# SUMMARY MINUTES

## CIRCULATORY SYSTEM DEVICES PANEL MEETING

## MEDICAL DEVICES ADVISORY COMMITTEE

August 22, 2023
9:00 a.m. EST

## Attendees

### Chairperson

Richard Lange, MD, MBA
Endowed President
Texas Tech University Health Sciences Center
Paul L Foster School of Medicine - El Paso, Texas

### Members

Keith Allen, MD
Director Surgical Research
St. Luke's Hospital of Kansas City – Kansas City, MO

James Blankenship, MD
Director Cardiac Catheterization Laboratories
University of New Mexico Health Sciences – Albuquerque, NM

Randall Starling, MD, MPH
Professor of Medicine
Heart, Vascular and Thoracic Institute
Cleveland Clinic – Cleveland, OH

Robert Yeh, MD, MSc, MBA
Director
Center for Outcomes Research in Cardiology
Beth Israel Deaconess Medical Center – Boston, MA

### Consultants

Julia Lewis, MD
Professor of Medicine
Division of Nephrology
Vanderbilt University School of Medicine – Nashville, TN

Patrick Nachman, MD, FASN
Director
Division of Nephrology and Hypertension
University of Minnesota – Minneapolis, MN

### Temporary Voting Members

Eric Bates, MD
Professor of Cardiology
Frankel Cardiovascular Center

University of Michigan Health – Ann Arbor, MI
Matthew Corriere, MD, MS
Frankel Professor of Cardiovascular Surgery
Michigan Medicine
University of Michigan – Ann Arbor, MI

Abdulla Damluji, MD, PhD, MPH
Interventional Cardiologist
Inova Health – Fairfax, VA

John Hirshfeld, Jr., MD
Emeritus Professor of Medicine
Perelman School of Medicine
University of Pennsylvania – Philadelphia, PA

Mark Lockhart, MD, MPH
Professor
Department of Radiology
University of Alabama at Birmingham School of Medicine – Birmingham, AL

Benjamin Saville, PhD
Director & Senior Statistical Scientist
Trial Design & Analysis
Berry Consultants – Austin, TX

John Somberg, MD
Professor Emeritus of Medicine
Pharmacology & Cardiology
Rush Medical College – Chicago, IL

Janet Wittes, PhD
Principal
Wittes LLC – Washington, DC

**Consumer Representative**

William Vaughan
Consumer Advocate – Falls Church, VA

**Industry Representative**

Wes Cetnarowski, MD, BCMAS
Senior Vice President Scientific Affairs
B. Braum Medical, Inc. – Center Valley, PA

**Patient Representative**

Deneen Hesser, MSHSA, RN
Research Advocate National Cancer Institute
Innovative Molecular Analysis Technologies
Program – Chicago, IL

**FDA Participant**

Bram Zuckerman, MD
Office Director
Office of Cardiovascular Devices, CDRH, FDA – Silver Spring, MD

**Designated Federal Officer**

Jarrod Collier, MS
Designated Federal Officer
Office of Management, CDRH, FDA – Silver Spring, MD

**Sponsor Presenters**

Leslie Coleman, DVM, MS, DACLAM
Vice President, Regulatory & Medical Affairs
ReCor Medical, Inc. – Palo Alto, CA

Michael Weber, MD
Professor of Medicine
SUNY Downstate College of Medicine – Smithtown, NY

Ajay Kirtane, MD, SM
Professor of Medicine
Director, Cardiac Catheterization Laboratories
Columbia University Irvin Medical Center – New York, NY

Glenn Chertow, MD, MPH
Professor of Medicine
Stanford University – Stanford, CA

Helen Reeve-Stoffer, PhD
Vice President, Clinicial Affairs
ReCor Medical, Inc. – Palo Alto, CA

Naomi Fisher, MD
Director, Hypertension Service &
Hypertension Specialty Clinic
Brigham and Women's Hospital

Associate Professor
Harvard Medical School – Boston, MA

**FDA Presenters**

Paul Warren, PhD
Biomedical Engineer
Office of Cardiovascular Devices
CDRH, FDA – Silver Spring, MD

Wei-Chen Chen, PhD
Statistician
Office of Clinical Evidence and Analysis
CDRH, FDA – Silver Spring, MD

Douglas Silverstein, MD
Nephrologist
Office of Gastrorenal, ObGyn, General Hospital,
And Urology Devices
CDRH, FDA – Silver Spring, MD

David Gebben, PhD
Health Economist
Patient Science and Engagement Team
Office of Strategic Partnerships and Technology Innovation
CDRH, FDA – Silver Spring, MD

## CALL TO ORDER & INTRODUCTIONS

**Dr. Richard Lange**, the Panel's chairperson, called the meeting to order, advised the panel members participating in today's meeting have received training in FDA device law and regulations, and announced the agenda for the meeting: to discuss, make recommendations, and vote on information regarding the premarket approval application (PMA) for the ReCor Paradise Ultrasound Renal Denervation System by ReCor Medical. The Paradise Ultrasound Renal Denervation System is a safe, minimally invasive, catheter-based procedure that significantly reduces blood pressure for patients. **Dr. Lange** prompted committee members and FDA attending virtually to introduce themselves.

## CONFLICT OF INTEREST STATEMENT

Upon completion of introductions, **Jarrod Collier**, the Designated Federal Officer, read the conflict of interest statement and made general announcements, noting that conflict of interest waivers have been issued to **Dr. Julia Lewis**, **Dr. Patrick Nachman**, **Dr. Randall Starling**, and **Dr. Robert Yeh** regarding their professional involvement with firms related to the Sponsor. The doctors reported they are not involved in the study and receive no personal

remuneration from the study's funds, allowing them to participate fully in the panel deliberations.

**Dr. Wes Cetnarowski** is serving as industry representative active on behalf of all related industry. **Jarrod Collier** reminded all members and consultants that if the discussions involve any other products of firms not already on the agenda for which the FDA participant has a personal or imputed financial interest, that participant needs to exclude themselves from such involvement and their exclusion will be noted for the record.

**Jarrod Collier** read the appointment to temporary voting status and appointed the following individuals as voting members of the Circulatory System Devices panel: **Dr. Eric Bates, Dr. Matthew Corriere, Dr. Abdulla Damluji, Dr. John Hirshfeld, Dr. Mark Lockhart, Dr. Benjamin Saville, Dr. John Somberg, and Dr. Janet Wittes.** In addition, **Dr. Richard Lange** was appointed to act as temporary voting chairperson.

**SPONSOR PRESENTATION – RECOR MEDICAL**

**Leslie Coleman,** Vice President of Regulatory and Medical affairs at ReCor Medical began the presentation by stating that hypertension is a major public health burden in the US and throughout the world. Treatment guidelines recommend lifestyle modifications and anti-hypertensive medications based upon the severity of hypertension. Managing blood pressure is important, as reducing blood pressure can reduce the risk of cardiovascular morbidity and mortality. Standard of care therapies are often insufficient to adequately control blood pressure for many patients. Patients may be inadequately responsive to or intolerant of anti-hypertensive medications or unwilling or unable to comply with prescribed treatment regimens and, therefore, remain at high risk for cardiovascular events. Patients need a safe and effective alternative that can reduce their blood pressure with the potential to improve outcomes.

The Paradise Ultrasound Renal Denervation System, which will be referred to as uRDN, is a novel, minimally invasive, catheter-based procedure which delivers circumferential ultrasound energy to thermally ablate and disrupt overactive sympathetic nerves along the renal arteries, while simultaneously preventing thermal damage to the arterial wall. The system has two key components, including the portable Paradise generator and a single-use six French balloon catheter. The generator facilitates each step by controlling the ultrasound energy delivery parameters through an automated process and actively adjusts the delivered energy based on catheter size to achieve a consistent target depth of one to six millimeters of ablation from the arterial wall, regardless of artery size. The catheter includes an ultrasound transducer centered within the balloon which converts electrical energy from the generator to ultrasound energy to heat and, thereby, ablate the renal nerves. Sterile water is circulated within the balloon in a closed loop system to cool the artery and protect the arterial wall from thermal damage. The ablation profile of the Paradise system was thoroughly evaluated and confirmed in preclinical animal studies. By delivering 360-degree energy waves, the system maximizes the likelihood of effective nerve ablation. At a target depth of one to six millimeters, the system effectively ablates the majority of the renal sympathetic nerves. The unique thermal profile and first of its kind cooling system protect the arterial wall and non-target tissues from thermal injury.

Treatment strategy was shown to effectively reduce blood pressure in the clinical studies. The Paradise system was designed to treat the main renal artery and accessories and proximal branches and does not require access into the renal parenchyma. Treatment includes delivery of two to three ultrasound emissions along each main renal artery, and one ultrasound emission

along the accessory arteries and proximal side branch arteries. **Ms. Coleman** showed diagrams depicting two common anatomies and how the treatment strategy is deployed. In preclinical studies, this treatment strategy was shown to significantly reduce kidney norepinephrine levels, a marker of sympathetic nerve activity. **Ms. Coleman** reviewed the procedure and treatment strategy in more detail.

**Ms. Coleman** explained that their clinical development program includes three independently powered, randomized, double-blind, sham-controlled studies, enrolling a range of hypertensive patients. RADIANCE II, and RADIANCE-HTN SOLO enrolled patients with mild to moderate hypertension who were taking two or fewer anti-hypertensive medications at screening. Primary efficacy endpoint was designed to demonstrate the benefit of uRDN in the absence of anti-hypertensive medications. This was done to minimize potential confounding of medications on the endpoint. RADIANCE-HTN TRIO enrolled patients with uncontrolled treatment-resistant hypertension who were taking at least three anti-hypertensive medications at screening. Prior to receiving uRDN, the treatment regimen for these patients was standardized on a single pill medication, which included a combination of three fixed dose anti-hypertensive therapies, specifically Valsartan, hydrochlorothiazide, and amlodipine. Therefore, the primary effectiveness endpoint in this study assessed the benefit of uRDN in the presence of a standardized, stable regimen. More than 500 patients have been randomized across the RADIANT studies, and there is now a follow-up out to 36 months post procedure. Evidence from these studies provide a robust assessment of the safety and efficacy of uRDN.

**Ms. Coleman** advised that data will be presented supporting that Paradise uRDN system is safe and significantly reduces blood pressure in patients with both mild to moderate and resistant hypertension; the Paradise uRDN system satisfies an unmet need for those patients not responsive to anti-hypertensive medications who remain at increased risk of major cardiovascular events; the Paradise uRDN system met the pre-specified primary effectiveness endpoint in all three studies; and patients receiving uRDN achieved statistically significant and clinically meaningful reductions across multiple measures of blood pressure. Importantly, this benefit was sustained through long-term follow-up. Moreover, the Paradise system has demonstrated a favorable safety profile. No significant safety risks have been identified acutely or through long-term follow-up in SOLO, TRIO, or RADIANCE II. In addition, the primary composite safety endpoint in RADIANCE II was met with no events meeting the definition of major adverse events. Finally, the proposed indication for the Paradise system is to reduce blood pressure in patients with uncontrolled hypertension who may be inadequately responsive to or who are intolerant of anti-hypertensive medications.

**Dr. Weber** took over to provide an overview of the unmet need in the treatment of patients with hypertension. He provided statistics regarding the number of patients in the US with hypertension and noted that there is a high rate of death attributable to this condition. He noted that for the first time for a non-communicable disease, the World Health Organization has labeled hypertension as the world's leading cause of premature death and disability. He provided some history and noted that drug therapy is a recently-implemented strategy for treatment of hypertension. He advised that based on the Sprint study, which will be revisited, and some compelling meta-analysis data, The American College of Cardiology American Heart Association 2017 hypertension guidelines defined hypertension as a blood pressure of 130 mmHg over 80 mmHg or higher, and drug therapy is recommended for hypertension patients at or above 130 mmHg over 80 mmHg in most cases.

**Dr. Weber** briefly explained the methods of blood pressure measurement used in the RADIANCE studies. Ambulatory blood pressure monitoring, ABPM, was the primary method based on multiple readings taken over a 24-hour period. A major virtue of ABPM is that the readings are unbiased because neither the patient, nor the medical staff who attach the device, can see the readings until the 24-hour period is completed. ABPM's second benefit is that when patient cohorts are studied, there is no placebo effect. So even in the absence of a control group, any changes in ABPM in a study represent a true treatment effect. They also measured office blood pressures using automated devices to obtain three readings, which were then averaged. In addition, they instructed patients to measure their own blood pressure at home, morning and evening, for seven days before each clinic visit with a device identical to the one used in the office. The average of these readings was a key endpoint in the studies, since it represents a powerful predictor of cardiovascular events.

**Dr. Weber** shared slides and detailed complications in the traditional multi-drug medication strategy for treating hypertension and how the involved nature of the medication regimen presents obstacles to adherence for many patients. This adherence problem is exaggerated by the fact that most patients with hypertension are taking medications for several other indications at the same time. Data from the NHANES study show that among patients in US with hypertension, fewer than 26% of patients actually achieve target reductions. The study shows that hypertension control rates significantly deteriorated during the four-year period prior to COVID. **Dr. Weber** emphasized that one of the main reasons for deteriorating control of blood pressure is that patient adherence to their medications is frequently poor, for which nine studies were provided as evidence. He showed data suggesting that, for patients who cannot be brought down to recommended levels by standard therapies, an intervention that provides a 10 mmHg blood pressure reduction provides a most valuable absolute reduction in cardiovascular risk, especially in those patients with more severe hypertension.

**Dr. Weber** shared original findings from the Sprint study that showed once patients returned to community care, the blood pressures in the intensive group rose to the same levels as in the control group, and the previously intensive treatment patients underwent a sharp increase in total mortaliy that wiped out their earlier benefits. He advised the big lesson here is that we cannot assume that prescribed medications represent a longstanding solution to hypertension and there is a need for other treatments, such as uRDN, that do not depend on patient adherence or the renewal of prescriptions. He reiterated in conclusion that many patients continue to experience high blood pressure because they are inadequately responsive, intolerant, or non-adherent to stand of care anti-hypertensive medications. These patients remain at increased cardiovascular risk, including stroke, coronary events, heart failure and death. He reminded the committee that there is a compelling need for safe, effective, and durable treatment options of which renal denervation is a strong example that can reduce blood pressure and so help prevent major outcomes in patients.

**Dr. Kirtane** was the US Principal investigator in the RADIANT studies. He reviewed clinical trial evidence demonstrating that the Paradise uRDN provides clinically meaningful blood pressure reductions among patients with uncontrolled hypertension. The RADIANCE program consisted of three randomized, blinded, sham-controlled studies across differing patient populations with uncontrolled hypertension. Each of the three independently powered clinical trials were intended to establish definitively whether uRDN lowers blood pressure in comparison with a sham procedure. RADIANCE II and RADIANCE-SOLO enrolled patients with mild to moderate hypertension who were taking zero, one, or two anti-hypertensive medications at the

time of enrollment. RADIANCE-TRIO enrolled patients with controlled hypertension despite the use of three or more anti-hypertensive medications. All three studies emphasized the stabilization of medication regimens in order to isolate the effect of uRDN versus sham.

In RADIANCE II and SOLO, patients first had to complete a four-week washout of all anti-hypertensive medications and did not restart medications unless emergently needed until the primary endpoint was assessed. In RADIANCE-TRIO patients had more severe hypertension and could not have stopped all medications safely, but standardization was still important. As a result, patients had their anti-hypertensive medications replaced with a single combination pill of three fixed-dose anti-hypertensive medications to try to keep the regimen as stable as possible. In all three studies, patients' blood pressures were reassessed after the one-month medication stabilization to ensure that they remained hypertensive. Eligible patients then underwent non-invasive anatomic screening. If they qualified, patients underwent invasive renal angiography. If angiography confirmed that anatomy was truly suitable and arteries were without stenosis, patients were randomized to uRDN or sham. Patients wore blinders and headphones during the procedure to ensure they did not know which study arm they were in. Before discharge, the adequacy of blinding was assessed, and after discharge patients were followed by a different study team also blinded to the randomized treatment.

The primary efficacy endpoint was ascertained at two months. The comparison was the change in blood pressure between uRDN and sham at two months. RADIANCE II additionally had a powered primary safety endpoint based upon a comparison of treatment patients to a performance goal derived from the literature. In total, the RADIANT studies randomized more than 500 patients: 293 to uRDN and 213 to sham. Studies were conducted globally, with the majority of centers and patients enrolled in the US. Long-term follow-up in each study is ongoing for up to five years. Beyond primary endpoint, secondary endpoints included systolic and diastolic blood pressure measures assessed at two months. A number of additional endpoints were explored to evaluate the longer-term effects of uRDN on blood pressure control and medication burden. Baseline demographics were similar between randomized groups. The majority of the patients were male with an average age in the mid-fifties, 15 to 20% of patients self-identified as Black or African American, and patients were generally overweight with a BMI of approximately 30.

Proportion of patients taking zero to two anti-hypertensive medications at screening was well-balanced across randomized groups in RADIANCE II and SOLO. In RADIANCE-TRIO, all patients were on three or more medications at screening, with an average of four medications taken. These data highlight the number of medications often prescribed by clinicians to achieve blood pressure control for patients. Following the four-week stabilization period, blood pressure was similarly elevated between treatment groups and across the three studies. Mean daytime ambulatory systolic blood pressure was approximately 150 mmHg, and mean daytime ambulatory diastolic pressure was over 90 mmHg across groups and studies. Office blood pressure was in the mid 150 mmHg over 100 mmHg. In all three studies, treatment was successfully delivered in over 95% of patients randomized to uRDN. Average procedure time ranged between 72 and 83 minutes. Patients received, on average, between five and six emissions, with a total emission time of less than a minute. The system does not require treatment beyond the distal bifurcation of the main rental artery.

Paradise uRDN met its pre-specified primary endpoint in both RADIANCE II and RADIANCE-SOLO with the difference between uRDN and sham in both studies 6.3 mmHg in favor of uRDN. Average drop in daytime ambulatory systolic blood pressure from baseline was

approximately 8 mmHg in patients treated with uRDN. Overall reductions in blood pressure were larger with uRDN compared with sham. Sixty-four percent of uRDN patients achieved a 5 mmHg drop in blood pressure compared with 34% of sham-treated patients. Nearly half of uRDN patients achieved a drop of 10 mmHg in blood pressure compared with only 16% treated with sham, and even larger drops were more frequently observed with uRDN. Daytime and nighttime blood pressure was lower at 2 months, including in the early morning higher-risk period. Greater reductions in blood pressure with uRDN extended beyond ambulatory blood pressure, were consistent across overall ambulatory home and office pressures, and were similarly consistent for measurements of both systolic and diastolic pressures. Treatments benefits were also consistently observed. **Dr. Kirtane** advised it's important to note that similar results were observed in the SOLO study with consistent treatment effects across pre-specified subgroups.

In RADIANCE-TRIO, the daytime ambulatory systolic blood pressure reduction compared with sham was 4.5 mmHg. The drop in daytime ambulatory systolic blood pressure from baseline was 8 mmHg in patients treated with uRDN. Of note, the somewhat smaller reduction in blood pressure in comparison with sham may have been influenced by the stringent approach to missing data pre-specified with the protocol. Overall results in TRIO are consistent with a difference of approximately 5 mmHg overall in favor of uRDN compared with sham. A greater proportion of patients had reductions in blood pressure with uRDN compared with sham, and this was especially true for larger reductions in blood pressure. Consistent blood pressure reductions with uRDN over baseline and also in comparison with sham were observed throughout the 24-hour circadian cycle, including in the early morning hours.

**Dr. Kirtane** pointed out it's interesting to note that there was a greater change in blood pressure in the sham group TRIO medical trial than was seen in RADIANCE II and SOLO, emphasizing the noise or greater difficulty in ascertainment of true device-related effects within the context of background medications. Treatment benefits were consistently observed, irrespective of pre-specified subgroups. He reviewed the six month results of these studies but pointed out that each of the RADIANT studies was specifically designed to demonstrate the effects of uRDN on blood pressuring lowering at two months. He reviewed results to support longer term durability of uRDN derived from these studies, which include follow-up through 36 months from SOLO and 24 months from TRIO. Average reduction in office systolic and diastolic blood pressure compared with screening was 8.4 mmHg and 4.4 mmHg respectively and the number of medications remained largely unchanged. Similar findings were observed in TRIO, a much more difficult population of patients to manage. After six-month follow-up visit, reductions in systolic blood pressure were sustained despite some attrition of medications used, a phenomenon which **Dr. Weber** described from other studies.

**Dr. Kirtane** summarized that the pre-specified primary endpoint of blood pressure lowering of uRDN was met in all three studies, achieving one of the highest bars of clinical science of a device-based technology. In all three trails, patients treated with uRDN achieved a consistent, clinically meaningful reduction in blood pressure compared with sham. Blood pressure reductions were observed irrespective of how blood pressure was measured and benefit was observed throughout the 24-hour circadian cycle. Reductions were durable with longer-term follow-up and, moreover, were additive to the effects of medications, which is notably the way uRDN will likely be used in clinical practice.

**Dr. Chertow** served as chair of the Data Safety and Monitoring Board for SOLO, TRIO and RADIANT studies. He reviewed the data demonstrating that the Paradise uRDN system has a favorable safety profile. Adverse events were consistently collected across the studies,

including all events and device events, irrespective of the time to onset post procedure. RADIANCE II is the only study to have included a primary safety endpoint, which was a composite of major adverse events adjudicated by an independent clinical events committee. The composite of these events was compared to a pre-specified performance goal of 9.8%. RADIANCE II met pre-specified primary safety endpoint with no patients experiencing major adverse events in either treatment group. Adverse events and serious adverse events occurred at similar rates between treatment groups across all three RADIANCE studies. Higher rates of adverse and serious adverse device and/or procedure events were seen in the uRDN groups. The majority resolved within 30 days. No unexpected adverse device events were reported, and there was no increase in adverse or serious adverse events that were non-device related. Detailed narratives are provided in sponsor's briefing documents. No other serious adverse device events occurred in more than one patient across the RADIANCE studies. Investigators determined that all deaths were not related to the procedure or the investigational device.

Data was reviewed regarding kidney function and vascular safety. At month 12, CT or MR angiography was required for all patients who received uRDN. Independent diagnostic radiologists reported on any injury to or any narrowing of the rental artery. Based on core lab adjudication, there was no evidence of kidney injury or clinically significant renal artery stenosis in the uRDN treated patients. Ninety-eight percent of treated patients had no measurable stenosis. The proportion of patients with any renal artery stenosis was balanced between treatment groups, and no patients experienced clinically significant flow limiting narrowing of more than 70%. Safety data was further characterized. In conclusion, Paradise uRDN has a favorable safety profile. While procedure related events did occur, all resolved without sequelae. There was no evidence of acute or long-term kidney injury and no evidence of renal artery injury or any clinically significant renal artery stenosis.

**Dr. Reeve-Stoffer** as Chief Clinical Officer stated that ReCor is fully committed to continuing to collect data on the long-term efficacy and safety of the Paradise system and is proposing a multi-component clinical program post-approval. Remaining subjects enrolled in RADIANCE studies will be followed for up to five years. ReCor plans to initiate a US arm of the Global Paradise System Registry to evaluate long-term safety and efficacy of uRDN in a real-world setting. They anticipate that enrolling 700 subjects will allow them to achieve 500 evaluable patients in five years. She detailed methods to ensure validity of this data.

**Dr. Naomi Fisher,** as a physician who has dedicated her career to helping patients with high blood pressure provided a clinical perspective. She emphasized there is a critical unmet need to control high blood pressure. She reiterated that lifestyle changes and medication alone are not working and additional treatment options are needed for clinicians. Benefits achieved at two months with Paradise uRDN represent a clinically robust outcome for patients in all three RADIANCE studies, aiding outcomes such as reduced major cardiovascular disease, stroke, and heart failure. Data showed that the Paradise system lowered blood pressure to a clinically meaningful degree at two months, the primary endpoint, but data across the studies also showed that it provides consistent reductions throughout a 24-hour circadian cycle. She emphasized the point that given the half-life of medications and given that most patients take their medications in the morning, drug concentrations in the blood are often lowest during critical early morning hours before the next dose, but uRDN lowered blood pressure below target during this vulnerable period of cardiovascular risk. The totality of safety data supports that uRDN is safe. Her clinical perspective is that she feels confident to recommend this therapy, it could fill a critical gap in care, and the benefits of uRDN far outweigh the risks.

**Q&A**

**Dr. Lange** gave the panel the opportunity to ask clarifying questions to the sponsor or ask the sponsor for additional data, but reminded the panel this is not the time for deliberations. **Dr. Allen** asked if crossover was allowed, when it occurred, and how it was put into the statistical analysis. **Dr. Reeve-Stoffer** said crossover was allowed for patients whose blood pressure remained uncontrolled, and the crossover was allowed after the six-month follow-up in all studies and showed a slide demonstrating a drop in blood pressure of at least 10 mmHg that was sustained over 12 months.

**Dr. Allen** asked if crossovers are taken out of the analysis in the long-term, and **Dr. Reeve-Stoffer** advised that he is correct, and they are analyzed separately.

**Dr. Somberg** asked three questions: How many patients didn't have an appropriate anatomy? Since it's a closed system, what happens if there is a leak? Was there a learning effect with the operators? **Dr. Reeve-Stoffer** advised that anatomy was looked at two different ways, and it was about 20 to 25% of patients that were excluded for this reason throughout the different studies. With respect to the closed system, if you have a pinhole in the balloon, which would be the equivalent of a leak, there's a pressure error that would indicate they could not move forward with the procedure. A formal analysis was not done of the learning effect, but there was no difference between outcomes of blood pressure changes, so they don't believe there was a learning effect.

**Dr. Lewis** asked if there were specific case report form questions that established a patient was intolerant to meds and the reason. How does training post-approval compare to PI training? Since sham patients with uncontrolled blood pressure were given the opportunity to crossover, he requested to show the number of sham patients who were uncontrolled versus the number that chose to crossover. **Dr. Reeve-Stoffer** advised that data was not collected about the meds. Training for post-approval will be similar, if not more stringent, than for the clinical trials. They are proposing that physicians have didactic and hands-on training, and they will be proctoring cases for at least first five procedures. She will get the sham patient information over break.

**Dr. Wittes** asked for data that shows crossover that included everybody in intention to treat analysis, specifically intention to treat data at six months? **Dr. Saville** and **Dr. Yeh** later joined in this request. **Dr. Reeve-Stoffer** will find this data over the break. **Dr. Wittes** wants to know the distribution of number of medications in SOLO and RADIANCE II at baseline compared to six months and 12 months. **Dr. Reeve-Stoffer** advised that distribution would be slightly different because the patients were taken off their medications and then titrated. **Dr. Wittes** clarified she wants to know how many were on one and then stayed on one, or two, and so on. She wants change from baseline and she understands it's baseline before the medications were discontinued. She asked where does the 9.8% performance goal come from, and, finally, if blood pressure starts going up, can a second ablation be done. **Dr. Reeve-Stoffer** stated performance goal is based on literature, mainly from renal stenting literature. As far as second ablation, they have not systemically or systematically performed a second renal denervation procedure in these study patients. There are small cohorts of published data showing patients who did receive a second one did well.

**Dr. Blankenship** understood from the briefing document that the exclusion for anatomy was about 10%, and **Dr. Reeve-Stoffer** advised 20 to 25%. What were the anatomic exclusion criteria? **Dr. Coleman** answered that exclusions with regard to anatomy were two-fold: anatomical criteria due to balloon size, which changed over time; so arterial size and exclusions

in regard to underlying pathology. Many of the reasons for screen failure were related to underlying pathology.

**Dr. Blankenship** asked about clinically meaningful differences in serum creatinine and estimated GFR. **Dr. Chertow** confirmed no statistically significant increases in serum creatinine or decreases in the corresponding estimated GFR.

**Dr. Corriere** asked about the sheath diameter of the device, was there protocolized access as part of study protocol, was the site of access predetermined, were there exclusion criteria, did they mandate use of closure devices, etc. **Dr. Reeve-Stoffer** stated it is a six French catheter, requires a seven French guide. There was no predetermined protocol regarding either access or closure. It's femoral access, and the majority of sites either only needed to use pressure or in a few occasional instances a closure device. No trans-radial access was performed.

**Dr. Bates** asked what were the difficulties in enrolling the patients who are screened for these protocols? **Dr. Reeve-Stoffer** stated the major challenge was the strict criteria around entry blood pressure. Particularly in TRIO, when they took patients off meds and put them on the single-triple pill, the majority of the patients became controlled, which proves medication adherence is an issue.

**Dr. Bates** said if his arithmetic is correct, only one to two patients were randomized per site per year. **Dr. Reeve-Stoffer** explained we had COVID during RADIANCE II, and these patients are normally seen within investigative sites, so they had to adapt enrollment methods. **Dr. Kirtane** added that patients had to be willing to come off their medications entirely, and that's also exceedingly difficult. When these trials were enrolling, most people felt this technology didn't work or prior studies showed that it didn't. So in that backdrop, it was remarkable that they were still able to randomize so many patients.

**Dr. Zuckerman** brought panel's attention to Sponsor's slide 45 where they have a p value of 0.022. It's important to recognize that this is not the p value shown by FDA and the FDA statistician. It will be covered in the next presentation, but he wanted the panel to be on notice.

**Deneen Hesser** asked if the Sponsor anticipates any obstacles or barriers to integration of this treatment into underserved communities where need may be greatest. Was use of RDN as an adjunctive treatment offered? **Dr. Reeve-Stoffer** recognized they did not have representative patients from underserved populations, but they plan to actively enrolling those groups in the post-approval study. Use of uRDN was an adjunctive treatment choice.

**Mr. Vaughan**, consumer rep, asked about cost, and **Dr. Lange** reminded him that the FDA and panel is not to consider cost.

**Dr. Starling** asked for more info on the medication regimen in TRIO. **Dr. Reeve-Stoffer** provided more detail.

In response to a question asked by **Dr. Cetnarowski, Dr. Lange** confirmed the sponsor would address similar questions asked previously after the break, including questions regarding slides 61 and 63. **Dr. Lange** asked the sponsor to address how diabetics versus non-diabetics responded after break as well.

**FDA PRESENTATION**

**Dr. Paul Warren** provided statistics from NHANES regarding the disease burden and shared the sponsor's history with FDA, including breakthrough device desingation in 2020, and provided definitions and parameters for the study. He introduced ReCor's three studies and summarized key design by criteria. Patients meeting a pre-specified blood pressure threshold and other initial criteria were enrolled. SOLO and RADIANCE II then discontinued their medications for a four-week washout period. TRIO had their medications replaced with a single, fixed-dose, triple combination pill and then underwent a four-week stabilization period on the triple pill. Then subjects who met the criteria for daytime AMBP were randomized. Some additional key design elements included a pre-specified medication escalation plan between two and six months, study blinding through 6 months through SOLO and TRIO and 12 months for RADIANCE II, and sham patients being permitted to cross over to uRDN group after six months in SOLO and TRIO and 12 months in RADIANCE II.

**Dr. Wei-Chen Chen** discussed the main differences in statistical analysis plans for the primary safety and effectiveness endpoints. In SOLO and TRIO, there was no pre-specified primary safety endpoint and primary effectiveness was pre-specified and tested. In RADIANCE II, the primary safety endpoint was defined as the occurrence of at least one major adverse event, MAE, at 30 days post-procedure or new hemodynamically, significant artery stenosis at six months. The safety event rate performance goal, PG, was set at 9.8% based on literature review. The hypothesis was a comparison of the proportion of subjects who had at least one safety endpoint event to the PG. The success was determined from the upper limit of a one-sided 95% confidence interval around observed safety event rate. Primary effectiveness endpoint for each of the trails was defined as the change in daytime ambulatory systolic BP from baseline to two months. A gatekeeping procedure was used to control the overall type one error rate for these secondary endpoints. However, P-values in other secondary additional and exploratory endpoint analyses were not adjusted for multiplicity and should be interpreted with caution.

**Dr. Silverstein** briefly recapped the three trials. Turning to baseline study subject characteristics, randomization resulted in an equal distribution between RDN and sham for all major criteria. He provided primary safety endpoint results as follows: Among 150 RADIANCE II subjects, safety event rate was 0% with a confidence interval of zero to 1.63%, which met the pre-specified PG of 9.8%. A pooled analysis of all three trials showed a 1.1% safety event rate with a confidence interval of 0.3% to 2.77%. Next he discussed observed safety events for the studies as follows: the overall percentage of events was low in all three trials. There was one hospitalization in SOLO trial. In TRIO, there were two deaths. There were two major vascular complications, a pseudo aneurysm and dissection, and one blood pressure related hospitalization in TRIO. There were no cases of decreased renal blood flow. Results were statistically significant, but FDA believes the differences are not clinically significant.

**Dr. Silverstein** summarized that the agency believes that despite all the data, a proportion of subjects achieving at least a 5 mmHg reduction in systolic BP is clinically meaningful. In all three studies, a greater proportion of RDN subjects achieved at least 5, 10, or 15 mmHg decline in daytime systolic BP than sham. P values were not adjusted for multiplicity. All results favored RDN. At two months, BP reduction was greater in RDN versus sham for all three studies. For RDN at two months, there is reduction in BP throughout the day. At six months, when all RDN and sham subjects could have been back on BP meds, RDN and sham curves appear to be similar. Thereafter, RDN subjects had greater declined in daytime BP compared to sham, and RDN group is receiving a numerically lower number of medications.

**Dr. Gebben** discussed PPI, patient preference information, and the role it can play in the regulatory decision. Sponsor conducted a PPI study engaging 258 respondents through a survey. At the early stage, sponsor discussed a PPI study with FDA; however, sponsor did not confer with FDA on the final level of attributes before conducting the PPI and submitting the results in the PMA. A few attribute levels are not supported by evidence, which may have tilted PPI study results toward the uRDN procedure. Greatest weight by respondents was placed on absolute reduction in 10 years of CV risk, which was more important to respondents than side effects and risk of treatments. While not in the FDA executive summary, sponsor estimated that 42% of respondents would choose uRDN over taking a pill when all other attribute levels are held constant.

**Dr. Warren** reiterated ReCor's proposed post-approval study, which **Dr. Reeve-Stoffer** mentioned during the sponsor presentation. As the study design has not been finalized, FDA would appreciate panel's feedback on key aspects of post-approval study. The summary of FDA conclusions is as follows: primary safety endpoint for the largest study, RADIANCE II, was met with safety event rate of 0% and 1.1% safety event rate in the pooled analysis of uRDN subjects across all three studies. The primary effectiveness endpoint was met for SOLO and RADIANCE II. Strengths: clinical investigation included three sham-controlled, randomized trails that were independently powered for effectiveness. Limitations: small sample size for long-term data in uRDN patients with data on 51 SOLO subjects at three years and 51 TRIO subjects at two years, as well as challenges in interpreting durability of BP reduction due to BP medication changes after two months, subject blinding, and sham subject crossover to uRDN, which reduced control group sample size. The PPu study found that some patients may prefer uRDN treatment to taking an additional pill, all else being considered equal.

**Q&A**

**Dr. Hirshfeld** asked if they are really looking at the analysis in the right way, when the entire analysis is based on group mean differences. Is efficacy being overstated? **Dr. Silverstein** addressed there was a differential effect depending on the patient's baseline BP. **Dr. Zuckerman** interjected that this is a breakthrough device designation, and they need the panel's help with should they be looking more closely at these questions regarding predictors of success.

**Dr. Wittes** stated that the FDA looked at residuals from ANCOVA, residuals were not normally distributed, so that made them switch to a ranks analysis. **Dr. Chen** confirmed that is what happened. **Dr. Wittes** asked how big outliers were, were multiple imputations used for SOLO AND TRIO, and why, in RADIANCE-II, were almost a full third of the patients on no medication before they entered the study. **Dr. Reeve-Stoffer** said this could be answered after lunch.

**Dr. Bates** wanted clarification on the direction of how to evaluate today's meeting. Should this be considered a treatment option after five drugs or two drugs? **Dr. Zuckerman** said that the panel, as expert clinicians, needs to provide advice to the FDA regarding how this technology can diffuse out into the real world patients and what are reasonable indications.

**Dr. Lange** made a list of questions for the Sponsor and FDA to gather data for over lunch and respond when they reconvened. **Dr. Lange** advised that it was lunch time and the panel would reconvene at 1:30 PM for the Open Public Hearing.

**OPEN PUBLIC HEARING**

**Dr. Lange** called the meeting back to order a couple of minutes after 1:30. **Mr. Collier** read the Open Public Hearing disclosure statement. The FDA received seven requests to speak. The first six were pre-recorded, followed by one live presentation.

**Dr. Giri** spoke as a treating physician of a need for a potential novel treatment for hypertension. He felt uRDN had passed with flying colors. He recommended that everyone look favorably upon the data as it was presented.

**Dr. Rader**, a treating physician, noted that RDN lowers blood pressure in a meaningful way and will be a vastly beneficial treatment for many.

**Candyce Anderson**, a patient of the ReCor trial, saw positive benefit and recommended this be made available to patients.

**Gerald Gray, aka "Jerry"** provided another anecdote of an excellent clinical trial experience.

**Gene Barnett** shared his clinical trial experience and has seen dramatic reduction in medication and improved quality of life.

**Cynthia Brown** echoed another positive clinical trial experience as a crossover patient.

**Jessica Copeland** spoke on behalf of the National Center for Health Research. She showed that the anti-hypertensive efficacy of the Paradise system compared to other medication shows that the BP lowering effect of the Paradise system is less than every other single anti-hypertension medication, with the exception of one. She advised that the data presented does not support that the threshold of reduction in ASBP has been met, and there is a larger concern that the magnitude of BP reduction from RDN in general is thought to decrease over time. She asserted data on the long-term risks are very limited and that a more sound, evidence-based solution is necessary.

**PANEL DELIBERATIONS**

**Dr. Lange** announced the Open Public Hearing to be officially closed. He advised, first, that there were additional questions and/or slides or data requested either from the FDA or Sponsor that would help in the deliberations, and he wanted to let them speak to that, including one from **Dr. Lewis** about the number of uncontrolled patients in sham that proceeded to crossover and how many did not. **Dr. Reeve-Stoffer** advised for clarification, due to a large number of questions falling into the same categories, that they grouped their data by category. **Dr. Lange** asked to hold questions until the end of additional info, and then if any weren't answered, they would be addressed.

In response to many questions about crossover questions, **Dr. Reeve-Stoffer** advised she needed to clarify how the protocols were written. For RADIANCE HTN, which contained both TRIO and SOLO cohorts, crossover could occur at six months with the caveat that the primary efficacy endpoint had to have been met, which meant patients weren't crossing over before 12 months. RADIANCE II was a pivotal study and already based on primary effectiveness being demonstrated, so patients could cross over at 12 months. **Dr. Saville** clarified that "met" meant they achieved statistical significance on the primary endpoint. **Dr. Reeve-Stoffer** confirmed. She provided both percentage and number of patients that crossed over in TRIO and the SOLO and stated their numbers are higher than the FDA presentation because crossover was ongoing. **Dr. Lange** reiterated that none of these patients, SOLO or TRIO, had crossed over by the 12 month period. **Dr. Reeve-Stoffer** confirmed. **Dr. Lewis** confirmed her question was answered.

**Dr. Reeve-Stoffer** showed a slide addressing the question about ambulatory blood pressure ITT analysis, including crossover for SOLO and TRIO at six and 12 months. **Dr. Wittes** asked for information regarding sham-treatred patients **Dr. Reeve-Stoffer** advised they have a copy of the FDA data that shows the data. **Dr. Lange** asked even though ITT includes a core of crossover patients at 12 months, none of them had crossed over? **Dr. Reeve-Stoffer** confirmed.

**Dr. Kirtane** spoke about the unique study designs employed for these trials. They had a primary endpoint assessed at two months where there was a comparison between RND versus sham treatment. He gave an example of what actually occurred within these studies, but summarized that after two months, due to titration of medication after randomization, it became difficult to determine between group differences because both groups were being titrated under blinded circumstances with the exact same goal, to lower blood pressure. So they expected pressures to be similar at six or 12 months. They looked for ways to discern if there was actually a difference between groups, and there was no statistical heterogeneity between groups. He presented slide and explained if you looked at the six-month differences between blood pressures, adjusting for differences in medications, you require all three studies together to get the power to discern that there is an actual difference in blood pressure. But you do see persistence of effect.

**Dr. Zuckerman** interjected and asked panel to understand that this mixed model has not been independently verified by FDA statistics.

**Dr. Saville** asked, based on the last graph they observed, if the mixed model was adjusting for number of meds that visit and if that was a post-randomization value that was being adjusted for. **Dr. Kirtane** affirmed. **Dr. Saville** asked, all things being equal, what was the difference in systolic blood pressure? **Dr. Kirtane** stated this was an exploratory analysis and there were post-randomization covariates. He summarized that at six months, there were double the number of patients in the RDN group that were on zero meds compared to sham treatment. More patients in the sham-treated group were on three or more meds.

**Dr. Wittes** advised this didn't answer her question because she wanted to know what happened per person, and this just gives total. **Dr. Kirtane** said he would see if they can provide that data. He pointed out that based on the ITT analysis shown in the FDA breifing document the RDN blood pressures were lower than the sham group from 12 to 24 months. **Dr. Lange** pointed out this was office blood pressure and asked if home blood pressure looks like that. **Dr. Kirtane** said they don't have home or daytime beyond 12 months.

**Dr. Wittes** stated this is not really ITT because it's missing all types of data. It's good for the first six months and then missing info. There was not an imputation. **Dr. Kirtane** responded that the FDA generated this graph. His understanding is it did include crossover patients and included all available data for follow-up time point that was available to the FDA. **Dr. Wittes** said it was missing 24-hr data, which is about one-third of patients and the 12 month data is missing 10% of patients.

**Dr. Saville** questioned if an analysis comparing patients with missing data to those with complete data had been perforned.

**Dr. Kirtane** stated those could be conducted. He presented other helpful data, and then noted that slide 47 shows ITT analysis, all the patients that had their ABPMS, and ITT with multiple imputations because it was done after the fact. He also gave examples of 10 patients, in both groups, where they imputed a zero and advised if they had accounted for those 10 differently, they might have actually observed a greater treatment effect. **Dr. Kirtane** presented waterfall plots showing the RDN group and sham group. In all data presented, RDN was favored over sham treatment.

**Chris Mullin** stated that some colleagues had run a proportional odds model over the lunch break. This was a post-hoc analysis, and the FDA had not

had a chance to review with all the caveats that need to be provided, but they found increased odds of greater reduction in blood pressure for treatment compared to sham with an odds ratio of approximately 2.2 and a p-value of about 0.018.

**Dr. Saville** stated this was helpful and gives a two-sided p-value.

**Dr. Reeve-Stoffer** advised that there was a question regarding energy from the device at presence of calcification. **Dr. Coleman** clarified that energy could potentially be deflected towards arterial wall due to calcification, but because they are actively cooling and protecting the arterial wall from thermal injury, they do not anticipate safety concerns.

**Dr. Kirtane** provided more detail about medication burden. **Dr. Reeve-Stoffer** provided an answer about BP response in diabetic versus non-diabetic patients. Although there was a small number with diabetes in the study group, there was no statistical difference.

**Dr. Reeve-Stoffer** advised there was a question asked about interaction with abdominal obesity at six months, there was no interaction.

She advised the last question regarding clinical implication of six-month durability could be answered by **Dr. Fisher. Dr. Fisher** reminded the panel that the primary outcome in these studies was at two months. They were not designed to look at results at six month and beyond. Durability in a blood pressure trial comparing sham, untreated patients, was really unprecedented. Longer trials comparing active BP treatment versus placebo for extended periods (ie, many months) had not been conducted

for ethical reasons. Patients considering RDN are looking for a lasting effect.

**Dr. Kirtane** presented one shift table for the SOLO trial and explained its implications. He said it showed more patients in the green than other groups and in the RDN group compared to sham treatment. **Dr. Wittes** stated this was useful.

**Dr. Lange** asked FDA if there was any outstanding data they need to present.

**Dr. Zuckerman** stated no but underlined Dr. Fisher's point that Sponsor and FDA had to come up with a length of time that was ethical and scientifically justified, and that's why two to three-month endpoint was there. **Dr. Lange** advised the panel to take a break and be prepared for a robust and meaningful discussion of the FDA questions at 3:00.

**FDA QUESTIONS**

**Dr. Lange** called the meeting back to order at 3 PM Eastern time to focus all discussion on the FDA questions to the panel.

**QUESTION ONE**

**Dr. Warren** read question 1, related to safety: As a reminder, the primary safety endpoint was a composite of the rate of major adverse events (MAEs) through 30 days and new renal artery stenosis greater than 70% through six months. For RADIANCE-II, the safety event rate was 0% with an upper bound of the 95% confidence interval of 1.63%, which means that the pre-specified performance goal of 9.8% was met. The pooled safety event rate from all three studies was 1.1% with the upper bound of the 95% confidence interval being 2.75%. Of the six MAEs, two were deaths, two were major vascular complications, one was a hypotensive crisis, and one was hospitalization for pre-syncope. For renal artery stenosis, 238 subjects had evaluable CTA or MRA imaging at 12 months across all three studies. There were no cases of hemodynamically significant renal artery stenosis greater than 70%, but there were a small number of cases of mild to moderate

narrowing, as you can see in these sub-bullets here. In terms of renal function, there were no clinically significant changes in eGFR or serum creatinine. So, overall, the safety event rate was low. No significant renal artery stenosis was observed. Although mild to moderate narrowing was not associated with a functional reduction in renal blood flow, the long-term follow-up data are limited and it was not clear if renal artery lesions would change over time. So, the panel was asked to discuss the acute and midterm procedural and device safety profile of uRDN and the clinical significance of renal artery responses to uRDN treatment.

**Dr. Hirshfeld** did not feel safety was an identifiable issue at this point. He did agree that long-term follow-up is still appropriate. **Dr. Lange** asked **Dr. Bates,** as an interventionalist, if he has concerns. **Dr. Bates** suggested that he suspects the complications from the access site are undercounted. Although he doesn't see a major safety endpoint, it's a little too "rosy" to say there are no safety outcome problems. **Dr. Lange** asked if there are any dissenting views from Dr, Blankenship and Dr. Allen. **Dr. Blankenship** agreed with Dr. Bates that the data showed primarily access complications. He felt complication rate was low for femoral access. He suspects that radial access will be most commonly used in the community setting.

He has no significant safety concerns. **Dr. Allen,** from a vascular surgery standpoint, feels this is a relatively low risk procedure with this device. He doesn't think safety is an issue. **Mr. Vaughan** said to note company's last month press release recommending RND should be performed in experienced, specialized centers. He advised that should be talked about later in terms of the warning labels.

**Dr. Lange** summarized that the panel generally believes that procedural risks are related to vascular access and very little, if any, risk assigned to uRDN. He asked **Dr. Zuckerman** if the summary was sufficient. **Dr. Zuckerman** asked if **Dr. Corriere,** as a vascular surgeon, would also comment on safety. **Dr. Corriere** stated he agrees with previous comments. Event rates in this study were much lower than usually with six French access site catheters. If there were higher rates of complications it would have a drastic effect on the benefit versus risk for this intervention.

**QUESTION TWO**

**Dr. Warren** read question two related to effectiveness. Data had been presented using both ambulatory blood pressure and office blood pressure measurements. Most prior hypertension trials used office blood pressure measurements. However, ambulatory blood pressure measurement had been shown to have greater prognostic value and was identified as preferable at the 2018 FDA panel meeting. This may had been due to the large number of blood pressure assessments made for ambulatory blood pressure that are free from potential biases, for example, the white coat effect. The FDA presented these figures earlier, in the morning presentation. The data showed blood pressure reduction iat two months in the active-treated and sham-treated patients in all three studies. They also show 24-hour ambulatory blood pressure reduction, daytime ambulatory blood pressure reduction, and office blood pressure reduction. In SOLO and RADIANCE-II, the office blood pressure reduction was greater than the ambulatory blood pressure reduction for both active treatment and Sham treatment. However, in TRIO, the office blood pressure reduction was comparable to the 24-hour and daytime ambulatory blood pressure reductions in the treatment group. For the Sham-treated group, the office blood pressure reduction was actually smaller than either of the ambulatory blood pressure reductions. The panel was asked to discuss the relative value of ambulatory versus

office blood pressure measurement in assessing changes in blood pressure, for purposes of evaluating the effectiveness of uRDN.

**Dr. Somberg** stated they are both useful. He stated differences and pros and cons for both, but advised there is a value to measuring both, and he felt it was succesfully lowered with RDN in all three studies at that two-month endpoint. **Dr. Starling** and **Dr. Blankenship** consider ambulatory as the gold standard, and noted that Hypertension Academic Research Consortium endorses ambulatory blood pressure. **Dr. Lange** asked FDA to put up slides 54 and 55. He reviewed the data and advised he doesn't trust an office reading. In his opinion, the home blood pressure measurement is more likely to represent what's going on throughout the day. **Dr. Zuckerman** asked to go back to question slide seven. He feels **Dr. Lange's** points about ambulatory are very important, but there are two types of ambulatory blood pressure, daytime and 24-hour. He asked the hypertension experts on the panel to further define what is meant by ambulatory and if there is a better one. **Dr. Somberg** is of the opinion it's better to look at the full 24-hour because they know patients with nocturnal hypertension are most at risk for cardiovascular events. **Dr. Lewis** believes ambulatory was ~~im~~portant based on limited sample size. **Dr. Lange** asked **Dr. Lewis** if they do a post-approval study that has hundreds of patients, if not thousands, would she recommend an ambulatory blood pressure or would she feel comfortable using only the office blood pressure.

**Dr. Lewis** answered ambulatory. In thinking for long-term, sponsor proposed a patient home mechanism of measurement. **Dr. Wittes** requested that it would be better and easier if the FDA could present these as box plots so they could see variability. **Dr. Saville** seconded that. **Dr. Starling** strongly favored the ambulatory.

**Dr. Lange** summarized that the panel's opinion is ambulatory blood pressure is the gold standard, especially if looking for relative differences in small sample sizes. No person said office blood pressure alone was sufficient. Some said they would like both. **Dr. Zuckerman** responded saying it is excellent, including the suggestions from **Dr. Wittes** and **Dr. Saville** regarding the presentation of the data.

**QUESTION THREE**

**Dr. Warren** read question three also related to effectiveness. The FDA and ReCor reviewed the discussions during the 2018 Circulatory System Devices Advisory Panel, and there was debate regarding the panel's opinion about the relative importance of absolute blood pressure reduction from baseline compared to the between-group difference in blood pressure reduction. In the FDA's interpretation of the panel's discussions, five mmHg difference in systolic blood pressure reduction measured by ABPM between treatment groups was considered to be clinically significant. The primary effectiveness endpoint in SOLO, RADIANCE-II, and TRIO was the difference in mean reduction in daytime ambulatory systolic blood pressure at two months between uRDN and Sham treatment. The ITT population results showed a between-group difference of 6.3 mmHg in favor of uRDN for the off-blood pressure medication studies in Solo and RADIANCE-II, and 4.5 mmHg difference in favor of uRDN for the on standardized medication study~~-~~, TRIO. The panel was asked to discuss the clinical significance of the absolute blood pressure reduction in uRDN subjects versus the difference in blood pressure reduction between uRDN and Sham-treated groups in evaluating the treatment effect for SOLO, TRIO, and RADIANCE-II.

**Dr. Lewis** was more impressed with the table that showed the percentage of patients in the two groups that achieved a greater than 5 mmHG or greater than 10 mmHg than the mean blood pressure differences. **Dr. Somberg** agrees with **Dr. Lewis.** The absolute reduction was not the metric. It was the difference between the sham compared to the intervention that was most critical. **Dr. Yeh** agreed with **Drs. Somberg and Lewis.** He feels heterogeneity would be one of the important goals of any subsequent study to understand treatment effect. **Dr. Hirshfeld** asked the sponsor to show the slide with individual responses stratified by directionality of response to illustrate what they are confronting. With the waterfall plot it was more possible to see what was going on in the whole patient population. **Dr. Saville** agreed with other panel members. He advised not to get too hung up on the data. You're still seeing a consistent trend across the studies that, he believes, is showing benefit. **Dr. Lange** remarked to **Drs. Wittes and Saville** that post-approval study would likely be single arm. If it's a single-arm, there likely won't be a sham group. Give FDA some direction on this. **Dr. Yeh** is of the opinion that single arm difference compared to baseline over time or number of medication over time is imperfect but probably most feasible to understand long-term durability. **Dr. Hirshfeld** thought this really emphasizes the heterogeneity of the population and oversimplification that is derived from converting all of this data into a mean value. It emphasizes the noise in the data. **Dr. Wittes** feels the question is on the long-term effect of this intervention compared to real-life where there would be changes of medication. She feels it would be complicated to do a controlled study, but it would be very important to collect not only safety data, but the data on the use of medications in the population that has the intervention. **Dr. Somberg** believe the sponsor had established duration of effect because BP goes down and stays down. He agreed with **Dr. Yeh** that in some post-marketing areas, a single arm is appropriate, but in others it may not be. **Dr. Saville** agreed with most of these comments. If one has really good data for comparison, a single arm study could be helpful for figuring out long-term benefit and how this intervention compares. Otherwise, long-term it would be difficult to show if the lower blood pressure was due to denervation or if it was due to medications. **Dr. Bates** stated he was going to say something similar. It would be impossible to get efficacy data on a post-marketing study for 500 patients with the confounding variables, but it would provide absolute and percentage blood pressure reduction achieved and in seeing a waterfall analysis safety data.

**Dr. Lange** summarized the panel was interested in absolute reduction and percentage achieved. They are interested in the waterfall plot. They were also interested in looking at effect/durability and whether there is a long-term effect in terms of decreasing number of medications or dosage. Everybody agrees it will be difficult to show a long-term effect or durability in a single-arm study. **Dr. Zuckerman** did not need any clarification on this response.

**QUESTION FOUR**

**Dr. Warren** read question four. The difference in daytime ASBP reduction favored uRDN over Sham treatment at two months, in all three studies. Further blood pressure lowering versus baseline was seen beyond two months but the difference in mean daytime ASBP reduction between uRDN and Sham treatment was not significant, at six months and beyond. Changes in medication may impact the blood pressure results. The medication burden in the uRDN and Sham-treated groups at two, six, and 12 months were shown in the table. In general, at six and 12 months, the Sham-treated group took more medications and had a higher medication load index compared to uRDN, but the differences appeared small.

Challenges in interpreting longer-term blood pressure data included blood pressure medication prescription following a pre-specified escalation protocol to attain a target blood pressure of less than or equal to 135/85 mmHg, between two and six months, for all studies; studies being unblinded at six months for SOLO and Trio and at 12 months for RADIANCE-II; a crossover from Sham to active treatment group being allowed starting at six months for SOLO and TRIO, and at 12 months for RADIANCE-II, which reduced the sample size of the Sham groups at later time points; and finally, RADIANCE-II, having limited data beyond six months. At 24 months office blood pressure data was available for 56 uRDN subjects in SOLO and 42 uRDN subjects in TRIO. Please discuss the strengths and limitations of longer-term blood pressure data in patients treated with uRDN, including whether uRDN provides a durable reduction in blood pressure, the clinical significance of longer-term blood pressure changes in uRDN subjects versus sham treated, and the clinical significance of blood pressure medication differences between uRDN and Sham treatment subjects.

**Dr. Somberg** said this has been covered before, and his take home message here is denervation is not superior to meds. **Dr. Lewis** agrees. **Dr. Starling** feels it's difficult to reach a conclusion. He is comforted that medication burden appears to be less in renal denervation group. **Dr. Allen** stated reasons why he grapples with approving this, including he doesn't think it will be durable. **Dr. Nachman** echoes his colleagues. His opinion is it seems the patient population with lowest risk and degree of severity may be the most to benefit. **Dr. Saville** says there is clearly acute short-term benefit but unclear about long-term. **Dr. Blankenship** said another way of looking at it is uRDN might make a huge difference for a substantial minority of patients and that may be a trade-off worth making. **Dr. Wittes** disagrees with what was just said. She would need to be convinced that getting less than one drug difference in six or 12 months would make her want to have an intervention.

**Dr. Lange** summarized that a lot of people expressed their point of view that intervention is not superior to medication. Is it clinically significant in terms of getting people off medications? The numbers are the same. Ben summed it up best that studies weren't designed to answer durability. The general feeling is if there is a benefit, it's relatively modest at most.

**Dr. Lewis** mentioned this should be addressed in labeling. **Dr. Nachman** is concerned that patients at highest risk are not likely to develop benefit from it.

**Dr. Somberg** dissented because he doesn't think the question is the benefit of this procedure over alternative approaches. **Dr. Zuckerman** interrupted and advised this was a great discussion, but the question really refers to durability of blood pressure reduction, and what I heard was a mixture of opinions regarding long-term durability due to problems with interpretation of data. So there's uncertainty regarding a unanimous opinion on this panel. He asked **Dr. Lange** if that is a fair summary. **Dr. Lange** agreed it's an excellent summary.

**QUESTION FIVE**

**Dr. Warren** read question five regarding PPI. ReCor conducted a patient preference study with 258 patients to ascertain preferences for the uRDN procedure compared to blood pressure pills only. Based on the preference weights, 42% of respondents would choose the uRDN procedure over an additional antihypertensive medication Two attribute levels did not correspond, however, to the available clinical

evidence which may have impacted the respondents' choices. Please discuss the degree of importance that the patient preference study results should be given when considering supplemental benefit-risk assessment information.

**Dr. Lewis** said the issue is patients are being asked to compare something they've never experienced, nor have much insight into. **Mr. Vaughan** noted the study showed 42% of patients willing to do this, yet a similar study to be presented tomorrow in a similar device with similar questions found 15 to 31% preference. **Dr. Lange** said that can be addressed tomorrow. **Mr. Vaughan** feels consumers are most concerned about cost of healthcare, and to have a PPI study without cost and cost-benefit is useless. **Deneen Hesser** feels that an overall high-level view of the study is that patients asked for a long-term reduction in their cardiovascular risk and as few drugs as possible, and they were willing to accept some amount of risk to do that. A post-market study should require a good patient education program so patients can accept whatever risk level they are interested in, and she feels patient-reported outcomes would have been helpful. **Dr. Corriere** said he thought discussion was good. It was great to see a PPI study. **Dr. Blankenship** noted it's striking that patients will consistently opt for an invasive procedure over ongoing medical therapy like medication. So data is not surprising. **Dr. Damluji** emphasized the importance of compliance and adherence. That is likely driving patient responses. **Dr. Saville** advise the question is to discuss the degree of importance that the PPI results should be given. There is a disconnect between the PPI study and the actual data seen in the trial. It's not clear that the PPI study, as it stands, translates well to the data.

**Dr. Lange** summarized safety and efficacy and patient desire and preference are of prime importance. The sponsor should work with FDA to provide a reasonable PPI study and, as **Ms. Hesser** said, look at patient-reported outcomes as well. It doesn't seem anybody puts a lot of confidence in this particular PPI study. **Dr. Zuckerman** agreed the response is helpful. He heard the panel say that obtaining a better connection between the clinical questions faced by a patient and the PPI is paramount. **Dr. Lange** advised he believes so.

**QUESTION SIX**

**Dr. Warren** read question six related to labeling. ReCor evaluated subjects with mild to moderate hypertension in SOLO, resistant hypertension in TRIO, and Stage 2 hypertension in RADIANCE-II, as defined in this table. The proposed indications for use are the Paradise uRDN system is to reduce blood pressure in patients with uncontrolled hypertension, who may be inadequately responsive to, or intolerant to anti-hypertensive medications. Please discuss whether the available clinical data support the proposed indications for use, Also, please discuss if the phrase "inadequately responsive to or intolerant to anti-hypertensive medications" should be further defined in the labeling, and if so, please discuss definitions.

**Dr. Hirshfeld** stated he was drawn to the word "may." Does it mean if someone decides you're inadequately responsive you're eligible. "May" is fuzzy, as opposed to "are" or "who are." **Dr. Somberg** agrees **Dr. Hirshfeld's** suggestion is important but feels indication of use should say it's no more effective than pharmacologic therapy. There was discussion between **Dr. Zuckerman** and **Dr. Somberg** but **Dr. Somberg** states it is an alternative modality. **Dr. Wittes** advised there is a big difference between inadequately responsive and intolerant. Was info collected on whether patients were inadequately responsive or intolerant? **Dr. Lewis** stated she asked that question and was told there wasn't. **Dr. Wittes** advised she doesn't know how this becomes operative without that info. **Dr. Lange** reminded everyone that

20% of the people that were intolerant or inadequately responsive were on no medications at the end of the study. **Dr. Nachman** echoed what was discussed earlier, but is also concerned about indication for use centered exclusively on blood pressure control. There was a large proportion of patients that were excluded who are arguably at greater risk. So labeling needs to be more granular. **Dr. Zuckerman** asked the panel to first concentrate on the general indications for us before getting into specifics.

After a very long discussion, **Dr. Lange** summarized that nobody feels comfortable with the definition. They may end up convening another panel to walk through this. **Dr. Zuckerman** wanted to summarize in a series of steps and panel can correct if wrong. First, "indications for use" do not cut it. Paradise uRDN is indicated as "possible adjunct" or "alternative" to reduce blood pressure. Second part would be a better description of patients in SOLO and TRIO trials. Warnings and precaution section would further elaborate who were in these studies. There could also be mention that this needs to be a careful decision. **Dr. Lange** said to **Dr. Lewis'** point to say "it may reduce blood pressure," or it may reduce medication usage." **Dr. Bates** asked how you define "indicated" from a regulatory standpoint? **Dr. Zuckerman** agreed this is good guidance.

**QUESTION SEVEN**

**Dr. Warren** read question seven. Please discuss whether labeling should contain recommendations for post-uRDN renal artery imaging, and if recommended, please discuss labeling language to be included. Also, please identify any other labeling recommendations.

**Dr. Somberg** said yes. **Dr. Allen** said yes, but he doesn't feel it needs to be part of labeling. **Dr. Lange** asked for show of hands. **Dr. Zuckerman** asked to summarize what the votes were for the record. **Dr. Lange** stated when asked if routine MRI or CT should be recommended, nobody was in favor. With regard to ultrasound, about 2/3 to 3/4 said that should not be recommended either. Regarding labeling recommendations. **Mr. Vaughan** said this should be done in specialized centers. **Dr. Zuckerman** was okay with advancing to the next question.

**QUESTION EIGHT**

**Dr. Warren** read question 8. Given the totality of evidence presented regarding the safety and effectiveness of the device, please comment on the benefit-risk profile.

**Dr. Somberg** feels benefit-risk has been established. **Dr. Allen's** take is risk is very low but benefit, if any, is acute and not durable and benefit is marginal. **Dr. Starling, Dr. Yeh,** and **Dr. Damluji** agree. **Dr. Wittes** is ambivalent.

**Dr. Lange** summarized panel feels there is low risk, and a small, modest benefit. There are questions about durability. Onus will be on the company, if approved, to conduct a rigorous post-approval study. **Dr. Zuckerman** accepted the summary.

**QUESTION NINE**

**Dr. Warren** read question 9. ReCor proposed a post-market registry study that will incorporate uRDN subjects home blood pressure measurements, but not 24-hour ambulatory blood pressure. Please comment on the sample size, proposed endpoints, and blood pressure measurement methods. Please discuss whether the PAS enrollment should pre-specify more diverse patient subgroups. Please discuss the strengths and limitations of a single-arm study design for the PAS. No renal

arterial imaging follow-up is planned. Please discuss the need for a pre-specified imaging follow-up protocol to confirm long-term uRDN safety.

There was a lot of discussion for this question regarding how studies should be conducted, pros and cons for different types of studies, **Dr. Lange** summarized there were two measurements that everybody agreed on, one is to have accurate blood pressure measurements, and ambulatory is the blood pressure of choice. Two is a very detailed list of meds, including numbers, types and doses. The objective is to make sure blood pressure was controlled and looking at absolute reduction. Many panel members emphasized the need for looking at underrepresented patient populations. Patient related outcomes, patient education, and a training program would be important. Clearly set numbers for target, change expected, what percentage of people are expected to meet the numbers, and how many people need to be seen to make sure data is meaningful. **Dr. Zuckerman** advised this was an excellent summary of a helpful panel discussion.

**VOTE**

**Mr. Collier** read two definitions to assist in the voting process. After a few questions/clarifications, the panel voted on the three voting questions. **Mr. Collier** read the results. On question one, panel voted 12 yes, zero no, and zero abstain. Question two, eight yes, three no, and one abstain. On question three, 10 yes, two no, and zero abstain.

There was discussion regarding panel member's decisions, closing remarks, and **Dr. Lange** adjourned the meeting.

I approve the minutes of this meeting as recorded in this summary.

Richard A Lange, MD, MBA
Digitally signed by Richard A Lange, MD, MBA
Date: 2023.10.23 06:44:56 -06'00'

Richard Lange, MD, MBA
Chairperson

Summary Prepared By:

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September 11, 2023

I certify that I attended this meeting on August 22, 2023 and that these minutes accurately reflect what transpired

Jarrod W. Collier -S
Digitally signed by Jarrod W. Collier -S
Date: 2023.10.24 08:59:09 -04'00'

Jarrod Collier, MS
Designated Federal Officer