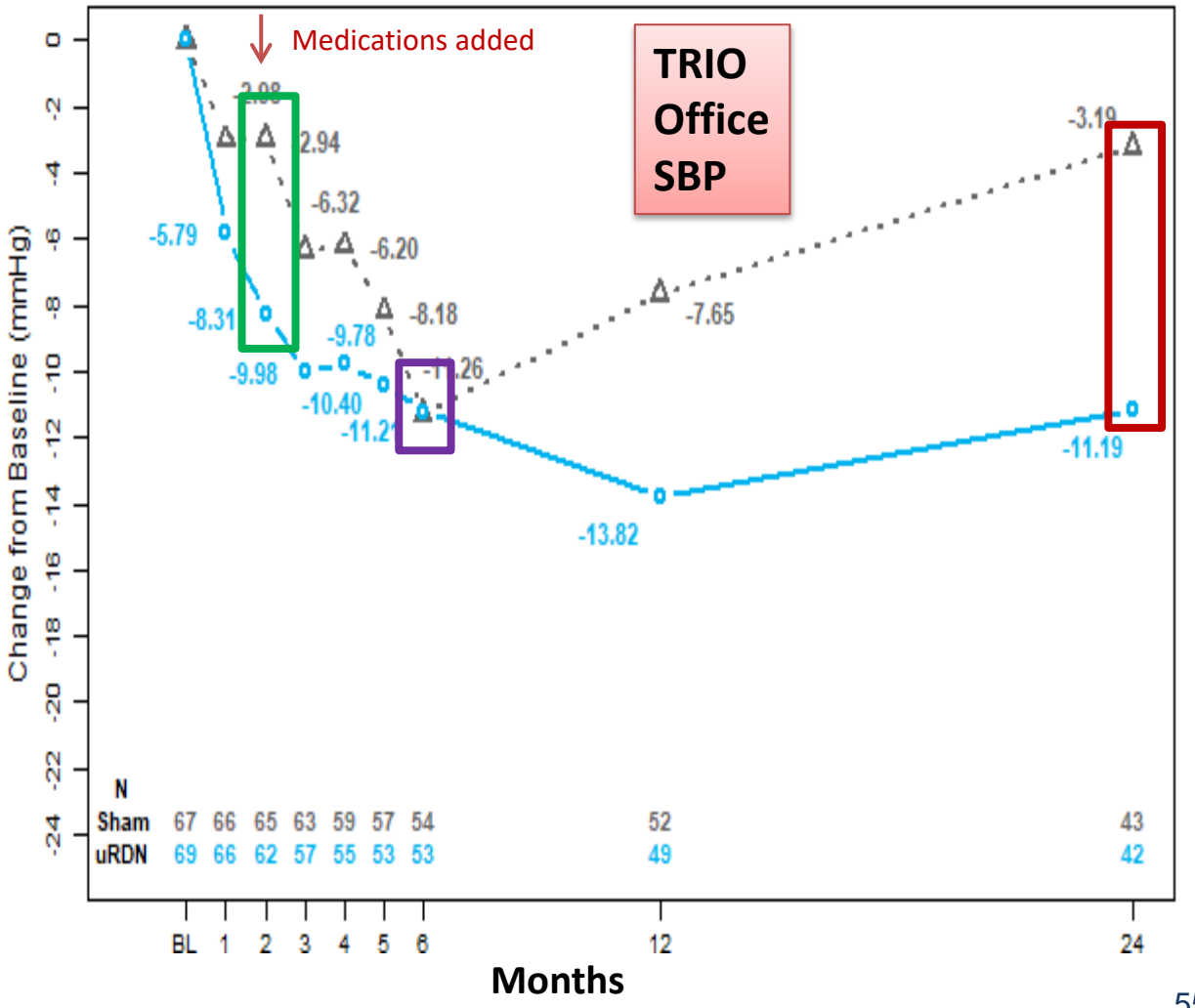
On Standardized Med Study

BP Δ from Baseline to Latest Available Follow-up

Sham

uRDN





Medication Burden

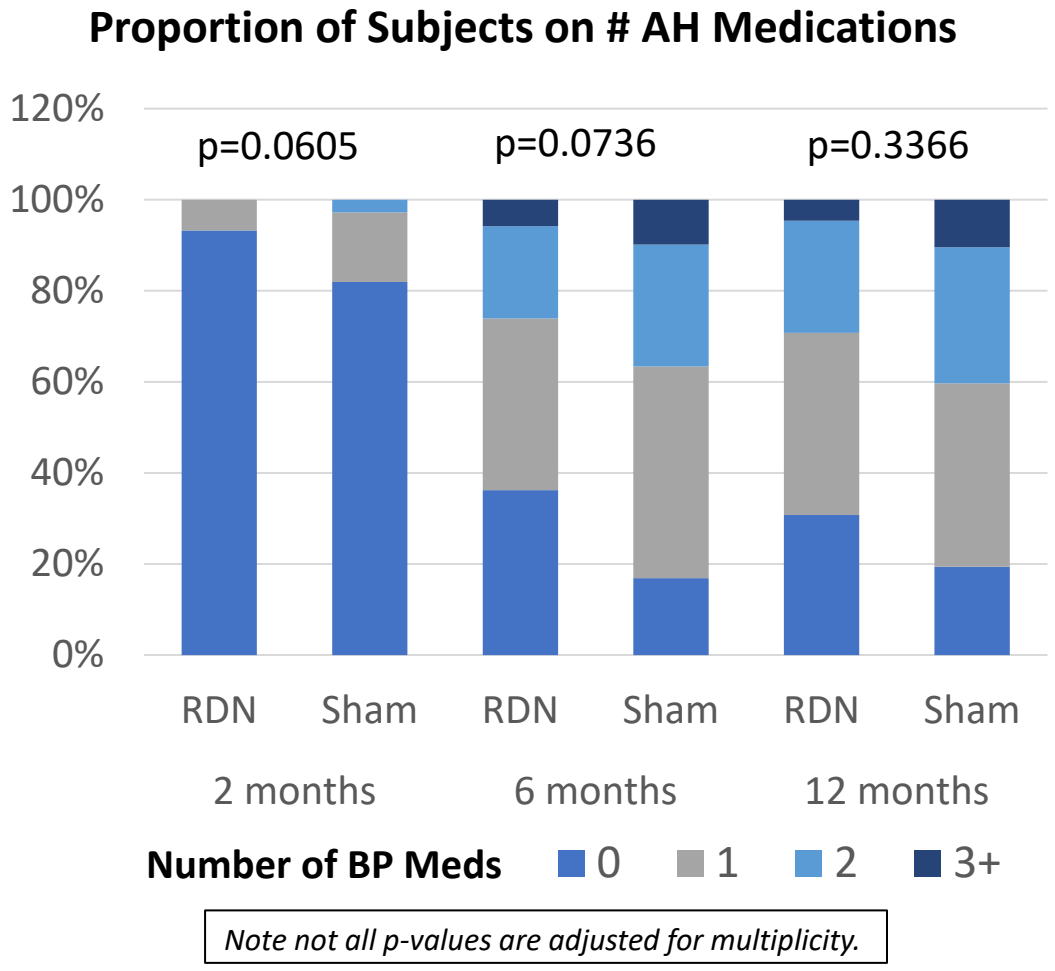
Assessments

- Number of prescribed antihypertensive medications
- Antihypertensive Medication Load Index: Composite based on the dosages of medications

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

Medication Burden – SOLO

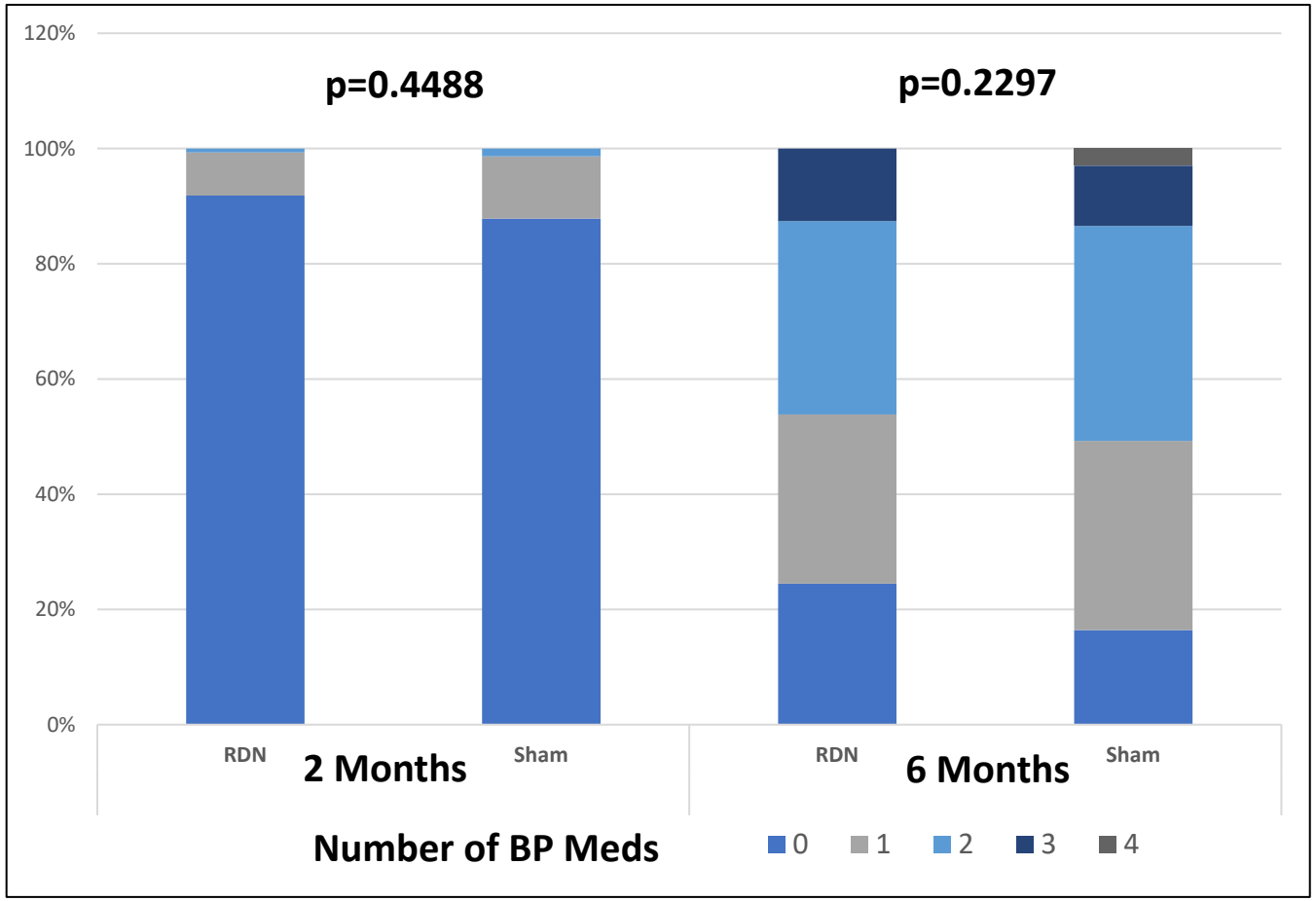
		Change in Daytime ASBP (mmHg)	Change in office SBP (mmHg)	Average number of BP Meds	Med Load Index
2 months	uRDN (N = 74)	-8.5 ± 9.3	-10.8 ± 13	0.1 ± 0.3	0.0 ± 0.1
	Sham (N = 72)	-2.2 ±10.0	-3.9 ±17.4	0.2 ± 0.5	0.1 ± 0.3
6 months	uRDN (N = 69)	-18.1 ± 12.2	-18.2 ± 14.2	1.0 ± 0.9	0.5 ± 0.4
	Sham (N=71)	-15.6 ± 13.2	-15.9 ± 17.2	1.3 ± 0.9	0.7 ± 0.5
12 months	uRDN (N = 65)	-16.5 ± 12.9	-18.1 ± 14.9	1.0 ± 0.9	0.5 ± 0.5
	Sham (N = 67)	-15.8 ± 13.1	-13.6 ± 17.2	1.3 ± 0.9	0.7 ±0.5



Note not all p-values are adjusted for multiplicity.

Medication Burden Off-Med Study
RADIANCE-II

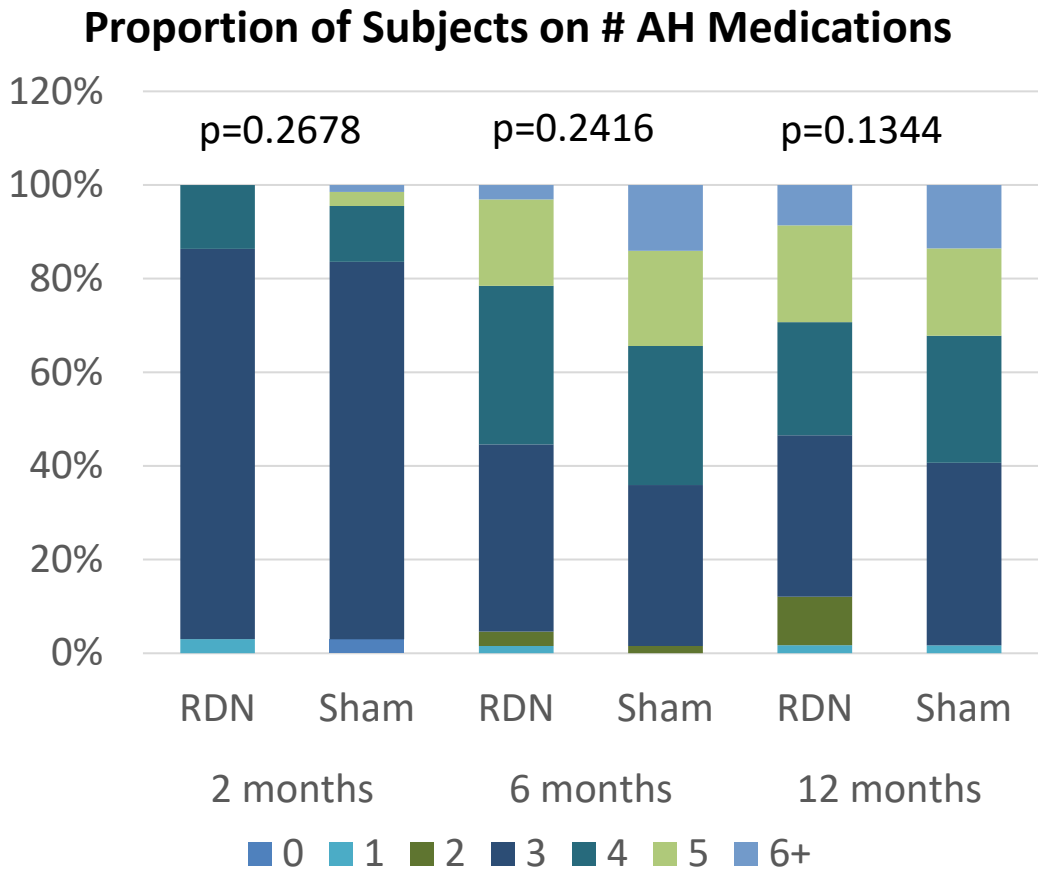
		Daytime ASBP Δ (mmHg)	Office SBP Δ (mmHg)	Average # of BP Meds	Med Load Index
2 months	uRDN	-7.9 ± 11.6 (145)	-11.0 ± 13.5 (137)	0.1 ± 0.3	0.1 ± 0.2
	Sham	-1.8 ± 9.5 (73)	-5.5 ± 12.9 (71)	0.1 ± 0.4	0.1 ± 0.2
6 months	uRDN	-17.5 ± 11.4 (143)	-20.9 ± 14.8 (143)	1.3 ± 1.0	0.7 ± 0.6
	Sham	-17.4 ± 14.0 (67)	-20.2 ± 16.4 (57)	1.5 ± 1.0	0.8 ± 0.6



Note not all p-values are adjusted for multiplicity.

Medication Burden – TRIO

		Change in Daytime ASBP (mmHg)	Change in office SBP (mmHg)	Average number of BP Meds	Med Load Index
2 months	uRDN	-9.0 ± 14.5 (69)	-8.5 ± 19.1 (64)	3.1 ± 0.5	2.1 ± 0.4
	Sham	-4.8 ± 15.9 (67)	-2.8 ± 20.7 (66)	3.1 ± 0.8	2.1 ± 0.5
6 months	uRDN	-11.8 ± 14.2 (65)	-10.4 ± 16.8 (63)	3.8 ± 1.0	2.3 ± 0.6
	Sham	-12.3 ± 14.2 (64)	-11.2 ± 22.7 (64)	4.1 ± 1.1	2.4 ± 0.6
12 months	uRDN	-12.1 ± 14.1 (59)	-12.6 ± 19.8 (59)	3.7 ± 1.5	2.3 ± 0.9
	Sham	-10.9 ± 18.3 (59)	-7.8 ± 28.9 (59)	4.0 ± 1.2	2.5 ± 0.7



Note not all p-values are adjusted for multiplicity.

Blinding Assessment

- Blinding generally maintained across 3 trials using Bang and James Blinding Indices
- In off-med trials, more sham subjects able to guess correct treatment at 6 months vs baseline.

Patient Preference Study

David Gebben, PhD
Health Economist
Office of Strategic Partnerships and Technology Innovation

Patient Preference Information (PPI)

CDRH Guidance Document: *Patient Preference Information – Voluntary Submission, Review in PMAs, HDE Applications, and De Novo Requests and Inclusion in Decision Summaries and Device Labeling. August 2016*

PPI Definition: Qualitative or quantitative assessments of the relative desirability or acceptability to patients of specified alternatives or choices among outcomes or other attributes that differ among alternative health interventions

- Not a patient-reported outcome (PRO) or other clinical trial endpoint or outcome

Benefit-Risk Determination

- Before considering benefit-risk (B-R), establish a reasonable assurance of safety and effectiveness
- CDRH recognizes the patient preference information can supplement the assessment of benefits and risks
- Patient preference studies consider how patients weigh the benefits and risks of treatment options*

**FDA Guidance: Factors to Consider When Making Benefit-Risk Determinations in Medical Device Premarket Approval and De Novo Classifications Guidance for Industry and Food and Drug Administration Staff (Issued August 30, 2019)*

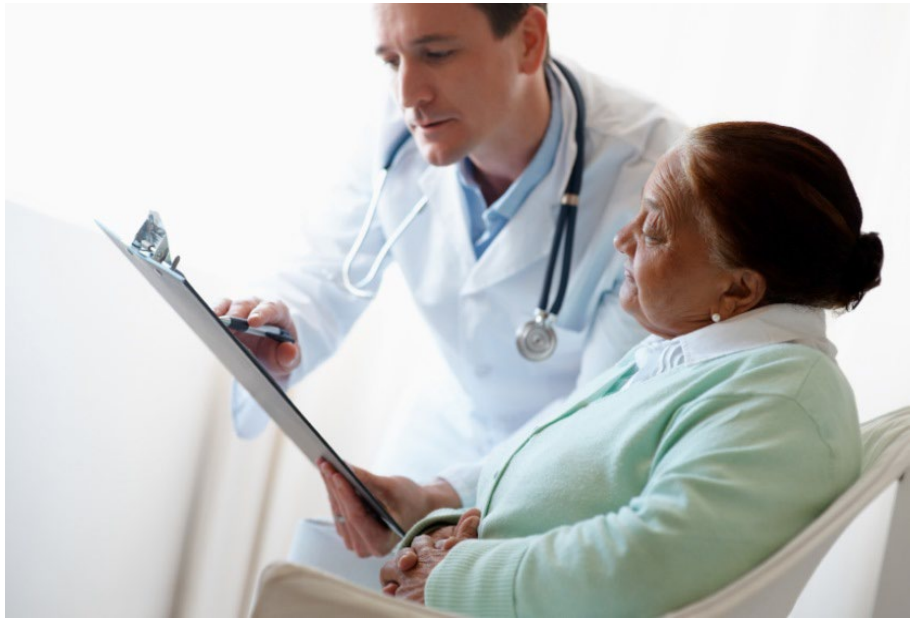
Recommended Qualities of Patient Preference Studies*

Well-designed and conducted patient preference studies can provide valid scientific evidence regarding patients' risk tolerance and perspective on benefit. This may inform FDA's evaluation of a device's benefit-risk profile during the PMA, HDE application, and De Novo request review processes.

A. All about Patients
   - Patient Centeredness
   - Sample Representativeness
   - Capturing Heterogeneous Patient Preferences
   - Comprehension by Study Participants

B. Good Study Design
   - Established Good Research Practices
   - Effective Benefit-Risk Communication
   - Minimal Cognitive Bias
   - Relevance

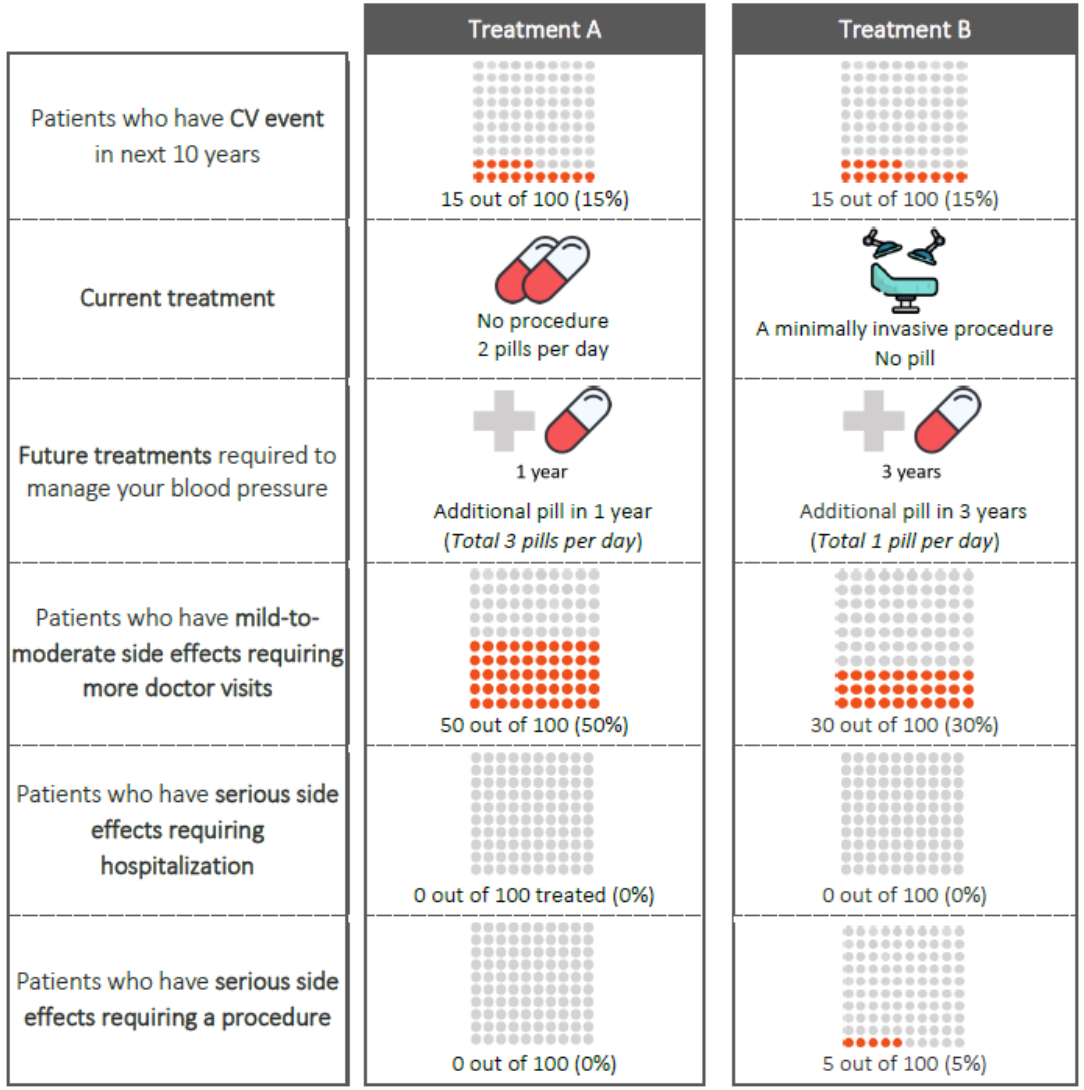
C. Good Study Conduct and Analysis
   - Study Conduct
   - Logical Soundness
   - Robustness of Analysis of Results



***FDA Guidance: Patient Preference Information - Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling (Aug 2016)**

ReCor PPI Study Qualities

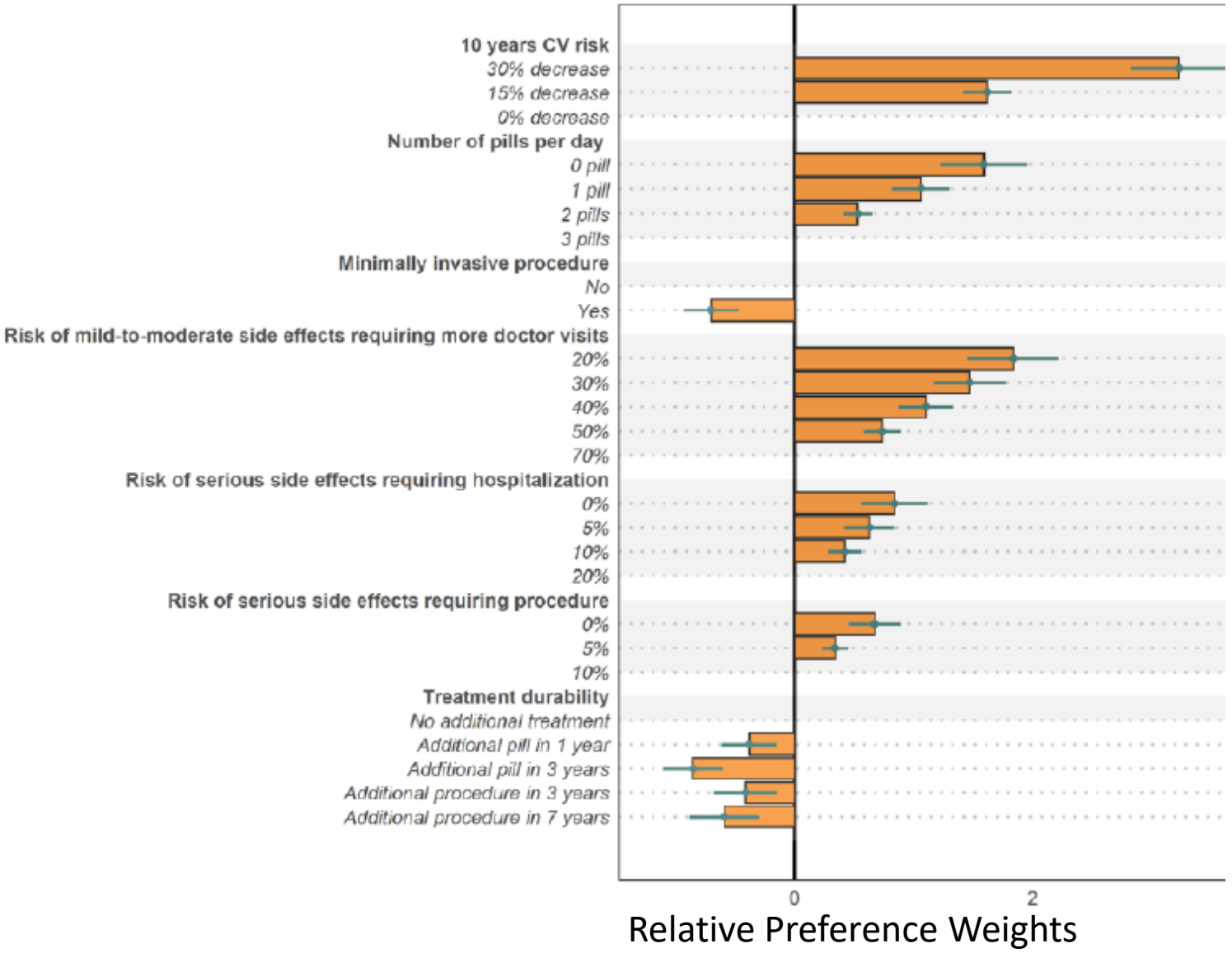
- 258 respondents to PPI survey
- Qualities consistent with CDRH PPI Guidance:
  - Follows guidelines for good research practices established by recognized professional organizations
  - Followed good ethical research practices
  - Survey understandable to respondents
- A few attribute levels do not correspond to levels supported by the evidence - may have tilted the patient preference study results toward the uRDN procedure.



Example Choice Task

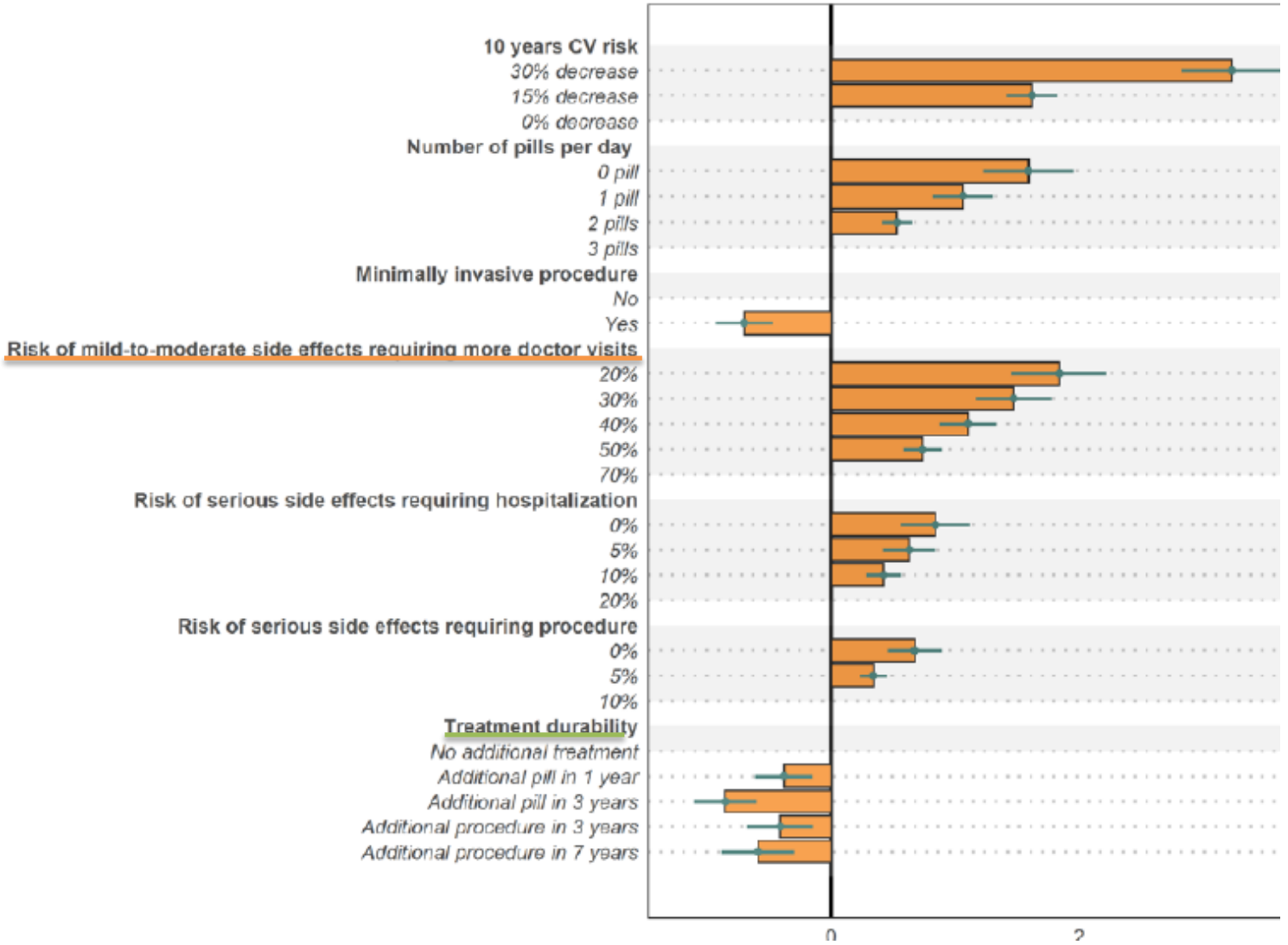
PPI Study Results by Attributes and Levels

- Results generally as expected with levels in order of expected preference
- Decrease in “10 years CV risk” was the main driver of preference choices



PPI Study Results

- 42%* of patients would choose uRDN procedure versus taking an additional pill all else being equal
- May be an overestimate due to levels
  - “Risk of mild-to-moderate side effects requiring more doctor visits” - Lowest risk presented as 20% - the highest risk for pills 10% based on the literature
  - “Treatment durability" - durability of the uRDN procedure 7 years - longer than currently available clinical data



*Recor Executive Summary page 43.

Proposed Post-Approval Study and FDA Conclusions

Paul Warren, PhD
Biomedical Engineer
Office of Cardiovascular Devices

Proposed Post-Approval Study

- Continued follow-up of SOLO and TRIO subjects through 3 years and RADIANCE-II subjects through 5 years
- Global Paradise System Registry (US-GPS) – new enrollment of 500 US subjects at up to 100 sites per the approved indication for use

Proposed Post-Approval Study Endpoints

Safety

30 days

- All-cause mortality
- Major vascular complications
- Hospitalization for hypertensive crisis
- Hospitalization for major cardiovascular- or hemodynamic-related events
- Renal artery injury requiring invasive intervention

6-month, 12-month, and annually to 5 years

- All-cause mortality
- New onset renal artery stenosis >70%
- Significant decline in renal function
- Hospitalization for hypertensive crisis
- Hospitalization for major cardiovascular- or hemodynamic-related events

Effectiveness

- Primary
  - Change in home SBP & DPB at 3 months
  - Change in office SBP & DBP at 3 months
- Secondary
  - Home & office BP, heart rate, and pulse pressure through 5 years
  - Number of BP meds
  - Quality of Life
  - Percentage of subjects with controlled office and home BP

Proposed Post-Approval Subgroup Analysis

- *Sex*
- *Race (Black versus non-black)*
- *Age*
- *Baseline Office systolic BP*
- *Baseline Home systolic BP*
- *Heart Rate*
- *Abdominal obesity*

- *Body Mass Index*
- *eGFR*
- *Heart Failure (NYHA I, II, III, IV)*
- *Isolated Systolic Hypertension*
- *Diabetes*
- *Number and class of antihypertension medications*

Conclusions (1)

- Primary safety endpoint met
  - In RADIANCE-II, no MAEs through 30 days and no cases of > 70% RAS through 6 months → primary safety event rate of 0%
  - Pooled safety event rate of 1.1%
- Primary effectiveness endpoint met for Off-med SOLO and RADIANCE-II trials at 2 months
  - Between-group difference in mean daytime ASBP reduction 6.3 mmHg for SOLO and RADIANCE-II in favor of uRDN
- In the On Standardized Meds TRIO trial, the between-group difference in mean daytime ASBP reduction was 4.5 mmHg in favor of uRDN at 2 months

Conclusions (2)

- Strengths
  - Three sham-controlled randomized trials
  - Studies independently powered for effectiveness
- Limitations
  - Small long-term RCT data sample size for uRDN patients
    - SOLO: 51 SOLO subjects at 3 years
    - TRIO: 51 TRIO subjects at 2 years
  - Challenges in interpreting the clinical significance of BP reduction durability
    - BP medication changes beyond 2 months
    - Subject blinding
    - Cross-over reduced the sample size of the control group
- Patient preference study
  - Some patients may prefer uRDN to an additional BP pill

PANEL QUESTIONS

QUESTION 1

#1. Safety Profile

Primary Safety Endpoint Results

- Composite of 30-day MAE & 6-month new onset RAS >70% DS
- RADIANCE-II: **0%** (0/150)
  - Upper 95% CI 1.63%, met the 9.8% pre-specified performance goal
- Pooled: **1.1%** (6/367; Upper 95% CI 2.75%)
  - 2 deaths
  - 2 major vascular complications (1 pseudoaneurysm, 1 DVT)
  - 1 hypotensive crisis
  - 1 hospitalization for presyncope

#1. Safety Profile

Renal Artery Stenosis

- Evaluable CTA/MRA imaging at 12 months (pooled between SOLO, TRIO, R-II)
- No hemodynamically significant RAS
  - 0.0% (0/238) of >70% DS
  - 0.8% (2/238) of 51-70% DS
  - 2.1% (5/238) of 31-50% DS
  - 1.3% (3/238) of 1-30% DS
- No clinically significant changes in eGFR or serum creatinine

#1. Safety Profile

- Safety events were low and generally transient in nature
- No significant RAS was observed. Although mild to moderate renal artery narrowing is not associated with a functional reduction in renal blood flow, long-term follow-up data are limited, and renal arterial lesions may progress over time.

Please discuss the acute and mid-term procedural and device safety profile of uRDN and the clinical significance of renal arterial responses to uRDN treatment.

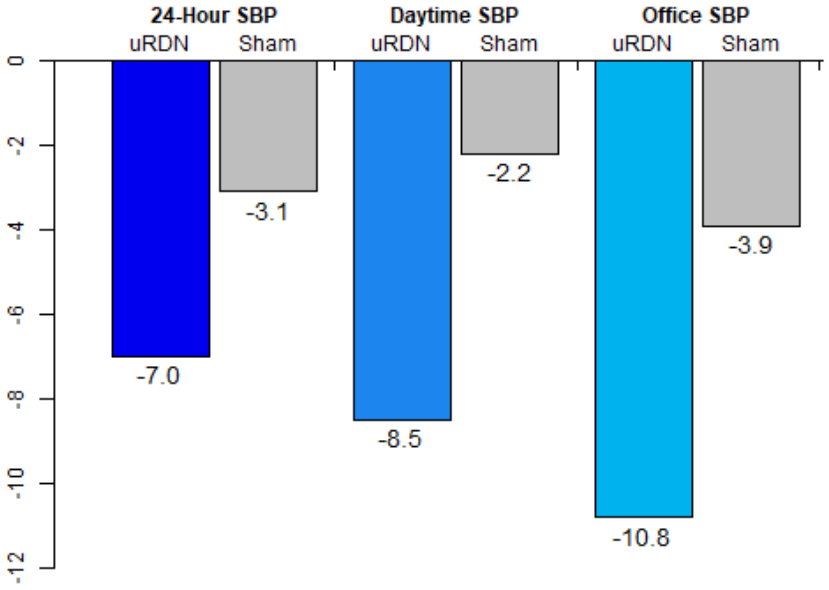
QUESTION 2

#2. Effectiveness – BP Measurement Method

- Data have been presented using both ambulatory blood pressure measurement (ABPM) and office blood pressure measurement (OBPM)
- Most prior hypertension trials have used OBPM
- ABPM has been shown to have greater prognostic value and was identified as preferable at the 2018 Panel Meeting. This may be due to the large number of measurements made for ABPM that are free from potential biases (e.g., white coat effect)

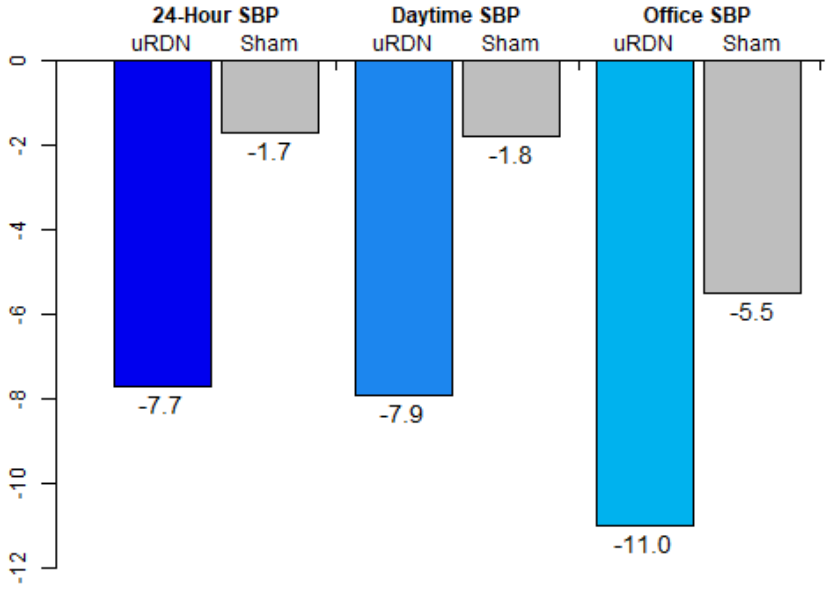
#2. Effectiveness – BP Measurement Method

SOLO (Off-medication)*



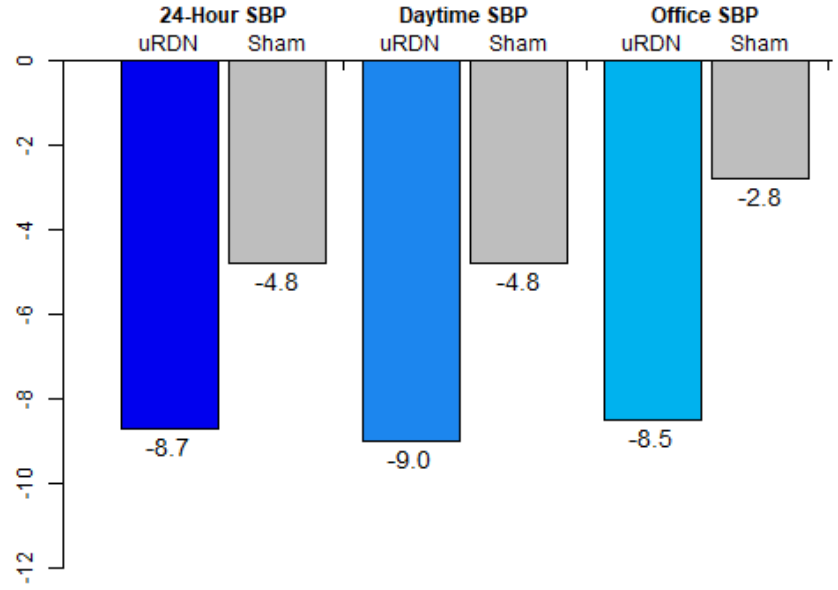
	24-Hour SBP		Daytime SBP		Office SBP	
BL Adj. Mean Diff.	-4.1		-6.3		-6.5	
95% CI	(-7.1, -1.2)		(-9.4, -3.1)		(-11.3, -1.8)	
p-value	0.0061		0.0001		0.0073	
N =	74	72	74	72	74	72
BL SBP	142.6	143.8	150.3	150.0	154.5	153.6

RADIANCE-II (Off-medication)*



	24-Hour SBP		Daytime SBP		Office SBP	
BL Adj. Mean Diff.	-6.2		-6.3		-5.4	
95% CI	(-9.1, -3.4)		(-9.3, -3.2)		(-9.0, -1.8)	
p-value	<.0001		<.0001		0.0035	
N =	144	72	145	73	137	71
BL SBP	143.2	144.5	150.2	151.3	156.8	156.7

TRIO (On standardized medication)*

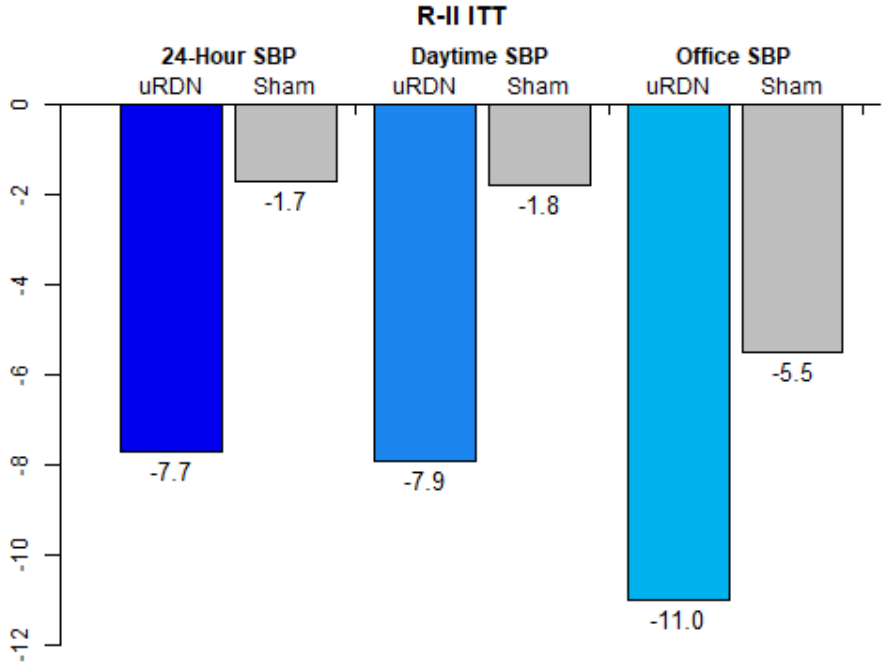


	24-Hour SBP		Daytime SBP		Office SBP	
BL Adj. Mean Diff.	-4.3		-4.5		-5.4	
95% CI	(-9.3, 0.7)		(-9.6, 0.6)		(-11.9, 1.1)	
p-value	0.0895		0.0809		0.1042	
N =	69	67	69	67	64	66
BL SBP	143.9	145.4	150.0	151.1	155.6	154.9

Note not all p-values are adjusted for multiplicity.

*At 2 months

#2. Effectiveness – BP Measurement Method



	24-Hour SBP		Daytime SBP		Office SBP	
BL Adj. Mean Diff.	-6.2		-6.3		-5.4	
95% CI	(-9.1, -3.4)		(-9.3, -3.2)		(-9.0, -1.8)	
p-value	<.0001		<.0001		0.0035	
N =	144	72	145	73	137	71
BL SBP	143.2	144.5	150.2	151.3	156.8	156.7

Note not all p-values are adjusted for multiplicity.

Off-medication study; at 2 months

Please discuss the relative value of ABPM and OBPM in assessing changes in blood pressure for purposes of evaluating effectiveness of uRDN.

QUESTION 3

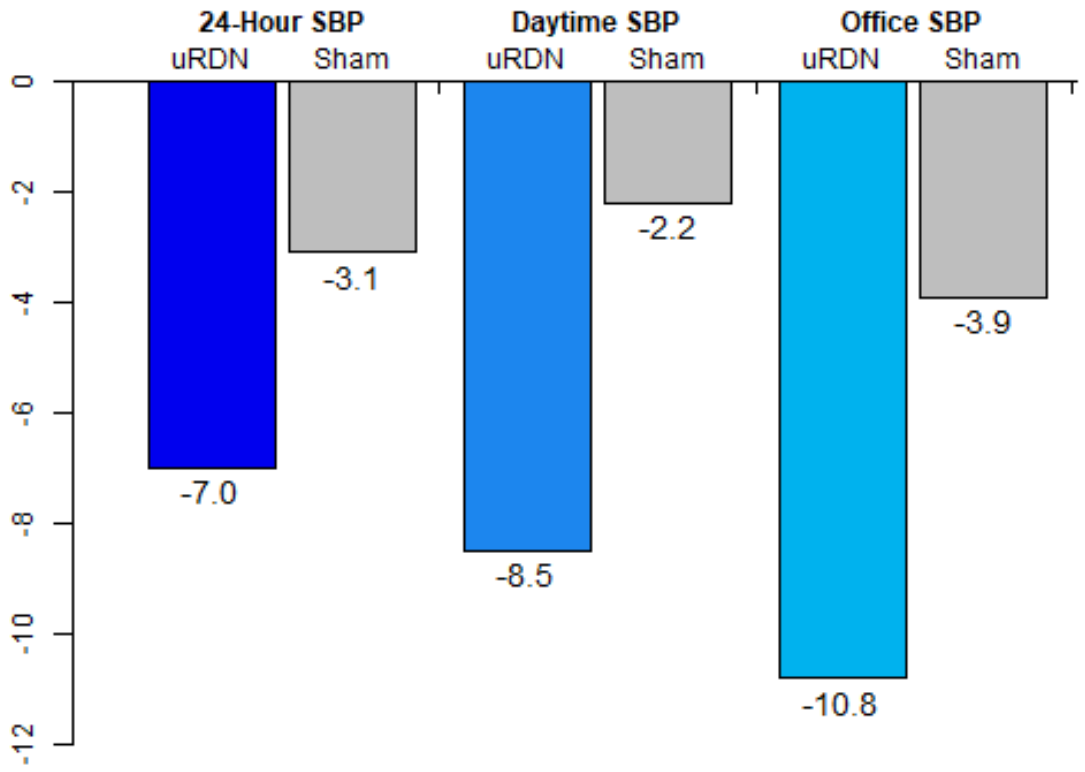
#3. Effectiveness – Magnitude of BP Reduction

- 2018 Panel recommendation for a clinically significant therapeutic effect:
  - Difference in SBP reduction between treatment and sham groups should be 5-7 mmHg (ASBP)
- Primary endpoints for the Paradise uRDN System
  - Adjusted difference in mean reduction of daytime ASBP at 2 months favored uRDN over Sham by 4.5 mmHg (on-standardized med) to 6.3 mmHg (off-med)

#3. Effectiveness – Magnitude of BP Reduction

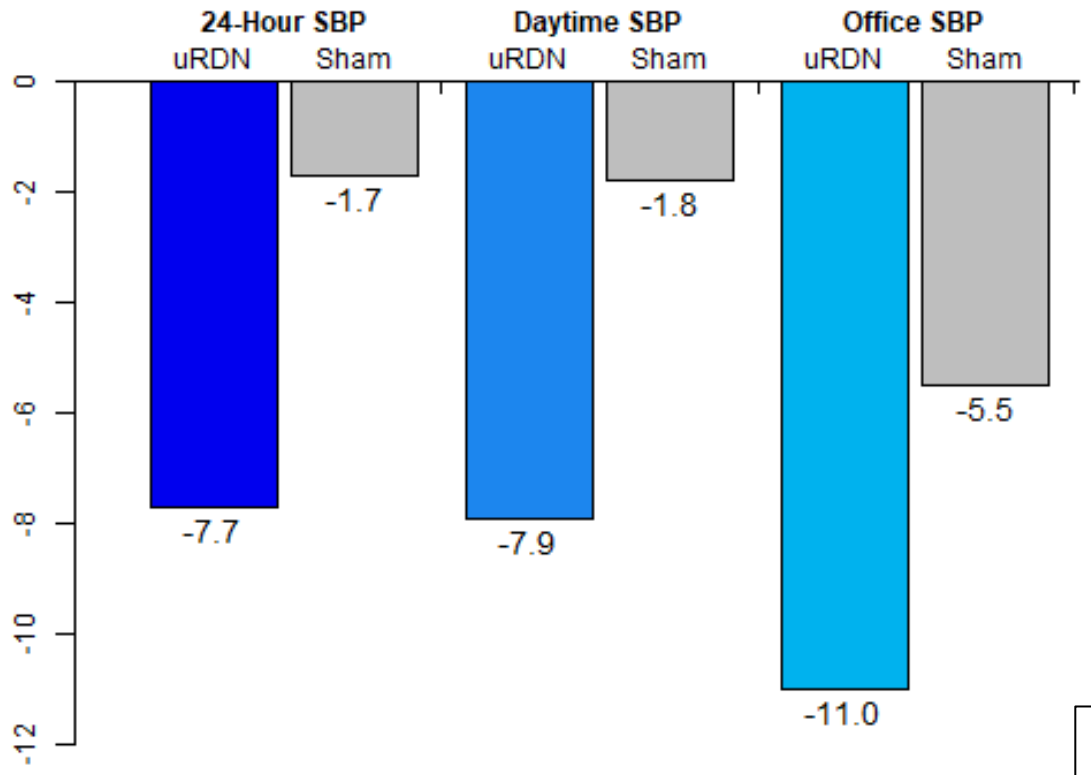
Off-Med Studies

SOLO ITT



	24-Hour SBP		Daytime SBP		Office SBP	
BL Adj. Mean Diff.	-4.1		-6.3		-6.5	
95% CI	(-7.1, -1.2)		(-9.4, -3.1)		(-11.3, -1.8)	
p-value	0.0061		0.0001		0.0073	
N =	74	72	74	72	74	72
BL SBP	142.6	143.8	150.3	150.0	154.5	153.6

RADIANCE-II ITT



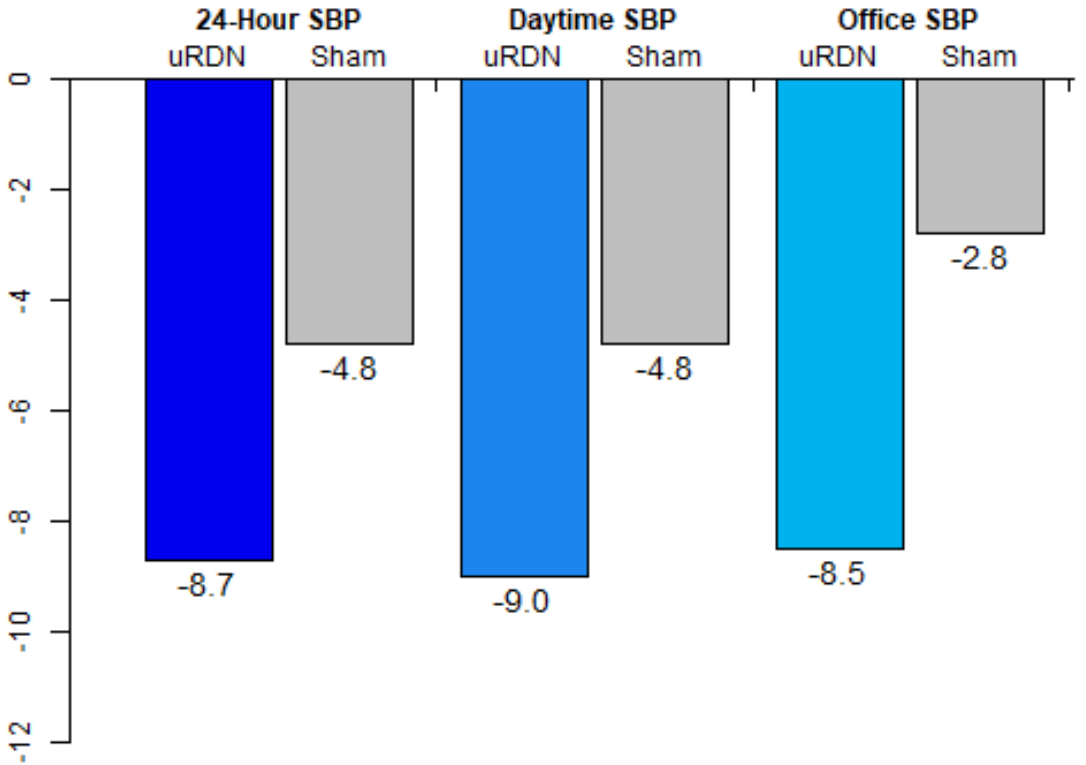
	24-Hour SBP		Daytime SBP		Office SBP	
BL Adj. Mean Diff.	-6.2		-6.3		-5.4	
95% CI	(-9.1, -3.4)		(-9.3, -3.2)		(-9.0, -1.8)	
p-value	<.0001		<.0001		0.0035	
N =	144	72	145	73	137	71
BL SBP	143.2	144.5	150.2	151.3	156.8	156.7

Note not all p-values are adjusted for multiplicity.

#3. Effectiveness – Magnitude of BP Reduction

On Standardized Med Study

TRIO ITT



BL Adj. Mean Diff.	-4.3		-4.5		-5.4	
95% CI	(-9.3, 0.7)		(-9.6, 0.6)		(-11.9, 1.1)	
p-value	0.0895		0.0809		0.1042	
N =	69	67	69	67	64	66
BL SBP	143.9	145.4	150.0	151.1	155.6	154.9

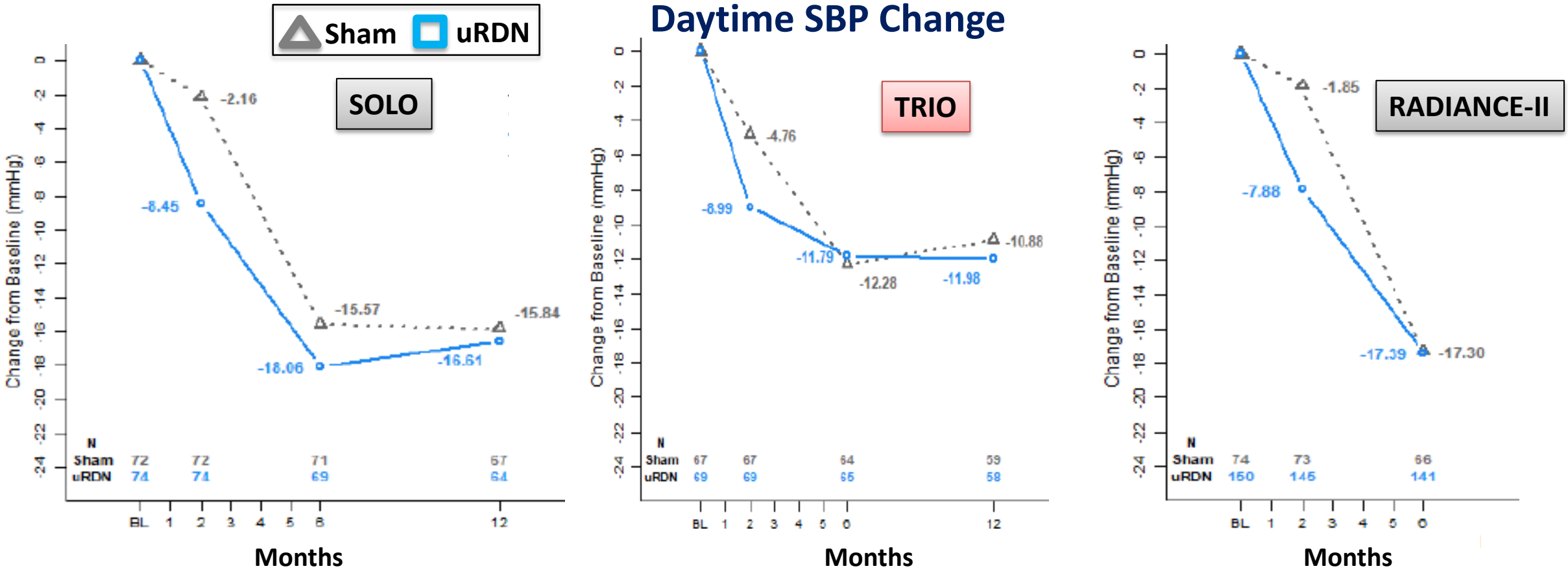
Note not all p-values are adjusted for multiplicity.

#3. Effectiveness – Magnitude of BP Reduction

Please discuss the relative importance of absolute BP reduction in uRDN subjects vs. the difference in BP reduction between uRDN and Sham groups in evaluating the treatment effect for SOLO, TRIO, and RADIANCE-II.

QUESTION 4

#4. Effectiveness – Durability of BP Reduction



- 2 months – differences between groups statistically significant
- After 2 months – absolute reductions persisted in both groups
- 6 months and later - differences in mean daytime ASBP reduction not significant

#4. Effectiveness – Durability of BP Reduction

Challenges in interpreting BP data beyond 6 months:

- **Medication** – From 2-6 months, medication escalation to target BP for all studies (med index only significantly different for SOLO at 6 and 12 mo)
- **Unblinding** – occurred at 6-mo for SOLO and TRIO; 12-mo for RADIANCE-II
- **Crossover** reduced Sham sample size for later timepoints – allowed at 6-mo for SOLO and TRIO; 12-mo for RADIANCE-II
- **Limited long-term data** – RADIANCE-II has limited data beyond 6-mo, OBP available for most patients at 24-mo for SOLO (68%) and TRIO (63%)

#4. Effectiveness – Durability of BP Reduction

Please discuss the strengths and limitations of longer-term BP data in patients treated with uRDN and what conclusions can be drawn about whether uRDN provides a durable reduction in BP.

QUESTION 5

#5 Patient Preference Study

- ReCor conducted a patient preference study with 258 patients to ascertain preferences for uRDN procedure compared to pills only.
- Generally, the study aligned with the CDRH PPI Guidance document.
- Based on the preference weights 42% of respondents would choose the uRDN procedure over an additional pill.
- Two attribute levels do not correspond to the evidence which may have impacted the respondents' choices.

#5 Patient Preference Study

Please discuss the degree of importance that the patient preference study results should be given when considering supplemental benefit-risk assessment information.

QUESTION 6

#6. Indications for Use

	SOLO (off-med)	TRIO (standardized med)	RADIANCE-II (off-med)
Patient Population	Mild-to-Moderate HTN	Resistant HTN	Stage 2 HTN
Sample size	146 (69 uRDN: 37 Sham)	136 (74 uRDN: 72 Sham)	224 (150 uRDN: 74 Sham)
OBP	• ≥140/90 & <180/110 mmHg on 0, 1 or 2 meds; *or* • ≤140/90 on 1 or 2 meds	• ≥140/90 on ≥3 meds, including a diuretic	• ≥140/90 & <180/120 mmHg on 0, 1, or 2 meds; *and* • Previous or currently prescribed AH therapy
Daytime ABP	≥135/85 & <170/105 mmHg after washout	≥135/85 mmHg after stabilization	≥135/85 & <170/105 mmHg after washout
Antihypertensive Medication	0, 1, or 2	At least 3	0, 1, or 2

#6. Indications for Use

The proposed indications for use are:

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

a. **Please discuss whether the available clinical data support the proposed indications for use.**
b. **Please discuss if "inadequately responsive to or intolerance to anti-hypertensive medications" should be further defined in the labeling, and if so, please discuss definitions.**

QUESTION 7

#7. Labeling

Please discuss labeling recommendations for post-uRDN renal artery imaging (e.g., imaging modality, follow-up imaging timing and frequency, and site training and expertise).

QUESTION 8

#8. Benefit/Risk

Given the totality of the evidence presented regarding the safety and effectiveness of the device, please comment on the benefit-risk profile of this device.

QUESTION 9

#9. Post-market Study

ReCor proposed a postmarket registry study that will incorporate uRDN subjects from RADIANCE-II and the continued access study with enrollment of up to 500 new subjects that meet the indications for use (uncontrolled hypertension, who may be inadequately responsive to, or who are intolerant to anti-hypertensive medications). This proposed study will collect office and home measured BP (and not 24-hour ABP).

a. Please comment on the sample size, proposed endpoints, and BP measurement methods.
b. Please discuss whether the PAS enrollment should pre-specify more diverse patient subgroups.
c. Please discuss the strengths and limitations of a single arm study design for the PAS.
d. No renal arterial imaging follow-up is planned. Therefore, please discuss the need for a pre-specified imaging follow-up protocol to confirm long-term uRDN safety.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Supplemental Slides

Study Design Elements

- Third Party Review
  - DSMB
  - CEC
  - Core labs
- Blinding
  - Patients blinded until 6 months (SOLO and TRIO) or 12 months (R-II)
  - Study personnel measuring BP blinded for study duration
  - Sponsor and DSMB blinded to primary effectiveness data

Follow-up Schedule

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

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

[1] SOLO/TRIO only

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

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

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

[5] procedure was conducted on uRDN treated subjects

Key Baseline Patient Features

	SOLO (Off-Med)		RADIANCE-II (Off-Med)		TRIO (On-Standardized Med)	
Measure	uRDN (n=74)	Sham (n=72)	uRDN (n=150)	Sham (n=74)	uRDN (n=69)	Sham (n=67)
Sex						
Male	46 (62.2%)	39 (54.2%)	103 (68.7%)	57 (77.0%)	56 (81.2%)	53 (79.1%)
Female	28 (37.8%)	33 (45.8%)	47 (31.3%)	17 (23.0%)	13 (18.8%)	14 (20.9%)
Age	54.4 ± 10.2	53.8 ± 10.0	55.1 ± 9.9	54.9 ± 7.9	52.3 ± 7.5	52.8 ± 9.1
Geography						
US	35 (47.3%)	34 (47.2%)	100 (66.7%)	46 (62.2%)	28 (40.6%)	25 (37.3%)
OUS	39 (52.7%)	38 (52.8%)	50 (33.3%)	28 (37.8%)	41 (59.4%)	42 (62.7%)
Race						
American Indian or Alaska Native	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.00%)	1 (1.52%)
Asian	1 (1.3%)	0 (0.0%)	0 (0.0%)	1 (1.3%)	1 (1.5%)	1 (1.5%)
Black	12 (16.2%)	13 (18.0%)	21 (14.0%)	15 (20.2%)	14 (20.6%)	13 (19.7%)
Caucasian	60 (81.0%)	52 (72.2%)	114 (76.0%)	56 (75.6%)	45 (66.2%)	51 (77.3%)
Hispanic or Latino	1 (1.3%)	4 (5.5%)	15 (10.0%)	2 (2.7%)	5 (7.4%)	0 (0.0%)
Native Hawaiian or other Pacific Islander	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other/Mixed Race	0 (0.0%)	0 (0.0%)	15 (10.00%)	2 (2.7%)	3 (4.41%)	0 (0.0%)
BMI	29.9 ± 5.9	29.0 ± 5.0	30.1 ± 5.2	30.6 ± 5.2	32.8 ± 5.7	32.6 ± 5.4
Abdominal circumference (cm)	101.5 ± 14.2	98.5 ± 15.1	102.4 ± 12.3	104.3 ± 13.1	109.4 ± 15.5	109.2 ± 12.9
Office SBP (mmHg)	142.6 ± 14.7	144.6 ± 15.9	155.8 ± 11.1	154.3 ± 10.6	161.9 ± 15.5	163.6 ± 16.8
Office DBP (mmHg)	92.3 ± 10.1	93.6 ± 8.3	101.3 ± 6.7	99.1 ± 5.6	105.1 ± 11.6	103.3 ± 12.7

Procedural Characteristics

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

Primary Safety Endpoint

RADIANCE-II

- The primary safety endpoint was defined as the occurrence of at least one of following major adverse events (MAE):
  a. 30-day
     1) All-cause mortality
     2) New onset (acute) end-stage renal disease (eGFR<15 mL/min/m2 or need for renal replacement therapy)
     3) Significant embolic event resulting in end-organ damage (e.g., kidney or bowel infarct, lower extremity ulceration or gangrene, or doubling of serum creatinine)
     4) Renal artery perforation requiring invasive intervention
     5) Renal artery dissection requiring an invasive intervention
     6) Major vascular complications (e.g., clinically significant groin hematoma, arteriovenous fistula, pseudoaneurysm) requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion (>2 units of packed red blood cells within any 24-hr period during the first 7 days post-randomization)
     7) Hospitalization for hypertensive or hypotensive crisis
     8) Hospitalization for major cardiovascular- or hemodynamic-related events (e.g., HF; MI; stroke)
     9) New stroke
     10) New MI
  b. 6 Month: New onset renal artery stenosis (RAS), defined as a >70% stenosis, confirmed by CTA/MRA

Additional analysis for pooled SOLO, TRIO, & RADIANCE-II trials

Primary Safety Endpoint – R-II Imaging Completed

Table X: RADIANCE-II Imaging Completed
(ITT subjects in window)

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

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

Safety - RAS data through 12 months

Study	Total	No measurable stenosis % (n)	1-30% stenosis % (n)	31-50% stenosis % (n)	51-70% stenosis % (n)	71-99% stenosis % (n)	Renal artery occlusion % (n)
RADAIANCE-II	90	94.4% (85)	3.3% (3)	2.2% (2)	0.0% (0)	0.0% (0)	0.0% (0)
SOLO*	64	96.9% (62)	0.0% (0)	1.6% (1)	1.6% (1)	0.0% (0)	0.0% (0)
TRIO	53	100.0% (53)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
RADIANCE-II CO	6	83.3% (5)	0.0% (0)	16.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)
SOLO CO	25	92.0% (23)	0.0% (0)	4.0% (1)	4.0% (1)	0.0% (0)	0.0% (0)
Combined	238	95.8% (228)	1.3% (3)	2.1% (5)	0.8% (2)	0.0% (0)	0.0% (0)

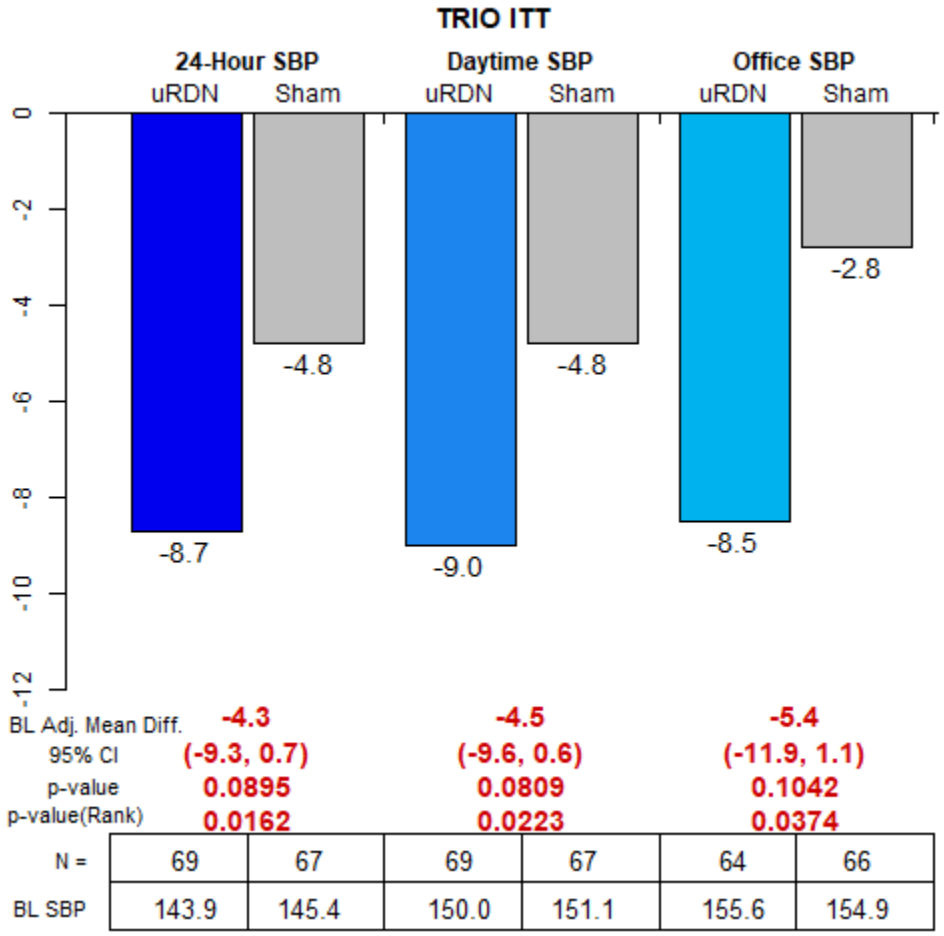
Data included in listing is based on data available from the Core Lab
Not all Crossover (CO) subjects have reached 12M CO f/u.
** One SOLO subject randomized to treatment was not treated, and subsequently crossed over.*
Their data is included in the SOLO CO summaries.

Pooled Renal Artery Diameter Stenosis
(uRDN Subjects at 12 Months by CTA or MRA)

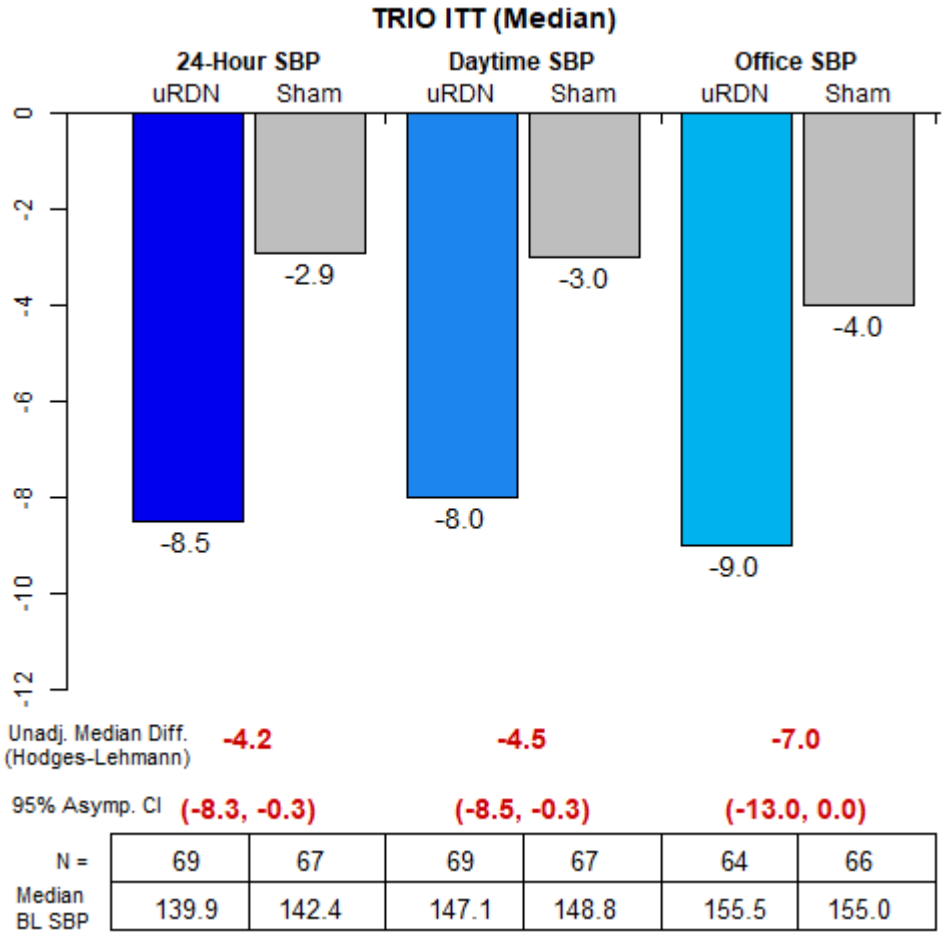
		Renal Artery Diameter Stenosis					
Study	**N**	**0%**	**1-30%**	**31-50%**	**51-70%**	**71-99%**	**Occluded**
SOLO	64	96.9% (62)	0.0% (0)	1.6% (1)	1.6% (1)	0.0% (0)	0.0% (0)
RADIANCE-II	112	92.9% (104)	2.7% (3)	2.7% (3)	1.8% (2)	0.0% (0)	0.0% (0)
TRIO	53	100.0% (53)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
SOLO CO	25	92.0% (23)	0.0% (0)	4.0% (1)	4.0% (1)	0.0% (0)	0.0% (0)
RADIANCE-II CO	6	83.3% (5)	0.0% (0)	16.7% (1)	0.0% (0)	0.0% (0)	0.0% (0)
Total	**238**	**95.8% (228)**	**1.3% (3)**	**2.1% (5)**	**0.8% (2)**	**0.0% (0)**	**0.0% (0)**

CO = Crossover Subjects

Means and Medians for TRIO



	24-Hour SBP		Daytime SBP		Office SBP	
BL Adj. Mean Diff.	-4.3		-4.5		-5.4	
95% CI	(-9.3, 0.7)		(-9.6, 0.6)		(-11.9, 1.1)	
p-value	0.0895		0.0809		0.1042	
p-value(Rank)	0.0162		0.0223		0.0374	
N =	69	67	69	67	64	66
BL SBP	143.9	145.4	150.0	151.1	155.6	154.9



	24-Hour SBP		Daytime SBP		Office SBP	
Unadj. Median Diff. (Hodges-Lehmann)	-4.2		-4.5		-7.0	
95% Asymp. CI	(-8.3, -0.3)		(-8.5, -0.3)		(-13.0, 0.0)	
N =	69	67	69	67	64	66
Median BL SBP	139.9	142.4	147.1	148.8	155.5	155.0

Note not all p-values are adjusted for multiplicity; p-value is based on ANCOVA; p-value(Rank) is based on ANCOVA on the ranks.

Figure X: SBP at 2 months for TRIO (means and medians)

Primary Safety Results: Imaging Performed (SOLO, TRIO)

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

Secondary & Observational BP Changes @ 2 months

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

Note not all p-values are adjusted for multiplicity.

Subgroup analysis of primary effectiveness endpoint at 2 months – US vs OUS

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

Note not all p-values are adjusted for multiplicity.

Medication Burden

- Medication Burden also assessed via Defined Daily Dose (DDD)
- DDD = sum of the average maintenance dose per day the subject is taking

Statistical Backup Slides

Statistical Analysis Populations

- **Intention-to-Treat** (ITT) cohort: subjects according to their randomization assignment
- **Per-Protocol** (PP) cohort: subjects treated per their assigned treatment group without deviation from major enrollment criteria
- **Complete ABPM** (CA) cohort: subjects treated per their assigned treatment group that have ABP values at both baseline and follow-up
- **Crossover** (CO) cohort: subjects who received uRDN after being randomized to Sham.
  - Crossover allowed:
    - After 6-months follow-up in SOLO and TRIO
    - After 12-months follow-up in RADIANCE-II

Sample Size and Power

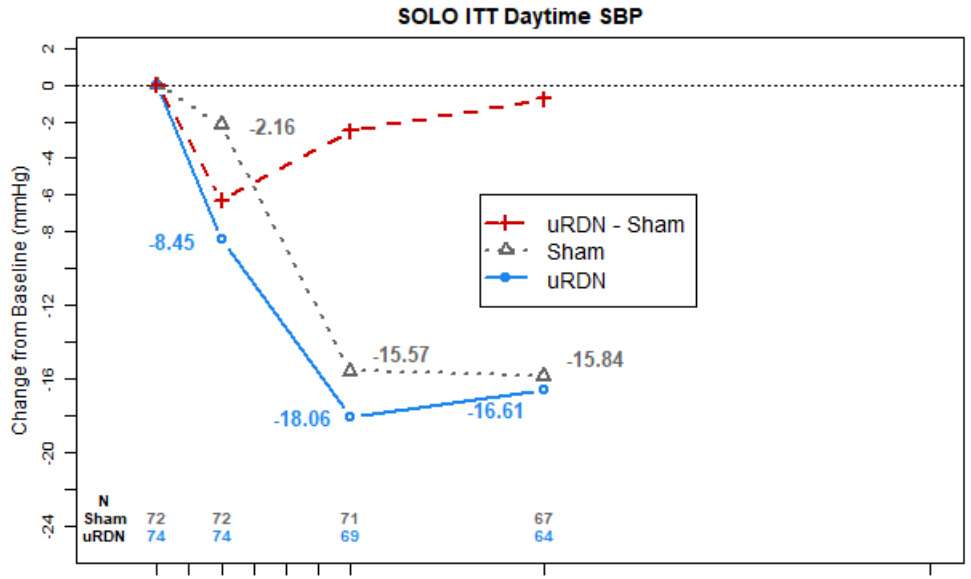
- Primary safety endpoint (at 6 months):
  - RADIANCE-II only:
    - The evaluable sample size of 128 uRDN subjects provides about 95% power for the performance goal of 9.8% if the composite MAE rate is expected at 3.0% and analyzed by the upper one-sided exact 95% confidence bound (i.e., one-sided 0.05 alpha level).
- Primary effectiveness endpoint (at 2 months):
  - SOLO and TRIO:
    - Based on a two-sample t-test, for an assumed mean ± standard deviation difference of 6±12 mmHg with a two-sided 0.05 alpha level, a planned evaluable sample size of 128 subjects provides about 80% power (i.e., 64 subjects per arm).
  - RADIANCE-II:
    - Based on a 2:1 randomization, two-sample t-test, for an assumed mean ± standard deviation difference of 6±12 mmHg with a two-sided 0.05 alpha level, a planned evaluable sample size of 192 subjects provides about 90% power (i.e., 128 subjects in uRDN and 64 in Sham).

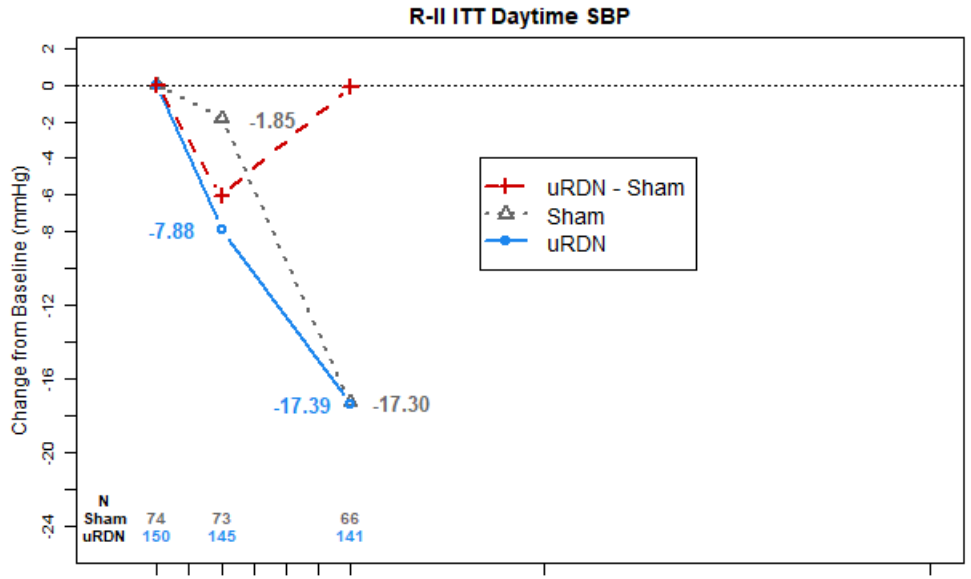
Proportion of Subjects with ≥5, ≥10, & ≥15 mmHg Reduction in Daytime SBP at 2 Months

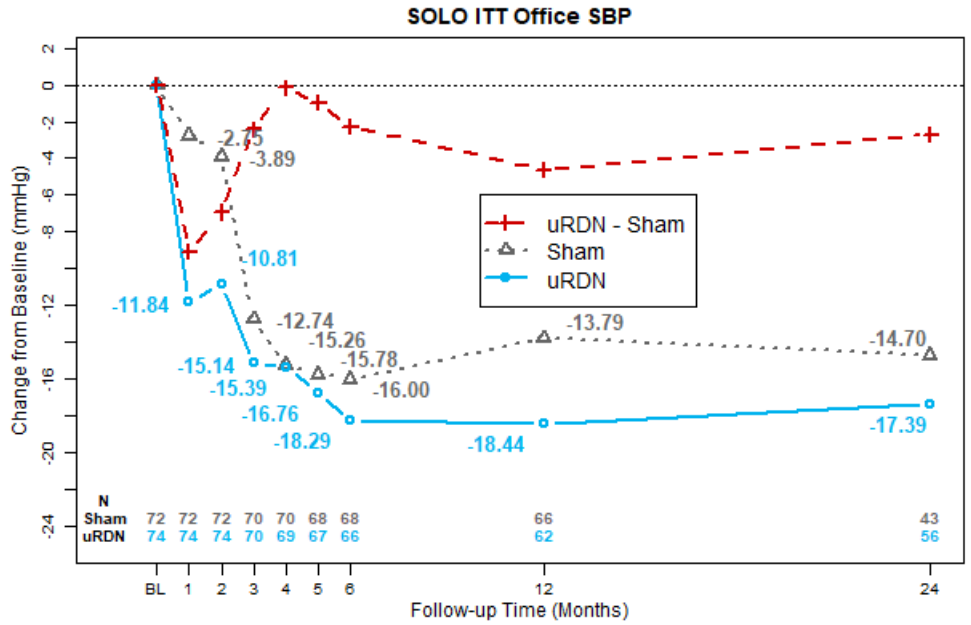
Daytime SBP Reduction	uRDN	Sham Procedure	p-value
SOLO (Off Med)	(n=74)	(n=72)	
≥5 mmHg	49/74 (66.2%)	24/72 (33.3%)	<.0001
≥10 mmHg	32/74 (43.2%)	13/72 (18.1%)	0.0010
≥15 mmHg	19/74 (25.7%)	8/72 (11.1%)	0.0234
RADIANCE-II (Off Med)	(n=150)	(n=74)	
≥5 mmHg	64.1% (93/145)	34.2% (25/73)	<.0001
≥10 mmHg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

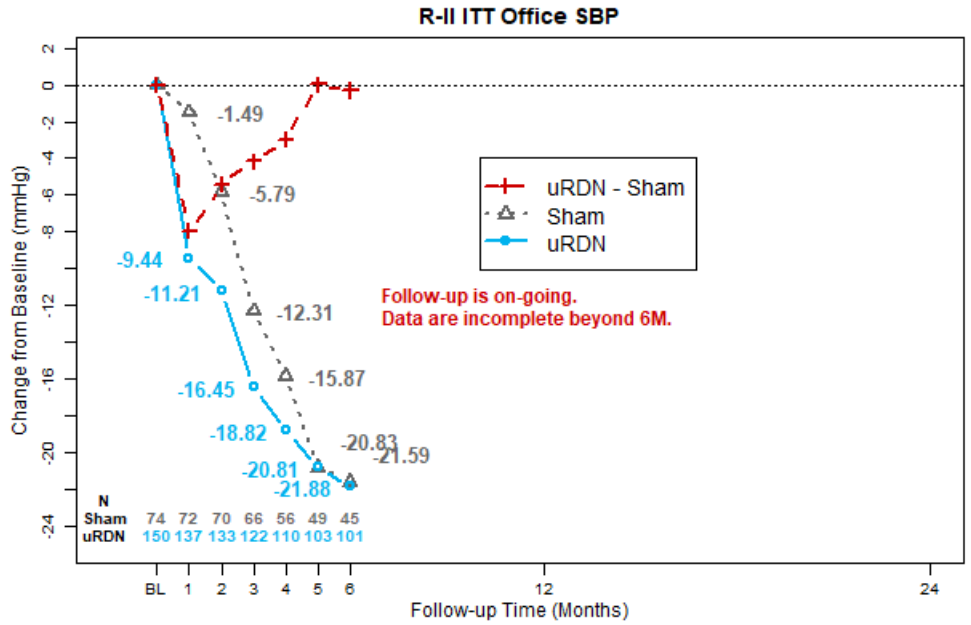
Note not all p-values are adjusted for multiplicity.

Durability of Effect – SOLO & RADIANCE-II

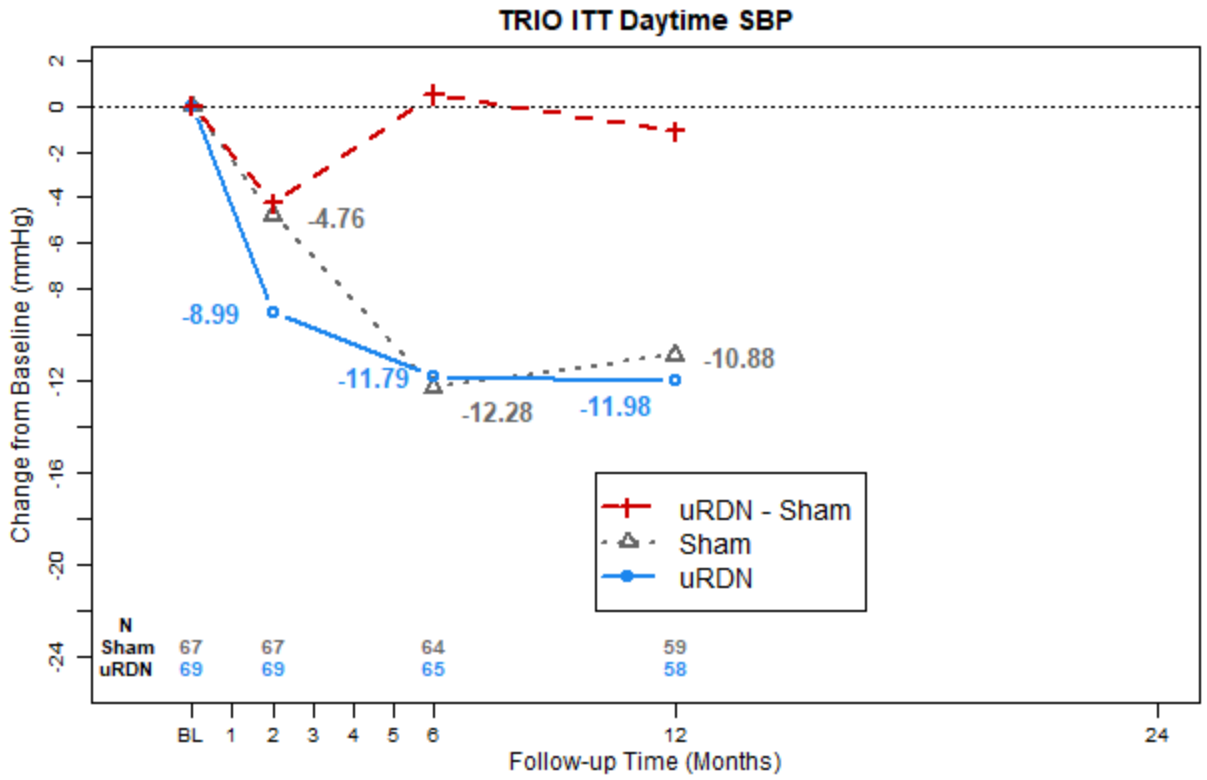


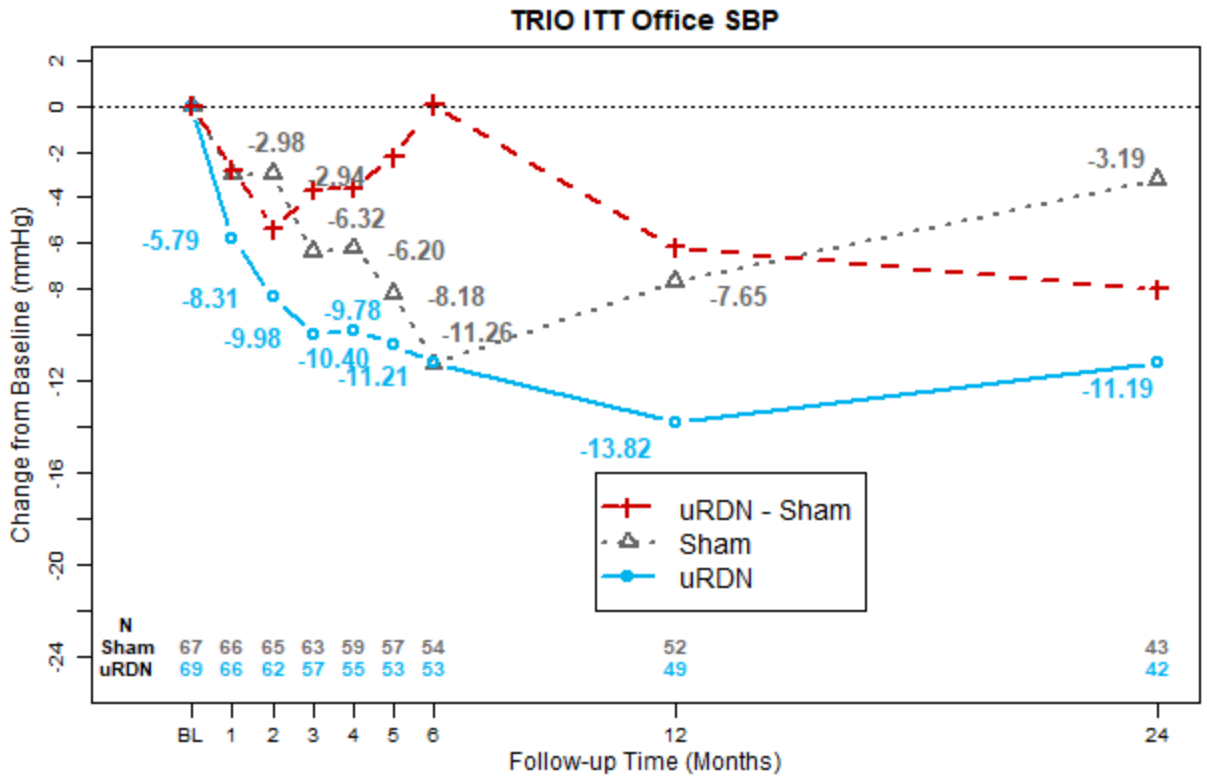






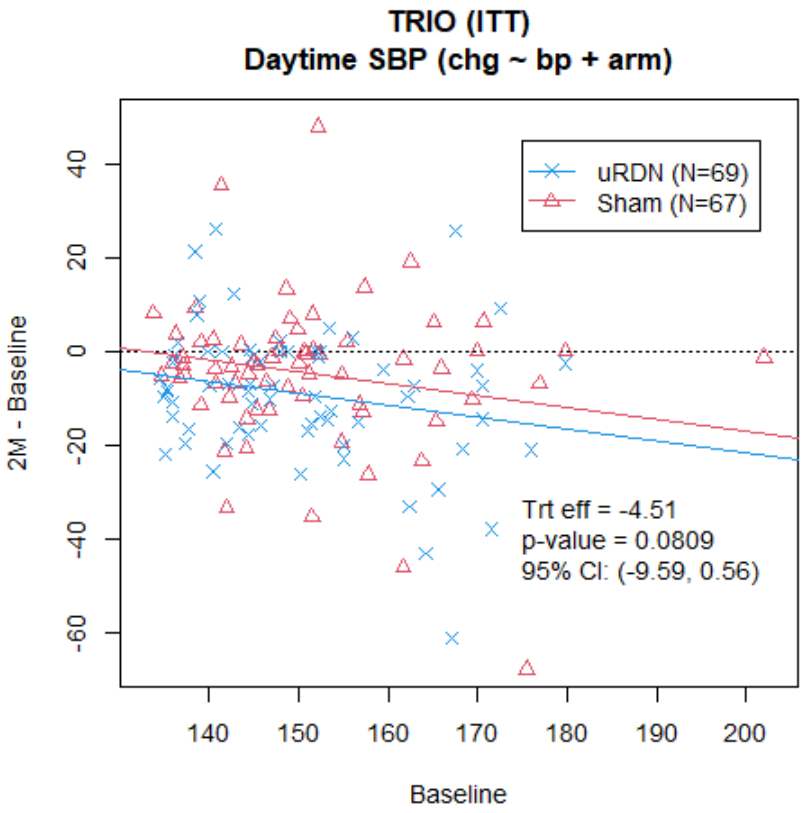
Durability of Effect – TRIO

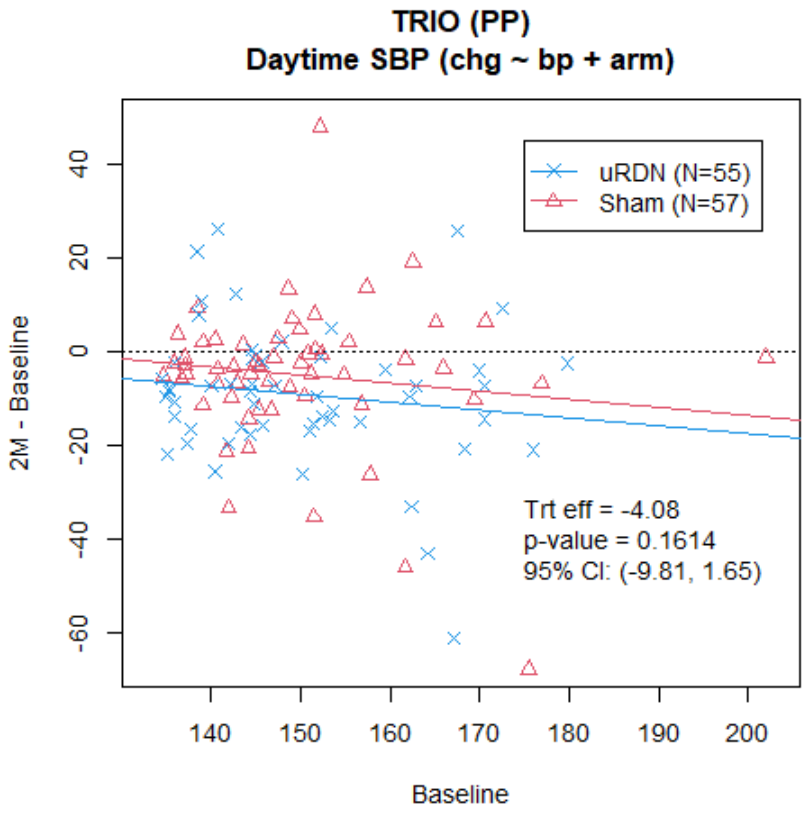


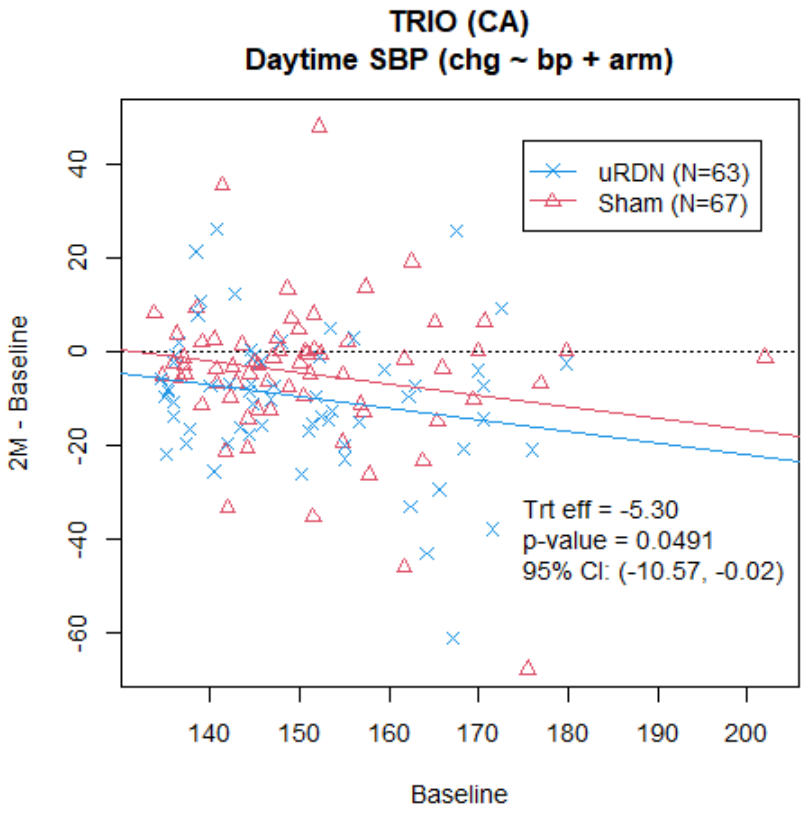


TRIO, 2 months

ANCOVA Results (ITT & PP & CA)







Note not all p-values are adjusted for multiplicity.

TRIO, 2 months, ITT

- Diagnostics for normality assumption of ANCOVA model
- In the middle row and left column, outlies can be seen at each end of the tails
  - Dots deviate away from the theoretical line derived from the normal distribution

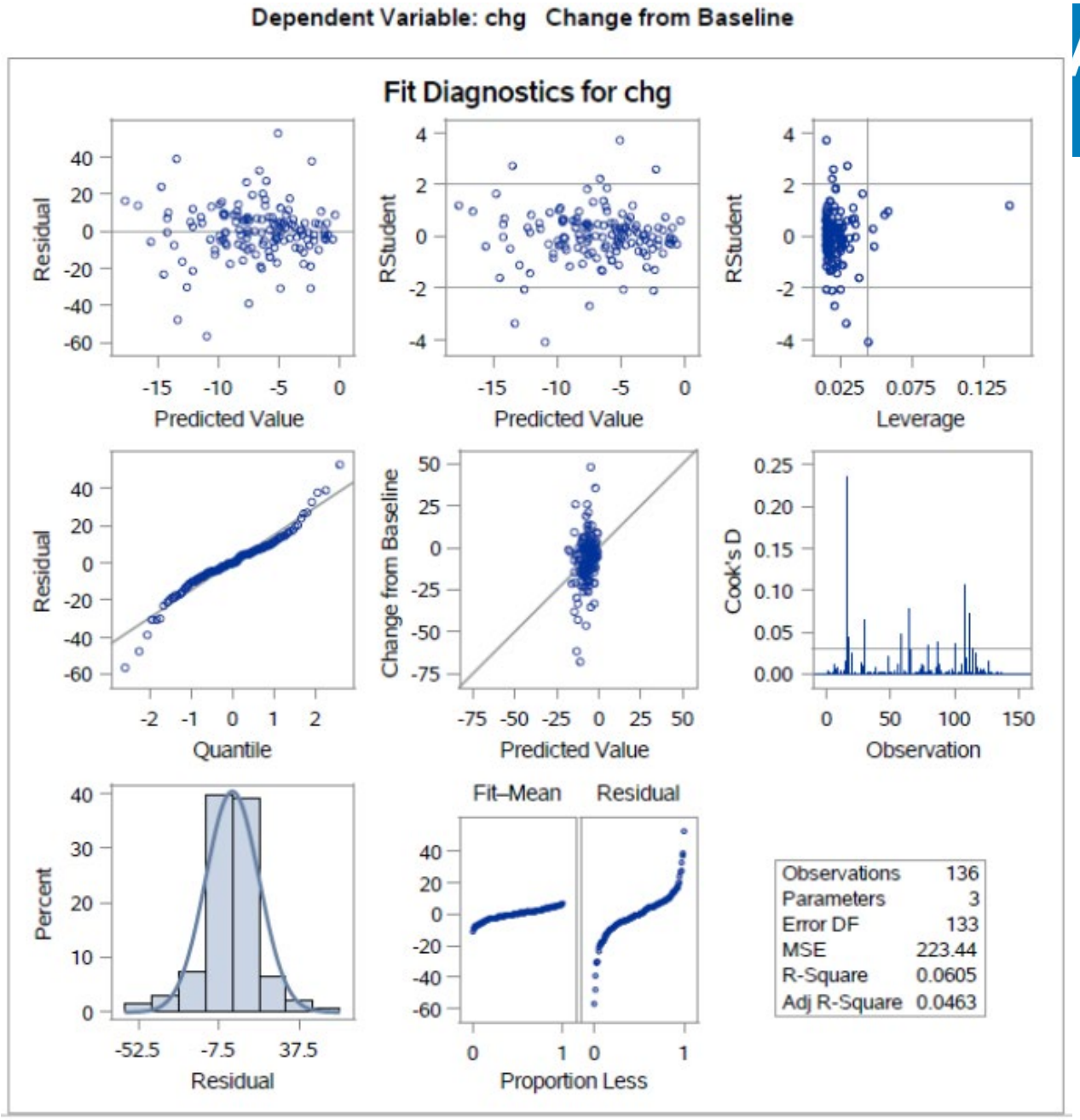
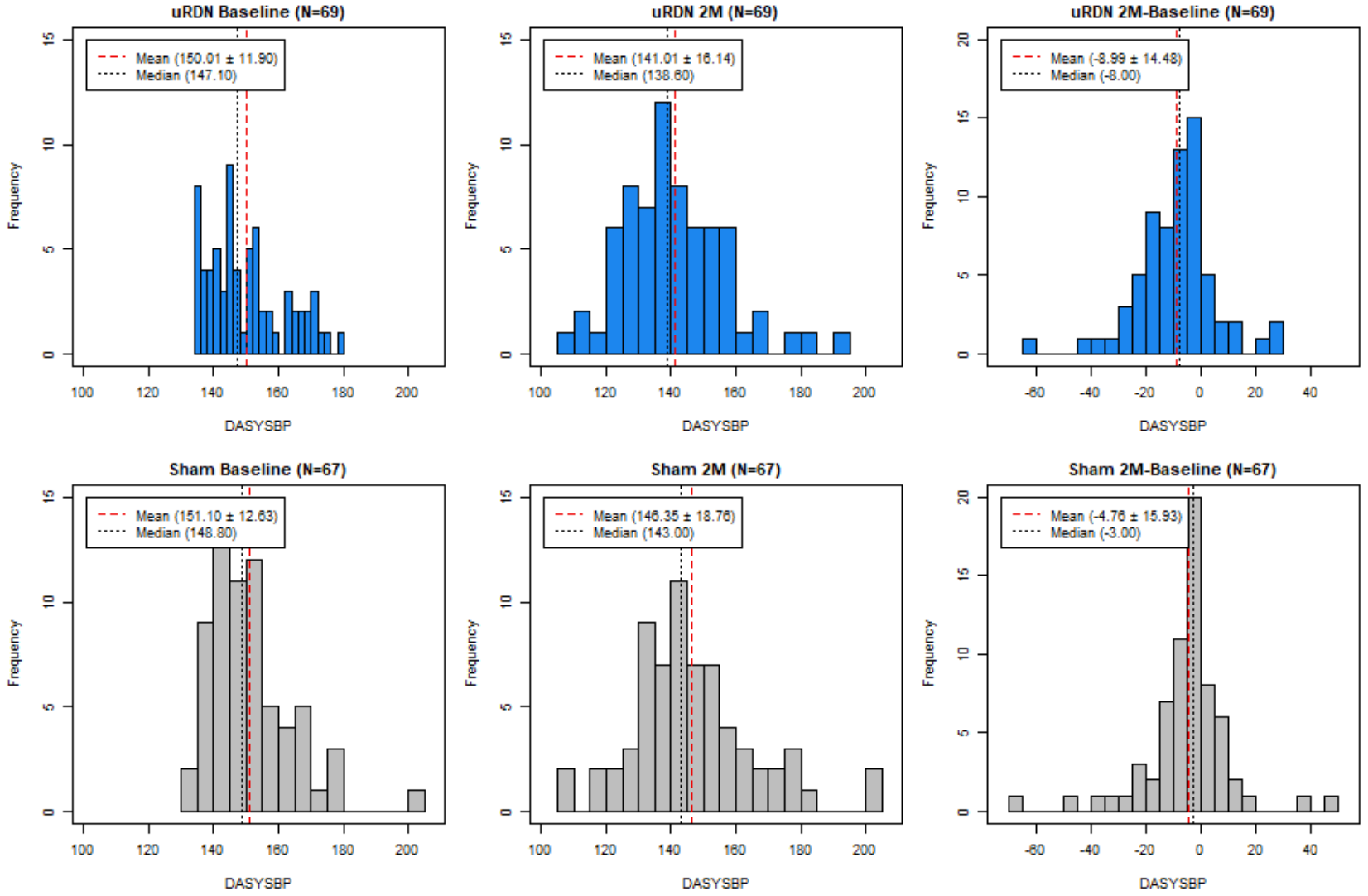


Figure 6: TRIO Goodness of fit daytime ASBP 2-month ITT baseline adjusted

TRIO, 2 months, ITT

- Top: uRDN
- Bottom: Sham
- Left: Baseline
- Middle: 2 Months
- Right: Difference
- x-axis: Daytime SBP (mmHg)
- y-axis: Frequency



ANCOVA for Adjusting Baseline BP

- FDA Guidance: "Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products Guidance for Industry"
  - *This guidance provides recommendations for the use of covariates in the analysis of randomized, parallel group clinical trials that are applicable to both superiority trials and noninferiority trials.*
  - *The ICH E9 guidance strongly advises prespecification of "the principal features of the eventual statistical analysis," including "how to account for [covariates] in the analysis to improve precision and to compensate for any lack of balance between treatment groups."*
  - *The ICH E9 guidance also cautions against adjusting for "covariates measured after randomization because they could be affected by the treatments."*

ANCOVA on the ranks

- Quade (1967) JASA, Vol. 62, No. 320, pp. 1187-1200.
  - *The problem is then to test the hypothesis H_0 that the conditional distribution of Y given X is the same for each population, where the alternatives of interest are those which imply that some populations tend to have greater values of Y than others for all fixed values of X.*
  - Note:
    - H_0: The conditional distribution of BP change given baseline BP is the same for each group.
      - Rejecting this H_0 may be due to the difference of distribution, either in shape or in location and both combined.
      - This estimand is different from the treatment effect obtained by the ANCOVA model.

Hodges-Lehmann Estimates

- Hodges and Lehmann (1963)
  - The median of all paired differences (one subject from each group)
- Hollander and Wolfe (1999)
  - The asymptotic lower and upper confidence limits are for the location shift.
- Note:
  - Point estimate and confidence limits are neither adjusted for baseline BP nor associated with ANCOVA or ANCOVA on the ranks.
  - Symmetric distribution is preferred when summarizing the population parameter of distribution location (e.g., median of treatment effect).