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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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MEDICAL DEVICES ADVISORY COMMITTEE

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CIRCULATORY SYSTEM DEVICES PANEL

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August 22, 2023

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Via Web Conference

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Participants

Chairperson	Richard Lange, MD, MBA	Endowed President, Texas Tech University Health Sciences Center, Paul L. Foster School of Medicine	El Paso, TX
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	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
	Julia Lewis, MD	Professor of Medicine, Division of Nephrology, Vanderbilt University School of Medicine	Nashville, TN
	Mark Lockhart, MD, MPH	Professor, Department of Radiology, University of Alabama at Birmingham School of Medicine	Birmingham, AL
	Patrick Nachman, MD, FASN	Director, Division of Nephrology and Hypertension, University of Minnesota	Minneapolis, MN
	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. Braun Medical, Inc.	Center Valley, PA

Patient Representative	Deneen Hesser, MSHSA, RN	Research Advocate, National Cancer Institute, Innovative Molecular Analysis Technologies Program	Chicago, IL
FDA Participants	Bram Zuckerman, MD	Office Director, Office of Cardiovascular Devices, CDRH, FDA	Silver Spring, MD
	Jarrod Collier, MS	Designated Federal Officer, Office of Management, CDRH, FDA	Silver Spring, MD
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, Office of Strategic Partnerships and Technology Innovation, CDRH, FDA	Silver Spring, MD
Sponsor Presenters	Leslie Coleman, DVM, MS, DACLAM	Vice President, Regulatory & Medical Affairs, ReCor Medical, Inc.	Palo Alto, CA
	Helen Reeve-Stoffer, PhD	Vice President, Clinical 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 Irving Medical Center	New York, NY
	Glenn Chertow, MD, MPH	Professor of Medicine, Stanford University	Stanford, CA
	Naomi Fisher, MD	Director, Hypertension Service & Hypertension Specialty Clinic, Brigham and Women's Hospital; Associate Professor, Harvard Medical School	Boston, MA
Open Public Hearing Speakers	Giri, Jay, MD, MPH	Catheterization Laboratories, Assistant Professor of Medicine, University of Pennsylvania	
	Rader, Florian, MD	Medical Director, Hypertension Center, Co-Director, Clinic for Hypertrophic Cardiomyopathy and Aortopathies, Associate Director of Echo Lab, Cedars Sinai Hospital	
	Anderson, Candyce		
	Gray, Gerard (Jerry)		
	Barnett, Gene		
	Brown, Cynthia		
	Copeland, Jessica, MD, MPH	National Center for Health Research	
	Nine Zeldes, PhD	Public Citizen, Health Research Group	

Contents

Call to Order and Panel Introductions

Dr. Lange: It's 9 a.m. I would like to call this meeting of the Circulatory System Devices Panel to order. My name is Dr. Richard Lange. I am President of Texas Tech University Health Sciences Center in El Paso and Dean of the Paul L. Foster School of Medicine, and I have the privilege of being the Chairperson for this panel today. I note for the record that the members present constitute a quorum as required by 21 C.F.R. Part 14. I would also like to add that the panel members participating in today's meeting have received training in FDA device law and regulations. For today's agenda, the panel will discuss, make recommendations, and vote on information regarding the premarket approval application, or the PMA, for the ReCor Paradise Ultrasound Renal Denervation System by ReCor Medical.

Before we begin, I would like to ask our distinguished committee members and FDA attending virtually to introduce themselves. Committee members, if you have not already done so, please turn on your video monitors and unmute your device before you speak. When I call your name, please state your area of expertise, your position, and your affiliation.

And, Dr. Keith Allen, we'll start with you.

Dr. Allen: Yeah. Hi. My name's Keith Allen. I'm a cardiac and vascular surgeon. I'm Director of Surgical Research and the Surgical Director of Structural Heart at the MidAmerica Heart Institute in Kansas City, Missouri.

Dr. Lange: Thank you, Keith.

Dr. Allen: Thank you.

Dr. Lange: Dr. Jim Blankenship.

Dr. Blankenship: Good morning. Jim Blankenship, interventional cardiologist, Director of the Cardiac Cath Lab and the cardiology division at the University of New Mexico.

Dr. Lange: Thank you, Jim, for joining us. Dr. Randy Starling.

Dr. Starling: Good morning. Randall Starling, heart failure cardiologist at Cleveland Clinic. Interim Director of the Heart failure section. Professor of Medicine, Cleveland Clinic Learner College of Medicine.

Dr. Lange: Thank you, Randall. Dr. Robert Yeh.

Dr. Yeh: Robert Yeh. I'm an interventional cardiologist. I'm the Director of the Smith Center for Outcomes Research at Beth Israel and Section Chief of Interventional Cardiology here, and Professor of Medicine at Harvard Medical School.

Dr. Lange: Thank you, Bob, for joining us. Dr. Eric Bates.

Dr. Bates: Interventional cardiologist for almost four decades now. A clinical cardiologist, Professor of Medicine at the University of Michigan.

Dr. Lange: Eric, you and I would be the two reformed interventionalists on this panel. So welcome, Eric. Glad you're here. Dr. Matthew Corriere.

Dr. Corriere: Hi. I'm Matt Corriere. I'm a vascular surgeon at the University of Michigan. I'm also the Director of our operating rooms, Cardiovascular Center here.

Dr. Lange: Great, Matt. Thank you. Dr. Abdulla Damluji.

Dr. Damluji: Yes. Abdulla Damluji. I'm an interventional cardiologist at Inova Heart and Vascular Institute in Northern Virginia, and I'm the Director of the Inova Center of Outcomes research and Associate Professor at Hopkins.

Dr. Lange: Thank you, Abdulla. Dr. John Hirshfeld.

Dr. Hirshfeld: I'm John Hirshfeld. I'm also a reformed intervention cardiologist at the University of Pennsylvania.

Dr. Lange: John, I don't know if you've been reformed or not yet. Okay. But thanks for joining us again on this panel. Dr. Mark Lockhart.

Dr. Lockhart: Hi. I am Mark Lockhart. I'm a Professor of Radiology in the abdominal imaging section at the University of Alabama at Birmingham.

Dr. Lange: Thank you, Mark. Dr. Benjamin Saville.

Dr. Saville: Hi, I'm Ben Saville. I'm a bio statistician. I'm a Director of Consulting and a Senior Statistical Scientist at Berry Consultants.

Dr. Lange: Great, Ben. Thank you. Dr. John Somberg.

Dr. Somberg: I'm Professor Emeritus of Medicine, Cardiology and Pharmacology at Rush University, and I'm a Cardiovascular Pharmacologist and formerly did cardiac electrophysiology.

Dr. Lange: Great to serve with you again, John. Dr. Janet Wittes.

Dr. Wittes: Hi. I'm Janet Wittes. I'm a statistician, have been working in clinical trials for over 50 years, and right now I'm a consulting statistician.

Dr. Lange: Thank you, Janet. Dr. Julia Lewis.

Dr. Lewis: Hi. I'm a Nephrologist, a Professor of Medicine at Vanderbilt in the Division of Nephrology. I'm a clinical trialist, and I just completed my second term as chair of the FDA Cardiorenal Advisory Committee.

Dr. Lange: Julia, thank you for joining us.

Dr. Lewis: My pleasure.

Dr. Lange: Dr. Patrick Nachman.

Dr. Nachman: Yeah. Good morning. Patrick Nachman. I'm a Professor of Medicine. I'm a Nephrologist at the University of Minnesota, and I'm Division Director of the Division of Nephrology and Hypertension.

Dr. Lange: Thank you, Patrick. Deneen Hesser.

Ms. Hesser: Thank you, Dr. Lange. I am Deneen Hesser, the patient representative for this meeting. I'm an HTN patient and a nurse whose career has been in research advocacy.

Dr. Lange: Deneen, really appreciate you joining us today. Thank you. I've got Wes Cetnarowski, Dr. Wes Cetnarowski. Sorry, Wes.

Dr. Cetnarowski: Good morning. Thanks. I'm Wes Cetnarowski. I am Chief Medical Officer for B. Braun Medical, primary care as my background, and I am the industry representative on this panel.

Dr. Lange: Thank you, Dr. Cetnarowski. William Vaughan.

Mr. Vaughan: Hi. I am also a patient representative. I'm mostly retired now. I do some Medicare counseling and used to work for a bunch of consumer organizations.

Dr. Lange: So thank you for being our consumer advocate. Appreciate it, William. Dr. Bram Zuckerman.

Dr. Zuckerman: Good morning. My name is Bram Zuckerman. I'm the Director, FDA Office of Cardiovascular Devices. By background, I'm a cardiologist. Thank you.

Dr. Lange: Great. And Jarrod Collier, will you introduce yourself?

Mr. Collier: Yes. Good morning. My name is Jarrod Collier, and I am the Designated Federal Officer for today's Circulatory System Devices panel meeting. Thank you.

Dr. Lange: Great. Well, Jarrod, as such, you'll now provide the conflict of interest statement, as well as the appointment to temporary voting status member for today's meeting. So let me turn it over to you, sir.

Conflict of Interest Statement

Mr. Collier: Thank you, Dr. Lange, and good morning, everyone. I will now read the conflict of interest statement: The Food and Drug Administration is convening today's meeting of the Circulatory System Devices Panel of the Medical Devices Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the panel are special government employees or

regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations. The following information on the status of this panel's compliance with federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 are being provided to participants in today's meeting and to the public.

FDA has determined that members and consultants of this panel are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have financial conflicts when it is determined that the agency's need for a particular individual’s services outweighs his or her potential financial conflict of interest. Related to the discussions of today's meeting, members and consultants of this panel who are special government employees or regular federal employees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouses or minor children, and, for the purposes of 18 U.S.C. Section 208, their employers. These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

For today's agenda, the panel will discuss, make recommendations, and vote on information regarding the pre-market approval application for the ReCor Paradise Ultrasound Renal Denervation System by ReCor Medical. The proposed indication for use statement is as follows: The ReCor Paradise Ultrasound Renal Denervation System is indicated to reduce blood pressure in adult patients with uncontrolled hypertension who may be inadequately responsive to or who are intolerant to anti-hypertensive medications, which is intended to be used in renal arteries of diameters ranging from 3.0 to 8.0 millimeters.

Based on the agenda for today's meeting and all financial interests reported by the panel members and consultants, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Julia Lewis, Dr. Patrick Nachman, Dr. Randall Starling, and Dr. Robert Yeh. Dr. Lewis's waiver addresses her employer's contract with the PMA sponsor as a clinical study site for three studies that support the PMA. Dr. Lewis's employer was awarded funding between $501,000 and $700,000 by the PMA sponsor. Dr. Lewis reported that she is not involved in these studies in any way and receives no personal remuneration from the study's funds.

Dr. Nachman’s waiver addresses his involvement in a leadership position as Councilor at Large for a professional organization that received contributions from the parent firm of the PMA sponsor and a competing firm. The professional organization received between $1 million and $1,500,000 from the parent firm of the PMA sponsor, and between $100,000 and $200,000 from a competing firm. Dr. Nachman does not receive any personal remuneration from the funds, and he is not compensated for services to the professional organization.

Dr. Starling's waiver and Dr. Yeh's waiver address their employer's contract with the PMA sponsor as a clinical study site for one study that supports the PMA being discussed. Dr. Starling's employer was awarded between $50,001 and $70,000, and Dr. Yeh's employer was awarded between $200,001 and $300,000 from the PMA sponsor. Both Dr. Starling and Dr. Yeh reported they are not involved in the study in any way and receive no personal remuneration from the study's funds.

The waivers allow these individuals to participate fully in the panel deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website. Copies of the waivers may be obtained by submitting a written request to the agency's Division of Freedom of Information, 5630 Fisher’s Lane, Room 1035, Rockville,

Maryland 20857. Dr. Wes Cetnarowski is serving as the industry representative acting on behalf of all related industry. Dr. Cetnarowski is employed at B. Braun Medical Incorporated. We would like to remind 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, the participants need to exclude themselves from such involvement and their exclusion will be noted for the record. FDA encourages all participants to advise the panel of any financial relationships that they may have with any firms at issue. A copy of this statement will be available for review and will be included as part of the official transcript.

Appointment to Temporary Voting Status

Mr. Collier: At this time, I will now read the appointment to temporary voting status: Pursuant to the authority granted under the Medical Devices Advisory Committee Charter of the Center for Devices and Radiological Health, dated October 27th, 1990, and as amended August 18th, 2006, I appoint the following individuals as voting members of the Circulatory System Devices panel for the duration of this meeting on August 22nd, 2023: 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, I appoint Dr. Richard Lange to act as temporary voting chairperson for the duration of this meeting. For the record, these individuals are special government employees or regular government employees who have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. This was signed by Dr. Jeffrey Shuren, Director for the Center for Devices and Radiological Health on July 26th, 2023. Thank you.

Sponsor Presentation — ReCor Medical

Dr. Lange: Thank you, Jarrod. We will now proceed to the ReCor medical presentation, and I would like to invite the ReCor representative to begin shortly. I will remind public observers that

while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel chair. That's me. The sponsor representative will have 75 minutes to present, and I would remind the committee members, as this is a public hearing and all the presentations and all the deliberations will take place in a public forum, there will be no behind the scenes conversation, and we will not be using the chat function, except if you have some technical difficulties and need to get hold of audio visual. So with that, I'll ask the sponsor now to begin their presentation.

Dr. Coleman: Good morning. My name is Leslie Coleman, and I'm the Vice President of Regulatory and Medical Affairs at ReCor Medical. We want to thank the FDA, the Chair, and members of the panel for the opportunity to present data supporting the Paradise Ultrasound Renal Denervation System for patients with uncontrolled hypertension. As you will see, the system is a safe, minimally invasive, catheter-based procedure that significantly reduces blood pressure for these patients.

Hypertension is a major public health burden in the United States and throughout the world. Treatment guidelines recommend lifestyle modifications and anti-hypertensive medications based upon the severity of hypertension. For patients, managing blood pressure is important, as reducing blood pressure can reduce the risk of cardiovascular morbidity and mortality. Unfortunately, standard of care therapies are often insufficient to adequately control blood pressure for many patients. Those who are inadequately responsive to or intolerant of anti-hypertensive medications or unable or unwilling to comply with prescribed treatment regimens remain at high risk for cardiovascular events. These 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 we will refer to as uRDN, is a novel, minimally invasive, catheter-based procedure. The Paradise uRDN 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 Paradise system has two key components, including the portable Paradise generator and a single-use six French balloon catheter. The Paradise generator facilitates each step of the procedure 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 Paradise catheter includes an ultrasound transducer centered within the balloon. The transducer 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.

The treatment strategy was developed based on preclinical learnings and 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. The diagrams shown here depict two common anatomies and how this treatment strategy is deployed. The diagram on the left illustrates two emissions in the main renal artery, and one in a proximal side branch. The diagram on the right shows two emissions in

the main renal artery, and one in an accessory artery. In preclinical studies, this treatment strategy was shown to significantly reduce kidney norepinephrine levels, a marker of sympathetic nerve activity.

Next, I will review the procedure and treatment strategy in more detail. First, the Paradise catheter is introduced via a standard guide wire in advance to the distal end of the main renal artery. Through a proprietary algorithm, the Paradise generator regulates the inflation of the balloon with sterile water automatically centering the ultrasound transducer in the artery. Throughout the procedure, the generator continuously manages balloon pressure to ensure a constant low pressure is applied to the vessel wall. Once positioned, the generator uniformly delivers ultrasound energy circumferentially through the artery wall. The circulation of fluid in the balloon cools the arterial surface during energy delivery to protect the arterial wall and non-target tissues from thermal injury. Once delivery at the target site is complete, the balloon automatically deflates, and the paradise catheter can then be moved proximally for subsequent emissions. Two to three, seven second emissions are delivered to the main renal artery and accessory or proximal side branches depending on the patient's anatomy. Once bilateral treatment is complete, the Paradise catheter is removed from the body, and the procedure is completed according to standard interventional techniques.

Our 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. The primary efficacy endpoint was designed to demonstrate the benefit of ultrasound renal denervation 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 ultrasound renal denervation, the treatment regimen for these patients was standardized on a single pill medication, which included a combination of three fixed dose antihypertensive 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 Radiance studies, and we now have follow-up out to 36 months post procedure. Evidence from these studies provides a robust assessment of the safety and efficacy of Paradise uRDN.

The data we will present today support that the 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 standard of care, anti-hypertensive medications who remain at an increased risk of major cardiovascular events. The Paradise Ultrasound Renal Denervation System met the pre-specified primary effectiveness endpoint in all three studies. 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. Our proposed indication for the Paradise Ultrasound Renal Denervation 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.

Turning now to the agenda for the remainder of today's presentation: First, Dr. Weber will provide an overview of the unmet need and the treatment of patients with hypertension. Next, Dr. Kirtane and Dr. Chertow will review the efficacy and safety data from the Radiance studies. Then, Dr. Reeve-Stoffer will describe our proposed post-approval study. Finally, Dr. Fisher will share her clinical perspective. All external experts have been compensated for their participation in today's meeting. We also have additional experts with us today to answer your questions. Thank you. I will now turn the presentation over to Dr. Weber.

Dr. Weber: Thank you. My name is Michael Weber. I'm a Professor of Medicine in the cardiovascular division at SUNY Downstate Medical Center in Brooklyn. I'm a former President of the American Society of Hypertension and former Chairman of the ASH Clinical Hypertension Specialist Program that certifies hypertension specialists in the United States. My main interests are in the prevention of cardiovascular, stroke, and renal outcomes in patients with hypertension.

Well over a hundred million patients in the United States have hypertension with a high rate of death attributable to this condition. Of note, 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. It's only since around 1970 that we've had clear evidence that treating hypertension with drug therapy significantly reduces fatal and non-fatal cardiovascular outcomes. These landmark studies from the VA that showed for the first time in a randomized trial that anti-hypertensive therapy reduced fatal and non-fatal outcomes, changed the whole approach to treating hypertension, making drug therapy a central strategy for treatment.

Based on the Sprint study, which we'll revisit in a moment, 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 over 80 or higher. And

consistent with this, starting drug therapy is recommended for hypertension patients at or above 130 over 80 in most cases. Before continuing with hypertension unmet needs, I think it would be helpful, particularly for those not familiar with contemporary methods for measuring blood pressure in hypertension trials, for me to briefly explain the methods of blood pressure measurement used in the Radiance studies.

Ambulatory blood pressure monitoring or ABPM was the primary method. It was based on multiple readings taken over a 24-hour period by an unobtrusive small device connected to a blood pressure arm cuff. 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. We also measured office blood pressures using automated devices to obtain three readings, which were then averaged. In addition, we instructed patients to measure their own blood pressures 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 our studies, since they represent a powerful predictor of cardiovascular events. You'll see the results of all these measurements in just a few minutes.

Now, with that explained, let's get back on track and look at the standard of care for patients with hypertension. If lifestyle changes are unsuccessful in controlling blood pressure, worldwide guidelines uniformly recommend treatment with one, two, or three drugs using agents as shown on the slide from the calcium channel blocker class ACE inhibitor or ARB classes and the diuretic classes. If control with combinations of these three types of agents is not adequate, adding an aldosterone antagonist should be considered. But there are limitations due to adverse effects, and so other drug types can be used. But as we increase the number of antihypertensive

medications, patient adherence to treatment, which is not complete even with simple drug regimens, deteriorates even further. And this adherence problem is exaggerated by the fact that most patients with hypertension are taking medications for several other indications at the same time.

These data from the NHANES Study show that among patients in the United States with hypertension, a large proportion failed to achieve the historical blood pressure target of less than 140 over 90, let alone the current 130 over 80 target, which fewer than 26% of patients actually achieve. Far worse, this slide shows that hypertension control rates significantly deteriorated during the four-year period prior to COVID. Therefore, we cannot blame COVID for this worsening situation. And let me again emphasize that one of the main reasons for deteriorating control of blood pressure is that patient adherence to their medications frequently is poor.

This slide summarizes a report based on nine separate studies in patients with uncontrolled hypertension where non-adherence to their treatment was dominant in explaining their poor treatment outcomes. In fact, about 50% of patients were either fully or partly non-adherent. Inconsistent adherence to taking medications is a pervasive and serious problem. This slide shows outcomes of two major meta-analyses that played an important part in the deliberations of the ACC / AHA Hypertension Guideline Committee. We see that across the spectrum of hypertension, starting in the low 120s and going up into the 160s and beyond, is that achieving 5 to 10 mmHg reductions in office systolic blood pressures consistently reduces major cardiovascular outcomes by 10 to 20% or more.

We should also recall epidemiology evidence that absolute levels of major events are twice as high at 160 as at 140. And so for those patients who, for whatever reason, cannot be brought down to recommended levels by standard therapies, an intervention that provides a 10 millimeter of mercury blood pressure reduction provides a most valuable absolute reduction in

cardiovascular risk, especially in those patients with more severe hypertension. The original findings from Sprint comparing the effects of intensive treatment to 120 mmHg, versus standard treatment to around 135 mmHg, showed a remarkable reduction favoring intensive treatment of 27% in the composite cardiovascular outcome and compelling reductions of 42% in cardiovascular mortality and 25% in all-cause mortality.

Sprint was continued beyond the study as a community-based observational study. The intensive group that had got down to near 120 mmHg and the control group that had stayed at around 135 mmHg were now followed for a much longer period. But 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 mortality, as you can see on the right side of the slide, that wiped out their earlier benefits. The big lesson here is that we cannot assume that prescribed medications represent a longstanding solution to hypertension. I will leave it to my colleagues to soon share with you the value of renal denervation, a technique that does not depend on patient adherence or the renewal of prescriptions.

In conclusion, many patients continue to experience high blood pressure because they are inadequately responsive, intolerant, or non-adherent to standard of care antihypertensive medications. These patients remain at increased cardiovascular risk, including stroke, coronary events, heart failure, and death. There remains a compelling need for safe, effective, and durable treatment options of which, as my colleagues are about to show you, renal denervation is a strong example that can reduce blood pressure and so help prevent major outcomes in our patients. And in line with that thought, I will now turn the presentation over to Dr. Kirtane.

Dr. Kirtane: Good morning. I'm Ajay Kirtane, Professor of Medicine at Columbia University Irving Medical Center in New York. I'm a practicing cardiologist and clinical trialist, and I was

the US Principal investigator in the Radiance Studies. I've also been a site principal investigator for several renal denervation studies. On a personal note, I myself am a patient with hypertension. I will review the clinical trial evidence demonstrating that the Paradise Ultrasound Renal Denervation System 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. In each of these three independently powered clinical trials, we sought 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 uncontrolled hypertension despite the use of three or more anti-hypertensive medications.

A key unifying principle across all three studies was the stabilization of medication regimens within the studies in order to isolate the effect of uRDN versus sham. We all know that medications lower blood pressure. In order to assess the effect of uRDN versus sham, it was, therefore, important to establish a stable baseline of medications in all three studies. If this were not done, if medications change during the observation period of treatment effectiveness, it would be much more difficult to discern whether the change in blood pressure was from uRDN or from a change in medications.

In Radiance II and Solo, patients first had to complete a four-week washout off 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 of the medical regimen 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 period to ensure that they remained hypertensive. Eligible patients then underwent non-invasive anatomic screening to ensure that their renal arteries were suitable for the uRDN procedure. If they qualified, patients underwent invasive renal angiography. If angiography confirmed that anatomy was truly suitable and the arteries were without stenosis, patients were randomized to uRDN or a sham procedure. During the procedure, patients wore blinders and headphones 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 of daytime ambulatory blood pressure was ascertained at two months. Each independently powered study hypothesis was based on a frequentist approach with a pre-specified fixed sample size. The primary efficacy 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 Radiance studies randomized more than 500 patients. 293 of whom were randomized to uRDN. 213 patients were randomized to receive a sham procedure, which consisted of additional time spent in the procedure room after invasive renal angiography in order to give patients the impression of additional procedures done.

These 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 the primary endpoint of daytime ambulatory systolic blood pressure, 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 in each of the Radiance studies. The majority of 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.

The proportion of patients taking zero, one, and two antihypertensive medications at screening was well balanced across randomized groups in Radiance II and Solo. In Radiance-Trio , all patients were on three or more antihypertensive medications at screening with an average of four medications taken. These data highlight the number of medications often prescribed by clinicians in our efforts to achieve blood pressure control for our 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 150s over 100.

Across the three studies, treatment was successfully delivered in over 95% of patients randomized to uRDN. Average procedure time from sheath insertion to sheath removal ranged between 72 and 83 minutes across the studies. On average patients received between five and six emissions with a total emission time of less than a minute. With the Paradise uRDN system, each circumferential emission is only seven seconds, and emissions are applied to the main and accessory arteries. This system does not require treatment beyond the distal bifurcation of the main renal artery. I'll turn now to the primary results of Radiance II and Radiance-Solo, which were conducted in patients with mild to moderate hypertension.

The Paradise uRDN system met its pre-specified primary endpoint in both independently powered studies. The between group difference between uRDN and sham in both studies with

6.3 mmHg in favor of uRDN. Notably, the average drop in daytime ambulatory systolic blood pressure from baseline was approximately 8 mmHg in patients treated with uRDN. This is likely a better estimate of the average drop in blood pressure that would be observed in clinical practice. By definition, the average change in blood pressure between groups is a mean of a distribution.

Another way of examining these data relates to specific drops in blood pressure. Overall reductions in blood pressure were larger with uRDN compared with sham. As shown in this figure, 64% of uRDN patients achieve a five millimeter of mercury drop in blood pressure compared with 34% with sham. Nearly half of uRDN patients achieved a drop of 10 mmHg in blood pressure compared with only 16% with sham and even larger drops were more frequently observed with uRDN.

A more detailed examination of the ambulatory blood pressure data from the Radiance II study is shown in this slide. Two-month values are shown in the solid darker lines. The baseline values are lighter and hashed. One can appreciate consistent blood pressure reductions with uRDN compared with sham throughout the 24-hour circadian cycle. Not only is daytime blood pressure lower at two months, but nighttime as well, including in the early morning higher risk period. These greater reductions in blood pressure with uRDN extended beyond ambulatory blood pressure measurements. Blood pressure reductions were consistent across overall ambulatory home and office pressures and were similarly consistent for measurements of both systolic and diastolic pressures. Treatment benefits were also consistently observed, irrespective of pre-specified baseline patient characteristics. One can appreciate consistent reductions in blood pressure in all pre-specified subgroups with uRDN relative to sham. It's important to note that similar results were observed in the Solo study with consistent treatment effects across pre-specified subgroups.

I'll now turn to the results from Radiance-Trio , starting with the primary and secondary endpoint results at two months. You'll recall that Radiance-Trio enrolled patients with uncontrolled blood pressure despite an average of four medications at screening, and randomized patients had to have elevated blood pressure despite taking a fixed-dose combination anti-hypertensive pill for a month. In Radiance-Trio , the daytime ambulatory systolic blood pressure reduction compared with sham was 4.5 mmHg. Similar to Radiance II and Solo, the drop in daytime ambulatory systolic blood pressure from baseline was eight 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 that was pre-specified within the protocol. In the strictest interpretation of intent to treat, we pre-specified that if an ABPM was missing at two months, we would assume that there was no change in blood pressure from baseline. In Radiance-Trio , six uRDN patients had missing ABPM values at two months. Therefore, for the primary analysis, these six patients in the uRDN group had their two month ABPM imputed to be the same as their baseline, as if there were no change in blood pressure. We additionally have performed the primary endpoint assessment using either complete ABPM data or using multiple imputation in a more contemporary method to account for missing data.

This slide depicts the reductions in blood pressure in Radiance-Trio , based upon these analytic methods. The overall results are consistent with a difference of approximately five mmHg overall in favor of uRDN compared with sham. Looking more closely at the magnitude of blood pressure reduction from baseline across the distribution of blood pressure lowering, one can appreciate that a greater proportion of patients had reductions in blood pressure with uRDN compared with sham. This was especially true for larger reductions in blood pressure, such as a drop of 10 mmHg or 15 mmHg. A more detailed examination of the ambulatory blood pressure

data from the Radiance-Trio study is shown here. Consistent blood pressure reductions with uRDN over baseline and also in comparison with sham were observed throughout the 24-hour circadian cycle. Not only is daytime blood pressure lower, but nighttime as well, including in the early morning hours.

It's interesting to note that there was a greater change in blood pressure in the sham group in this on-medication 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. In Radiance-Trio, reductions in blood pressure were consistent across various assessments of blood pressure, including ambulatory, home, and office pressures and, similarly, for measurements of systolic and diastolic pressures. Treatment benefits in Radiance-Trio were also consistently observed, irrespective of pre-specified subgroups.

To summarize, we conducted three independently powered and sham-controlled studies demonstrating that uRDN consistently lowers daytime ambulatory systolic blood pressure. Blood pressure reductions compared with sham were 4.5 mmHg in Radiance-Trio or 5.8 mmHg if not imputing missing ABPM data, and 6.3 mmHg in Radiance II and Solo. The overall reduction in daytime ambulatory systolic blood pressure was approximately eight mmHg from baseline across studies, but greater drops were seen with a higher frequency among uRDN treated patients. As a specific point of emphasis, the data I've shown are from three independently powered studies utilizing a sham control group, achieving a level of rigor rarely seen in device-based clinical trials.

Next, I'll review the six month results of these studies. Before doing so, I want to point out that each of the Radiance studies was specifically designed to demonstrate the effects of uRDN on blood pressure lowering at two months. The unique study designs with medications stabilized across treatment groups in all three studies allowed the assessment of the isolated

effect of uRDN versus sham. After two months, investigators were instructed to actively add anti-hypertensive medications to try to achieve control of blood pressure at monthly office visits. This design element was especially important for patients in the sham group who frankly had been left untreated for three months, as part of the initial study designs, to investigate the effectiveness of uRDN compared with sham. As such, with medications changing and differentially so across treatment groups that started at different blood pressure measurements, when medications were initiated at two months, any blood pressure effects of uRDN versus sham are no longer isolated.

From months two to six, blood pressure measurements were recorded at home twice daily for a week prior to every monthly office visit. If a patient's blood pressure was not controlled, study teams were instructed to add medications, either a new pill or an increase in dose, according to a standardized medication titration protocol. For up to six months, this was actually done monthly, clearly a departure from conventional clinical practice where patients are less frequently seen. Patients returning for follow-up visits in the office were actually told in advance that their urine was going to be tested for adherence during that office visit, and this may have impacted adherence at the time of the visit. In addition, during that office visit, patients took their prescribed medications under direct observation of the study team. They then went home with an ambulatory blood pressure monitor. Due to these unique study processes, we believe that the home blood pressure, which was obtained prior to any witnessed medication intake or anticipated urine testing, probably represents the best real world estimate of patient blood pressure in the follow-up period.

This slide depicts the longitudinal change in home blood pressure in Radiance II in both treatment groups over the six month intensive follow-up period. Notably blood pressure decreased in both groups because medications were added in addition to the effect of

denervation. But the uRDN group drops occurred earlier and remained lower than sham throughout the follow-up period. This occurred despite a nominally lower medication burden in the uRDN group. Similar results were seen in the Radiance-Solo study with consistently lower home blood pressures throughout the follow-up period in the presence of an overall lower medication burden. Finally, in Radiance-Trio , home blood pressures dropped earlier and stayed lower with uRDN compared with sham, despite more use of aldosterone antagonists, the fourth agent added to an already three-drug regimen in the sham group.

Finally, I'll review the results supporting longer term durability of uRDN derived from these studies. These include follow-up through 36 months from Radiance-Solo and 24 months from Radiance-Trio. The longer-term blood pressure and medication data are shown for patients treated with uRDN in these studies. Unfortunately, comparisons to patients initially randomized to sham are confounded due to unblinding the active medication titration protocol that was employed from two to six months and crossover of uncontrolled sham patients who were subsequently treated with uRDN. This slide depicts blood pressure at 36-month follow-up from uRDN treated patients in Radiance-Solo. As a reminder, throughout long-term follow-up beyond 12 months, patients were unblinded but seen annually as part of the studies. At 36 months, there was an average reduction in systolic blood pressure of 17.7 and a reduction in diastolic blood pressure of 11.3 mmHg.

Medication burden is depicted on the bottom of the slide demonstrating that the population overall was on just over one medication. When examining where patients were in comparison to when they were screened for eligibility in the study, patients who received uRDN achieved durable reductions in office systolic and diastolic blood pressure without an average increase in overall medication burden. The 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 blood pressure findings were observed in Radiance-Trio , a study of a much more difficult population of patients to manage. Recall in this study, patients were uncontrolled despite an average of four medications in screening. After the six-month follow-up visit, reductions in systolic blood pressure were sustained despite some attrition of medications used, a phenomenon that Dr. Weber previously described from other studies. Putting this into perspective, when looking at the change in blood pressure compared with screening in Radiance-Trio, we see a substantial reduction in systolic and diastolic blood pressure among patients receiving uRDN. Systolic blood pressure was 14.6 mmHg lower and diastolic blood pressure was 8.4 mmHg lower, despite the fact that patients were taking fewer antihypertensive medications compared with what they were taking at screening, as depicted in the right panel of the slide.

In the previous slides, I've shown you quite a bit of data derived from three randomized studies. Let me summarize them as follows. The pre-specified primary endpoint of blood pressure lowering of uRDN was met in all three studies, each of which was independently powered and sham-controlled, achieving one of the highest bars of clinical science of a device-based technology. In all three trials, patients treated with uRDN achieved a consistent, clinically meaningful reduction in blood pressure compared with those receiving a sham procedure. Blood pressure reductions were observed irrespective of how blood pressure was measured, including ambulatory, home, and office measures, and benefits were observed throughout the 24 hour circadian cycle. These blood pressure reductions were durable and longer-term follow-up and, moreover, were additive to the effects of medications, which notably is the way that uRDN will likely be used in clinical practice.

Thank you so much for your attention. I will now turn the presentation over to Dr. Chertow.

Dr. Chertow: Good morning. My name is Dr. Glenn Chertow. I am Professor of Medicine and, by courtesy, Professor of Epidemiology and Population Health and Professor of Health Policy at Stanford University School of Medicine. I have been caring for patients with kidney disease and hypertension for more than 30 years, having served on the faculties at Harvard, UCSF, and Stanford. At Stanford, I served as Division Chief of Nephrology for more than 13 years. I am a certified hypertension specialist and see patients within our multidisciplinary American Heart Association designated Hypertension Center. I served as chair of the Data Safety and Monitoring Board for the Solo, Trio , and Radiance II studies.

I will briefly review the data demonstrating that the Paradise uRDN system has a favorable safety profile. Adverse events were consistently collected across the studies. These included all adverse events and adverse device events irrespective of the time to onset post procedure. Events were then stratified by those occurring within 30 days and after 30 days following the procedure. Relatedness to device or procedure was determined by the treating investigator. Other events of special interest were pre-specified in the protocol to fully characterize the system safety profile. Radiance II, however, is the only study to have included a primary safety endpoint. The primary safety endpoint was a composite of major adverse events occurring within 30 days and at six months post procedure. All primary safety events were adjudicated by an independent clinical events committee. The composite of these events was compared to a pre-specified performance goal of 9.8%. I will begin by reviewing the primary safety endpoint from Radiance II, followed by an overview of safety from all three Radiance studies.

Radiance II met the pre-specified primary safety endpoint with no patients experiencing major adverse events in either treatment group. These results were well below the pre-specified

performance goal of 9.8%, demonstrating a favorable safety profile of the Paradise uRDN system and procedure.

Turning now to a discussion of safety for all three Radiance studies. Adverse events and serious adverse events occurred at similar rates between treatment groups across the 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. There were no unexpected adverse device events reported, and there was no increase in adverse or serious adverse events that were non-device related. More patients experience severe device-related adverse events in the uRDN groups compared with sham. Vascular access site hematoma requiring intervention occurred in three of 293 patients treated with Paradise uRDN. Approximately 1% syncope occurred in two patients. An intraprocedural bradycardia occurred in two patients and was treated with drug therapy. All events resolved within 30 days without sequelae. Detailed narratives on these patients are provided in the sponsor's briefing document. No other serious adverse device events occurred in more than one patient across the Radiance studies.

Eight deaths occurred during the clinical development program. Three occurred in patients treated with uRDN, four occurred in patients receiving sham, and one occurred in a patient prior to randomization. Investigators determined that all deaths were not related to the procedure or the investigational device.

Next, I will review the data on kidney function and vascular safety. Given the importance of proteinuria as a proxy of kidney damage, we looked at proteinuria estimated by the urine protein creatinine ratio or UPCR in gram per gram along with the serum creatinine and corresponding estimated GFR at baseline and months two, six and twelve. The left panel shows geometric mean estimated UPCR along the left side Y axis and mean EGFR along the right side Y axis in patients treated with uRDN, and the right panel shows the same parameters in patients

who underwent sham procedures. There were no meaningful differences over time or between groups.

The Radiance studies included imaging to provide a thorough evaluation of potential renal artery injury. Pre-procedure, all patients were required to undergo CT or MR Angiogram to assess for anatomical eligibility. In Radiance II, all patients were required to undergo CT or MR Angiogram at six months, and only treated patients at 12 months post procedure. An independent core lab reviewed all imaging and reported on any renal artery injury and provided an estimate in percent of narrowing if there was any narrowing detected.

Follow-up imaging protocols in Solo and Trio differed from those in Radiance II. At month two and month six, renal duplex ultrasound imaging was performed to assess flow and changes in velocity that might indicate narrowing. If pre-specified parameters were exceeded, a CT or MR Angiogram was performed. At month 12, CT or MR Angiogram was required for all patients who received uRDN. Independent diagnostic radiologists reported on any injury to or narrowing of the renal artery.

Given the different imaging protocols, first I will review the six-month results from Radiance II, which provide a valid assessment of renal denervation compared with sham. Based on core lab adjudication, there was no evidence of kidney injury or clinically significant renal artery stenosis in the renal denervation treated patients. 98% of uRDN 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%.

Finally, I will review results from our pooled safety analysis starting with additional imaging evaluations. All studies required that CT or MR Angiogram be conducted in patients who received uRDN at 12 months. All 12-month images were read by an independent core lab as

part of the pooled safety analysis. 12-month imaging evaluation showed no evidence of renal injury in the uRDN treated patients across the Radiance studies. Based on core lab adjudication, the majority of patients had no evidence of detectable stenosis. A small fraction had minimal stenosis within the range of measurement error, and no patients had clinically significant renal artery stenosis, conventionally defined as more than 70%.

To further characterize the safety profile of renal denervation, we conducted a pooled analysis of major adverse events from all three Radiance studies. This analysis was possible because of the similarity between the studies. In each study, the procedure treatment strategy, renal anatomy treated, and device were all the same. 367 patients who were treated with Paradise uRDN were included. This includes crossover patients. The pooled analysis used the primary safety composite endpoint from Radiance II. The outcome was to compare against the performance goal of 9.8%. All events were adjudicated by an independent CEC.

Turning now to the results. Six events met the definition of major adverse events. These included two deaths, two major vascular complications, one hospitalization for hypotension, and one hospitalization for major cardiovascular event. All events were CEC adjudicated as unlikely to be related or not related to the uRDN device. The overall composite rate was 1.1%, which is significantly lower than the pre-specified performance goal. There was no newly recognized renal artery stenosis. In conclusion, the Paradise Ultrasound Renal Denervation System has a favorable safety profile. Its application did not result in an increased risk of any major adverse events compared with a sham procedure.

While procedure related events did occur, all resolved without sequelae. In addition, there was no evidence of acute or long-term kidney injury, and there was no evidence of renal artery injury or any clinically significant renal artery stenosis. I will now turn the presentation over to Dr. Reeve-Stoffer.

Dr. Reeve-Stoffer: Good morning. I am Helen Reeve-Stoffer, Chief Clinical Officer at ReCor Medical. I will discuss ReCor's proposal for post-approval study. 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.

First, ReCor will continue to follow all the remaining subjects enrolled in Radiance studies for up to five years. Secondly, ReCor plans to initiate a US arm of the Global Paradise System Registry to evaluate the long-term efficacy and safety of uRDN in a real-world setting. Based on historical attrition rates, we anticipate that enrolling 700 subjects will allow us to achieve 500 evaluable patients in five years. To reach this target, patients who are currently enrolled in the Radiance's continued access protocol will become part of the registry, and we will also enroll a minimum of 500 de novo patients, who will be treated according to the approved labeling. Up to a hundred sites will be included with a mix of experienced and new uRDN users.

While ambulatory blood pressure was important for evaluating efficacy outcomes in the Radiance program, other measures of blood pressure are more easily implemented in a real-world setting. As you have heard, home blood pressure is a very valuable out of office measurement and, based on our own data, correlates well with ambulatory blood pressure. For that reason, we are proposing that the primary measure of efficacy in the registry be home blood pressure. To facilitate data collection, patients will be provided with a telemetric home blood pressure system that can automatically transmit blood pressure information, allowing for remote patient management. To ensure consistent and robust data collection, all blood pressure measurements will be collected using the same methods we used in the Radiance program, which are based on the AHA / ACC 2017 guidelines for management of high blood pressure. We will continue to collect rigorous safety data on the Paradise System with an emphasis on procedure

and device related events, blood pressure, cardiovascular and hemodynamic clinical events, as well as any detrimental changes in renal function.

The sample size proposed would allow a 95% probability of detecting clinical events with an occurrence rate as low as 0.6%. There are no formal planned hypothesis tests. Descriptive summary statistics will be presented for all outcomes in enrolled subjects. To ensure that we can describe both safety and effectiveness data in understudied populations, we will actively facilitate enrollment in pre-specified subgroups. ReCor recognizes the importance of improving the diversity of subjects included in the registry and has created an advisory steering committee tasked with ensuring that both study design and recruitment emphasize patient diversity and accessibility.

Dr. Naomi Fisher will be the study PI. Other steering committee members are Dr. Mohammed Ansari, who is recognized for his work supporting inclusivity of the Hispanic population; Dr. Tiffany Randolph, who has supported the African-American population and, in particular, female African Americans; and Dr. Hunter Nichols, a PharmD, who is a patient navigator working closely with patients on their hypertensive journey. We look forward to working with the agency to finalize this post-approval plan. I will now turn the presentation over to Dr. Fisher to provide her clinical perspective.

Dr. Fisher: Thank you. My name is Naomi Fisher, and I'm the director of the Hypertension Service and Hypertension Specialty Clinic at the Brigham and Women's Hospital in Boston, an Associate Professor of Medicine at Harvard Medical School. I've participated in dozens of clinical hypertension trials, including studies with renal innovation therapies since 2016. I've been an investigator in the Radiance Studies as Site PI at the Brigham, but I'm also speaking as a cardiovascular endocrinologist and a clinical hypertension specialist.

As a clinician, I've been taking care of patients with high blood pressure for more than 25 years, patients who are self-referred or referred to me by colleagues because of challenges they face getting their hypertension under control. So as a physician who has dedicated her career to helping patients with high blood pressure reach control, I appreciate this opportunity to provide a clinical perspective on the data presented today. There is a critical unmet need to control high blood pressure for millions of people. Hypertension is highly prevalent. It affects one out of every two adults. High blood pressure is also the leading risk factor for death in the United States and around the world.

Studies have taught us that patients should achieve lower blood pressure to reduce risk, so the targets we are aiming for have been lowered. At the same time, the prevalence of hypertension is rising, making this already serious public health concern even more worrisome and challenging. Lifestyle modifications always come first, and we know these changes are effective, but my experience parallels what studies have found over and over again in large populations, it's hard for patients to achieve optimal blood pressure targets with lifestyle changes alone, and it's even harder for them to sustain these benefits because lifestyle changes are usually not sufficient.

We turn to antihypertensive medications. Unfortunately, there are many factors that also limit the ability of medicine to control hypertension. For one thing, adherence to prescribed treatment regimens is dismal. It has been shown to hover around 50% after a year. There are several reasons underlying non-adherence, including medication side effects, fear, and cost. Many factors limit the quality of care we can provide. To review an astonishing and I think sobering statistic among American patients with high blood pressure, three quarters fail to achieve optimal blood pressure control with standard medical therapy. So, despite options of weight loss and exercise and despite having multiple classes of medications that are affordable,

it's clear we need additional treatment options. We need to expand the chances for more patients to gain control of their hypertension, to live longer and healthier lives. We can do better for our patients, and we have to.

In this slide, the benefits achieved at two months with the Paradise System represent a clinically robust outcome for patients. All three Radiance studies showed that patients receiving ultrasound renal denervation achieved meaningful, important reductions across blood pressure measures, whether ambulatory blood pressure, home blood pressure, or office blood pressure. The efficacy data presented today focus mainly on two-month daytime ambulatory blood pressure, the primary study endpoint. But historically, office blood pressure has been used more often. So I'd like to focus there a moment. It's worth reinforcing data shared by Dr. Weber.

First, a 10-millimeter drop in office blood pressure is associated with significant meaningful benefit. Major cardiovascular disease is reduced by 20%, and stroke and heart failure by nearly 30% with a 10-millimeter fall in office pressure. Second, it is known clinically that an effective blood pressure medication, when started as monotherapy, results in a drop of about 10 points in systolic office blood pressure. This, in essence, was the case for all patients in Solo and Radiance II who were withdrawn from medications for at least one month before procedure. Therefore, the reductions in office blood pressure listed here are roughly equivalent in magnitude to an effective first antihypertensive medication.

Finally, large trials have taught us that reductions in ambulatory blood pressure are typically lower than reductions in office blood pressure, generally around 65 to 70%. Therefore, the ambulatory and home blood pressure reductions seen with renal denervation are also considered effective and clinically meaningful. Taken together, the consistency of these results shows that substantial benefit can be achieved with ultrasound renal denervation. These findings give me confidence to recommend this therapy for patients who could potentially benefit. The

data we presented today demonstrated that ultrasound renal denervation delivered by the Paradise System lowered blood pressure to a clinically meaningful degree at two months, our primary endpoint, but the data across three randomized studies also showed that renal denervation provides consistent reductions in blood pressure throughout a 24-hour circadian cycle. This translates into a meaningful outcome for patients.

I want to highlight the benefits of this always-on therapy that we can achieve with renal denervation. Here we see the ambulatory blood pressure results discussed earlier. There was a lowering of systolic blood pressure throughout the day and throughout the night at two months, and systolic blood pressure was at or near target at six months indicated with the red line. One more point is worth emphasizing. Given the half-life of anti-hypertensive medications and given that most commonly 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, in contrast, ultrasound renal denervation lowered blood pressure below target during this vulnerable period of cardiovascular risk. As with any new treatment option, of course we have to consider the benefits in the context of potential risks. The totality of safety data from the Radiance studies, including long-term follow-up through 36 months, supports that Paradise renal denervation is safe. While procedure related events were observed, they were minor. As a hypertension specialist and an investigator in the Radiance studies, I am completely comfortable recommending this procedure for my patients.

For patients with hypertension who are unable to achieve blood pressure targets despite being prescribed lifestyle modification and medications, ultrasound renal denervation represents an important treatment option. I'd like to clarify that some patients do well and have their blood pressure controlled with one or two medications. They have no need for additional treatment, but there are many patients for whom blood pressure control is not so straightforward. On the other

end of the spectrum are patients with true resistant hypertension whose blood pressure is uncontrolled despite taking three or more agents at optimal doses, including a diuretic. For these patients, renal denervation is likely to show reductions beyond what we could expect with medications alone.

But there are also many patients with uncontrolled blood pressure who do not have true resistant hypertension. As we discussed, up to 50% of patients who are prescribed medications for high blood pressure are not taking them. So it is no surprise that the most common treatment strategy used for these patients today, prescribing more medication, usually fails. The reality is that many people do not take or cannot tolerate enough antihypertensive medications, for a host of reasons, to control their blood pressure. For these patients, also, ultrasound renal denervation could fill a critical gap in care.

In conclusion, it is my clinical perspective that the benefits of ultrasound renal denervation far outweigh the potential risks. The risks are minimal, especially in light of the substantial benefits we observed. Like most healthcare providers, I have many patients who need their blood pressure lowered to allow them to live longer and healthier lives without the constant fear of a stroke or a heart attack or other major cardiovascular events. Unfortunately, the care we can currently provide is limited because lifestyle modifications and standard of care medical therapies alone have proven inadequate. Having access to renal denervation as a supplement to medical therapy would be a significant advance for patients. Thank you. I will now turn the presentation back to Dr. Reeve-Stoffer.

Dr. Reeve-Stoffer: Thank you, Dr. Fisher. We are happy to address any questions that the panel may have at this time.

Q & A

Dr. Lange: Great. I would like to thank the sponsor's representatives for their very clear and very good presentation. This is the opportunity for the panel to ask any clarifying questions to the sponsor. Again, this is not our time for deliberation, but if there's any questions you'd like to address to the sponsor that they can either answer now or additional data that you would like for them to get over the break. And so I see Keith's hand. I'll ask you either to raise your hand physically or to use the raise hand function. I've got Dr. Allen and Dr. Somberg. So, Keith, you first.

Dr. Allen: In the presentation there was mention of crossover, but I didn't see how that was adjudicated. Was crossover allowed, and, if it was allowed, when did it occur?

Dr. Reeve-Stoffer: Yeah. So crossover was allowed for patients that remained uncontrolled, and the crossover was allowed after the six-month follow-up in all of the studies.

Dr. Allen: So how then was that adjudicated or put into the statistical analysis, for example, the 24 and 36 month endpoints?

Dr. Reeve-Stoffer: So for the data that was shown on the longer-term follow-up, that does not include crossover data, but I can actually show you our crossover data. So we have data here, if we could put up slide A. This demonstrates the pooled crossover analysis. The pooled crossover analysis is for patients that were crossover, and you can see we saw a drop in blood pressure from those patients that were treated of at least 10 mmHg ambulatory systolic blood pressure that was sustained over 12 months.

Dr. Allen: If I understand you correctly then, crossovers are taken out of the analysis in the long term?

Dr. Reeve-Stoffer: That's correct. They are analyzed separately.

Dr. Allen: Thank you.

Dr. Lange: In this particular order, just to acknowledge, I've got Dr. Somberg, Dr. Lewis, Dr. Wittes, Dr. Blankenship, Dr. Corriere, Dr. Bates, Dr. Zuckerman, and then Deneen Hesser. So Dr. Somberg.

Dr. Somberg: Well, thank you. Excellent clinical program. Just a few clarification questions. How many patients didn't have an appropriate anatomy? I didn't catch that. And let me ask the other questions, and you can answer each of them. It's a closed system. So what happens if there's a leak? Does the machine give a signal or what have you? And also, was there a learning effect with the operators, or is it just so simple that there's no difference between the first one or two and the last one of an operator?

Dr. Reeve-Stoffer: So to address the first question, we did look at anatomy two different ways. So all of the patients had to have a prior CT or MRA, at which point the anatomy could be excluded so that the patients didn't move forward to randomization. And then also the patients that move forward to the cath lab, they would have a renal angiogram, which is the final point at which anatomy would be assessed, and they could be excluded. It was approximately 20 to 25% of patients that were excluded due to renal anatomy throughout the different studies. With respect to the closed system, if you have a pinhole in the balloon, which would be the equivalent of having a leak, there's a pressure error that would indicate to the physician that they could not move forward with the procedure.

Dr. Somberg: Okay. What about the learning effect?

Dr. Reeve-Stoffer: I'm sorry. Could you repeat the last question.

Dr. Somberg: The learning effect. Was there a difference in success between the first one or two and the subsequent manipulations with a person? Do they do this different over time?

Dr. Reeve-Stoffer: So we didn't do a formal analysis of the learning effect, in that we didn't look at those physicians that did the first case versus subsequent cases. But what we found is that

there was no difference between the outcomes of the blood pressure changes, independent of whether a physician did multiple procedures or only one. So we don't believe that there's a learning effect. This is a pretty straightforward procedure.

Dr. Somberg: Thank you.

Dr. Lange: Thank you. In addition to others I've mentioned, I'll add Dr. Saville and Dr. Vaughan at the end. First, Dr. Lewis.

Dr. Lewis: Thank you. I have three quick questions. In your labeling, you are proposing to give this to people who are intolerant or inadequately responsive. Did you establish or collect any data on intolerance to anti-hypertensives in any of the participants or that they were inadequately responsive to specific anti-hypertensives? My second question is, how does your training that you propose for the going forward post-approval compare to the PI training? And my last question is, you had uncontrolled sham patients who were given the opportunity to crossover. Could you please show us the number of sham patients who were uncontrolled versus the number that chose to crossover? Thank you.

Dr. Reeve-Stoffer: So for the first question regarding the labeling, the clinical trials all demonstrated or all included patients that were uncontrolled. We believe that inadequately responsive or intolerant is within that patient population. I'm gonna ask Dr. Fisher if she will provide her clinical opinion on the specific indication terminology.

Dr. Lewis: So no. No. No. I'm not asking about a clarification. I'm asking were there specific case report form questions that established this patient is intolerant to the following five anti-hypertensives for this reason, or were –

Dr. Reeve-Stoffer: I'm sorry. Thank you for the clarification. No, we did not collect that information.

Dr. Lewis: Okay. Thank you. And then the training of the proposed post-approval versus the PI training?

Dr. Reeve-Stoffer: So the training for the post-approval will be very similar, if not more stringent, than the actual training for the clinical trials. We are proposing that all physicians have both didactic and hands-on training, and we will be proctoring cases for at least the first five procedures until we feel that the physicians are adequately trained to be able to perform the procedure on their own. So the training program will be very robust and in line with what we've done through the clinical studies.

Dr. Lewis: Thank you. And then the total number of sham uncontrolled versus the number that chose to crossover.

Dr. Reeve-Stoffer: So for that we'll have to try to get that information for you after the break. So just to clarify, you're looking for the number of sham patients that crossed over versus those that chose not to?

Dr. Lewis: Yeah. Thank you.

Dr. Lange: And I'll keep a record of that. Thank you, Doctors. I've got Dr. Wittes, Blankenship, Corriere, Bates, Zuckerman, Deneen, Ben, Will, and Patrick. Go ahead, Janet.

Dr. Wittes: Okay. So I have one follow-up question about the crossovers, and then three quick questions of my own. What I understand is that the data that you've shown us for the long-term excludes the crossovers. And if that's true, do you have data that show the crossovers that include everybody in intent to treat? Because I don't know how to compare when I'm looking at two groups that are no longer based on randomization.

Dr. Reeve-Stoffer: Yes. So I think with respect to the longer term data that was demonstrated, so that would include patient data for those that crossover up to the point that they crossed over. So there will be data within there from patients in the sham groups prior to their crossover. And

then again, maybe I can show you in, slide a, please. So this is the data from all of the crossover subjects. So this is the pooled analysis from all those sham patients that did choose to crossover. And, again, you can see that there is a reduction in blood pressure of at least 10 mmHg that's maintained over 12 months.

Dr. Lange: The question is can you provide the intention to treat data at six months?

Dr. Wittes: Exactly.

Dr. Lange: Don't do it right now. We'll ask you to do it over the break.

Dr. Reeve-Stoffer: Okay. Thank you.

Dr. Wittes: Great. Okay. Then let me give you my three little questions. One, is the distribution of the number of medications in Solo and Radiance II at baseline compared to six months and 12 months.

Dr. Reeve-Stoffer: So the distribution of the medications at baseline would be slightly different than what we saw subsequently because the patients, of course, were taken off their medications and then titrated based on a predefined schedule. But we can provide to you the distribution of the blood pressure medications at baseline and also at subsequent follow-ups. But just to remind you, the data that we demonstrated at six months is going to be based on a predefined schedule. So it'll be different to the baseline medications that they came on during the study.

Dr. Wittes: Okay. And I don't want just the average. I want to know how many were on one and then stayed on one? How many were on two and went to one or two? I want the change from the baseline, and I understand it's the baseline before you put them on and then the follow up. Second question, where does the 9.8% performance goal come from? And the third is a little question, can you do a second ablation? If the blood pressure starts going up, can the procedure be done again?

Dr. Reeve-Stoffer: So the 9.8% performance goal for the safety endpoint and Radiance II is based on literature, mainly from the renal stenting literature. It was also used in an earlier Symplicity HTN III trial as the primary endpoint. It's a little difficult at this point with no precedence within the renal denervation world to use a composite that's based on renal denervation data. So the endpoint was based on renal stenting literature.

And then for the question related to whether you can do a second ablation or not, we have not systemically or systematically retreated patients. There are small cohorts of published data which show that patients treated with one renal denervation therapy who subsequently received ablation with a second renal denervation therapy did actually well.

Dr. Lange: Thank you.

Dr. Wittes: Thank you.

Dr. Lange: Dr. Blankenship.

Dr. Blankenship: Thank you. From the briefing document I understood that the exclusion for anatomy was about 10%. So I think you mentioned 25%. But, in any case, can you describe more fully what the anatomic exclusion criteria were? And then I have a small second question after that.

Dr. Reeve-Stoffer: Yes. Can I ask Dr. Coleman to answer the question regarding the exclusions on the anatomy.

Dr. Coleman: Leslie Coleman. So to clarify, the exclusions with regards to anatomy were essentially two-fold. So we had specific anatomical criteria with regards to balloon size, and some of this changed over time. So when we started the Solo study, we had a narrower balloon range, and then that expanded over time. And actually I can bring up a slide that will illustrate the criteria. So in addition to arterial size, we also had exclusions with regards to underlying pathology, and that was specifically whether patients had evidence of fibromuscular disease, if

they had a prior stented artery, evidence of a renal artery aneurysm, or any evidence of stenosis at any point along the renal artery that exceeded 30%. And the reasons for screen failure, in many cases, were related to underlying pathology. Thank you.

Dr. Lange: Thank you, Leslie. Go ahead, Dr. Blankenship, follow-up?

Dr. Blankenship: Just one little question. On the briefing document on section 7.3.3, lab evaluation of serum creatinine and eGFR, page 114, it says no clinically meaningful differences in serum creatinine and eGFR, and I'm curious about the no clinically meaningful differences. Does that term indicate that there might be statistically significant differences that are not clinically significant?

Dr. Reeve-Stoffer: Dr. Chertow, could you please respond to that question regarding the clinical meaningfulness of the changes in creatinine function? Dr. Chertow, I think you may be muted.

Dr. Chertow: So sorry. There were no statistically significant increases in serum creatinine or decreases in the corresponding estimated GFR.

Dr. Lange: So that was very soft. For those who couldn't hear, he said there was no statistically significant changes in GFR or –

Dr. Chertow: No. That’s correct. There were no statistically significant differences in the mean eGFR, and there were no patients who experienced large incremental increases in the serum creatinine. Right.

Dr. Lange: Thank you, Dr. Chertow.

Dr. Blankenship: Thank you.

Dr. Lange: Dr. Corriere.

Dr. Corriere: Thanks for your presentation. I just had a question about the sheath diameter for the device. And you had a pretty low observed access site complications. I was curious, did you

have protocolized access as part of your study protocol? Was the site of access predetermined? Were there exclusion criteria? Did you mandate use of closure devices, et cetera?

Dr. Reeve-Stoffer: So the Paradise Catheter is a six French catheter, so requiring a seven French guide. We did not have a predetermined protocol regarding either access or closure. Obviously it's a femoral access, and the majority of the sites either only needed to use pressure or in a few occasionally used a closure device.

Dr. Corriere: So no trans-radial access for this trial?

Dr. Reeve-Stoffer: Not at this point, no.

Dr. Corriere: Thank you.

Dr. Lange: Dr. Bates.

Dr. Bates: Yeah. I have two short questions on selection for these three very well-done trials and generalizability to my clinical practice. According to the pooled analysis paper, there were 2,830 patients screened. You accepted or you randomized 506, which is about 20%. And half of those were treated with a catheter, so that's about a 10% yield. So I wonder, in a complementary question to a previous question, what were the difficulties in enrolling the patients who are screened for these protocols?

Dr. Reeve-Stoffer: So I think the major challenge that we had with the study was the very strict criteria around entry blood pressure criteria. One of the things that we discovered, particularly in the Trio study, was that once we took patients off their multiple pills and put them on the single triple pill, many, in fact, the majority of the patients became controlled. So an interesting phenomenon which suggests that there is clearly an issue with adherence, but it was mainly blood pressure criteria with patients either becoming controlled on the triple pill or not meeting the eligibility criteria for blood pressure.

Dr. Bates: So the follow-up question is on generalizability, my arithmetic may be incorrect, but in Solo you enrolled 136 patients at 39 sites in 20 months. In Trio, 146 patients and 53 sites in 48 months. And in Radiance II, 224 patients at 61 sites and 35 months. So I think, if I'm correct, that comes out to only one to two patients randomized per site, per year.

Dr. Reeve-Stoffer: So I think there's a couple of things that we should consider, and then I'll ask Dr. Kirtane to speak to this too. We had COVID during the Radiance II program. So the program was actually closed for several months. The other challenge that we had, particularly with Radiance II, with Radiance Solo, is that these patients are patients that are not normally seen within the investigational sites. So we had to adapt our enrollment methods to be able to actually consider or to find the patients to bring them into the hospitals. So we adapted throughout the study. We used a lot of social media to increase the enrollment. So I don't believe that our enrollment rate would extrapolate to the number of patients and the time in which you would expect to see patients enrolled in the real world.

Dr. Kirtane, if you would like to add.

Dr. Kirtane: Good morning, everyone. This is Ajay Kirtane. Hey, I'd like to add also that on two of the three studies, patients had to be willing to come off of their medications entirely and be consented to randomize to a sham control. That's exceedingly difficult to do and what we felt it was super important to do to establish the efficacy of the device. The final point I'll make is that when these trials were enrolling, essentially on the basis of antecedent data, most people felt that this technology probably didn't work, or prior studies had showed that it didn't. And so I think in that backdrop, it's actually pretty remarkable that we were still able to randomize so many patients.

Dr. Lange: Right. Thank you. Eric, did that answer your question sufficiently?

Dr. Bates: Yeah. That’s very nice. Thank you.

Dr. Lange: Thank you. Dr. Zuckerman.

Dr. Zuckerman: Yes. First I'd like to thank the sponsor for a very nice presentation, but I would like to draw the panel to the sponsor's slide 45, where they show the main results of the Trio trial and 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. We'll go through our analysis in the next presentation. Nor is it the p value that's quoted in the FDA questions. So to put this matter to rest, I would like to put the panel on notice, specifically statisticians Drs. Wittes and Saville, should be able to help us out in our lunchtime discussion. And, secondly, for the clinicians on the panel, they should feel comfortable after hearing this statistical discussion to look more at the totality of data in putting together how Trio and the effectiveness of this particular device fits into the general schema. The sponsor may want to say a few words right now, but I would welcome any comments they have after lunch. Thank you. Dr. Lange.

Dr. Lange: Great. And so I'll ask the sponsor to make those comments after lunch because we have several other questions. Dr. Zuckerman, I appreciate you bringing the statistics to our attention, and we'll look forward to hearing the FDA presentation go into more detail about that. Thank you. Deneen. Deneen Hesser.

Ms. Hesser: Yes. I'm the patient representative. Enrollment in these trials by race did not reflect hypertension prevalence in the community. Do you anticipate any obstacles or barriers to integration of this treatment into our underserved communities where the need may be greatest? And then, secondly, in your patient prospective study, was the use of RDN as an adjunctive treatment offered as a choice?

Dr. Reeve-Stoffer: So thank you for the questions. Yeah. We recognize that within the clinical trial program, we did not have fully representative patients from underserved populations. For that reason, what we're proposing is that in our post-approval study, we will actively enroll in

those groups that were underrepresented within the Radiance program so that we can ensure that this therapy is both applicable and accessible to those patients. And then, I'm sorry, could you please repeat your question regarding the patient preference study?

Ms. Hesser: Well, in that study, was the use of RDN as an adjunctive treatment offered as a choice?

Dr. Reeve-Stoffer: Yes, it was. Yes.

Dr. Lange: Thank you.

Ms. Hesser: Okay. Thank you.

Dr. Lange: In the next 20 minutes, I have seven individuals, Dr. Saville, Dr. Vaughan, Dr. Nachman, Dr. Yeh, Dr. Cetnarowski, Dr. Lockhart, and Dr. Starling. So Ben.

Dr. Saville: Thank you. Just a couple questions. Like Dr. Wittes, I'm particularly interested in the long-term intent to treat durability comparisons of uRDN versus the sham. So, for example, on slide 61 and 63, I was expecting to see two lines there, one for the uRDN group and one for the sham. And I'm only seeing one. I'd like to see if you have two lines. I also understand there's missing data that goes into this because, as time goes on, you're going to have some patients who have to drop out, lost to follow up. You're going to have crossover. And I'd like to understand more about the missing data. And also I noticed on here, you know, the endpoint here, these graphs are focusing on the office systolic blood pressure and not the primary endpoint of the ambulatory. So I'm curious if you have long-term durability on the ambulatory systolic blood pressure decrease.

Dr. Reeve-Stoffer: So, firstly, the reason that we present the data without that sham control long term is because of the biased nature of the control group after the two-month endpoint. The patients become unblinded. That can affect their behavior. And as you indicated, the crossover occurs because the patients that crossover have to be uncontrolled. The patients that remain in

the sham group are automatically biased towards being controlled, and therefore we do not present the data. We present it as a treatment group only.

Dr. Saville: So I understand why you didn't do that either. You all can provide that over the lunch break?

Dr. Reeve-Stoffer: We can absolutely provide that information over the lunch break.

Dr. Saville: Terrific.

Dr. Reeve-Stoffer: So we can provide the graphs with the sham control data, as well as the treatment group.

Dr. Saville: Perfect. That would be helpful. And do you also have that for the ambulatory systolic pressure?

Dr. Reeve-Stoffer: So the protocol actually only collected ambulatory blood pressure out through 12 months, which is why the office systolic blood pressure is presented. Post 12-months, we have office blood pressure.

Dr. Saville: Okay. That’s helpful. But I would like to see those for the six and 12 months if we can.

Dr. Reeve-Stoffer: We can provide that to you.

Dr. Saville: That'd be helpful. Thank you. And the last thing is, you know, the efficacy data on slide 52, though that was helpful, showing the reductions in the means, but I think one thing that's really lacking here is a better visual representation of the raw data. So I understand the means are decreasing, but I don't have a good sense for what the distributions look like. So a graph that I'm really interested in seeing for these various trials for the primary endpoint, as well as the long term, but particularly the primary endpoint of two months, I'd like to see if you had side-by-side box plots of the two groups with some jittered data points that show what those actual raw data points are and –

Dr. Reeve-Stoffer: We have, sorry. I didn't mean to interrupt you. We do have waterfall plots. Would that be what you're looking for?

Dr. Saville: That would be certainly more helpful than this. Yes, if you have anything more granular that shows us more about the distribution, that would be helpful.

Dr. Reeve-Stoffer: So I can show you the waterfall plots for Radiance II.

Dr. Lange: Great. And so we'll show that after lunch.

Dr. Reeve-Stoffer: We have waterfall plots for all three, so we can show the remaining waterfall plots after the lunch break.

Dr. Lange: All right. We'll do that. Fine. Terrific.

Dr. Saville: Thank you.

Dr. Lange: I just want to get everybody's questions in. So thanks. Dr. Vaughan.

Mr. Vaughan: Not a doctor, just a consumer. But follow-up on Dr. Zuckerman's question, would it be possible to get some discussion of figure 19 from page 34 of the long paper first submitted by the company that, as I read it, shows after six months, sham tending to do better on some blood pressure reductions and appreciate a discussion of that. And then thank you for Dr. Fisher for raising or citing the cost of meds. As a consumer, we can't figure out value very much unless we have a feel for the cost of things. And is there any information on what you hope your launch price will be or what you're selling some of these devices for in Germany or Switzerland?

Dr. Lange: So, Dr. Vaughan, I'm sorry that, unfortunately, although that is of great interest, both as a consumer and as a patient, the FDA and the panel is not to consider cost when we talk about the safety and efficacy. So my apologies. Perhaps after the panel discussion, that information could come from the company, but we are not permitted to discuss that. So my apologies, sir.

Mr. Vaughan: My apologies.

Dr. Reeve-Stoffer: And then with respect to your question about the six months data, I'll have Dr. Kirtane speak to that.

Dr. Lange: Great. Super.

Dr. Kirtane: This is Ajay Kirtane. Recall that in the study designs after two months, investigators –

Dr. Lange: I'm sorry. Again, with all due respect, y'all are doing a great job. Can we answer that after lunch? Is that okay?

Dr. Kirtane: Sure.

Dr. Lange: We'll add that to the list. My apologies. I see five other hands up, but I want to make sure that we get their questions. So, again, not meant to be rude, but I promise you we'll look at that data.

Dr. Reeve-Stoffer: Thank you.

Dr. Lange: I've got it written down. Great. Dr. Nachman. You're on mute, sir.

Dr. Nachman: Yes. Sorry. Thank you very much, sir. Patrick Nachman. So one quick and maybe a little longer question. So in the exclusion criteria for participation in the trial, patients with the estimated GFR less than 40 were excluded. Can you give data and numbers actually on the number of patients in your trials that had a GFR less than 60 that might impact labeling issues? And then maybe this is something we'll discuss after lunch, but my understanding of the medication load index is that it takes into account not just number of medications, but the dose adjustment and medications compared to the maximal dose possible for a drug. Can you comment later on the comparison of the number of medications necessary in the various trials, especially in the Trio trial maybe, between the intervention and the sham study?

Dr. Reeve-Stoffer: So with respect to those two questions, we can provide to you, after the break, the number of patients that we had which had a GFR less than 60. It was a very small

minority of the patients in my recollection, but we can provide you the data. And then with respect to the medication index and loads, we did do three different medication analyses, both average number, defined daily dose, and the medication load index. And we can provide that information to you after the break as well.

Dr. Lange: Thank you very much. Dr. Yeh.

Dr. Yeh: My primary requests are the same as Dr. Saville's actually, but maybe we could jump to slide 61 just for a quick second and take a look. At 61, there's just this negative 17.7 that we see here, and then compared to the next slide where we see what looks to me like a similar outcome but a different number for an 8.4. Can you just explain the differences that we're seeing between those numbers, which appears to be systolic blood pressure changes between baseline?

Dr. Reeve-Stoffer: Absolutely. I can have Dr. Kirtane speak to that.

Dr. Kirtane: Thanks so much. In this slide is actually the difference in blood pressure from screening. So this is prior to enrollment in the study, prior to the point at which patients were taken off their medications. And so that's, I think in some respects, a fair comparison of the two groups because remember, in this trial specifically, Radiance -Solo, patients had to be taken off their medications. And so that's why the drop is somewhat less because they were on medications at the time of screening. The overall change in medicines is negligible, as you can see on the right of the slide. If we go back to the other slide, in A, these are data that are from the time of baseline, which is when patients were taken off their medications through long-term follow-up.

And I just want to address the point of crossover really quickly. All analyses that we've shown from six and 12 months are actually intent to treat, because no patients actually crossed over before 12 months. Important point to make for everybody. No patients crossed over before 12 months. Thank you.

Dr. Yeh: Thank you.

Dr. Lange: Dr. Lockhart. And, by the way, Deneen and Wes, if you all still have questions, keep your hands up. If not, go ahead and great. Dr. Lockhart, Dr. Starling, the last two questions.

Dr. Lockhart: So mine's brief. It's not an exclusion if they have arterial wall calcifications without stenosis, but does the presence of calcifications affect the energy deposition into the wall and does it limit the extension of that energy into the advent tissues?

Dr. Reeve-Stoffer: So I'll have Dr. Coleman speak to that.

Dr. Coleman: Thank you. Leslie Coleman. As you mentioned, we did not specifically include vessels that had calcification. However, we did instruct sites to not treat at signs of calcification. So the impact of calcification on ultrasound, there could be changes to depth. I think perhaps slightly less penetration, but we are very specific about not treating up points of calcification.

Dr. Lockhart: Okay. Because, in theory, would that increase deposition into the wall area?

Dr. Coleman: No, we would have decreased energy into the wall at sites of severe calcification.

Dr. Lockhart: Okay. Because the energy won't go through, but it has to go somewhere. So where would it go?

Dr. Coleman: I think it would be best if we can try to get you that information after the break.

Dr. Lockhart: Okay. Thank you.

Dr. Coleman: Thanks.

Dr. Lange: Dr. Starling?

Dr. Starling: Yes. Thank you. I have a couple questions. The first has to do with reinnervation, whether there's any concern about that, and if so is there a mechanism to monitor or make that observation?

Dr. Reeve-Stoffer: So we specifically have not done any studies on reinnervation, but there are animal studies in the literature looking at renal denervation and reinnervation. It appears, based on those studies, that while there may be some level of nerve regrowth, that regrowth is

not functional. So there's no evidence that the nerve regrowth has any functional impact. And our data, which suggests that the reduction in blood pressure is sustained would also indicate that there is no reinnervation.

Dr. Starling: Second question relates to the Trio study where you described a single pill that had three components in it. Was this same fixed dosing pill administered to all patients?

Dr. Reeve-Stoffer: It was with one exception. So across all the geographies, they used a combination pill of 25 milligrams HCTZ, 160 Valsartan, and 10 amlodipine. That specific combination is not available in the UK, and so, therefore, the UK used a slightly different combination with equivalent potency, so 10 amlodipine, 25 HCTZ, and then a 40 Valsartan.

Dr. Starling: And my last question, could you clarify, was any imaging of the renal arteries done beyond 12 months, and are there plans in the post-approval study for any imaging?

Dr. Reeve-Stoffer: No. So the imaging protocol concluded at the 12 month follow-up. So all the patients had pre-procedure imaging and then also all the treated patients had imaging at 12 months, unless clinically indicated. So subsequent to or post 12 months, if there was any clinical indication, there would be imaging. We're not, at this point, proposing imaging within the post-approval study, but we're certainly open to discussion with the agency as to whether that would be appropriate.

Dr. Starling: Thank you.

Dr. Lange: Mr. Cetnarowski, you have your hand up. Do you have another question, sir?

Dr. Cetnarowski: The original question. Yes. I'm not sure if it's a follow-up to your question, Dr. Lange, but we looked at the pooled data for the crossover patients, and then you asked for ITT data or maybe even per protocol data, but I'd be particularly interested in pooled efficacy data for daytime ambulatory BP or home BP across two to six months. Was that what you were asking for? And is that available?

Dr. Lange: Right. And, in fact, here's what we requested of the sponsor, and I hope I've captured it. If I didn't ask the sponsor to address your issue, if you'll let me know. First of all, Dr. Lewis wanted to know how many individuals had uncontrolled hypertension, and some of which chose to undergo crossover and some of whom did not. Dr. Wittes asked about the ITT at six months that includes crossover, and that would be the systolic ambulatory blood pressure, also the distribution of the number of meds at baseline, two, four, and six months.

Dr. Saville, with regard to slides 61 and 62, wanted to show the data regarding the sham and the catheter treated individuals, asked for more information about the missing data, the long-term durability of the ambulatory blood pressure measurements, and specifically to see the ambulatory systolic pressures at six and 12 months. Dr. Saville, did I –

Dr. Saville: Yeah. Slides 61 and 63 specifically are the ones that I called out, not 62.

Dr. Lange: Okay. Thank you.

Dr. Saville: That captures it. Yes.

Dr. Lange: Okay, great.

Dr. Saville: But as well, sorry, there was also the question there to understand the missing data at those time points as well because that wasn't very clear.

Dr. Lange: Great. Thank you. Dr. Vaughan, discussion of –

Dr. Saville: I have one more request about the visual representation of the data that seemed more granular about the distribution of the data points so that the change in systolic blood pressure.

Dr. Lange: Right. Thank you, Ben. I wrote that down and didn't highlight it. Thank you. Dr. Vaughan wanted some explanation of why the six-month sham patients had a better blood pressure control than the treated patients. It has to do with figure 19, page 34, of the sponsor's

submitted data. Dr. Nachman, number of percentage of patients had a GFR of less than 60 and also the number of meds in Trio , both the intervention and sham patients.

And then one question for me. I'm going to have the final words from Dr. Zuckerman and Dr. Wittes. One is I know there were very few diabetic patients in the off-med, but there were some in the Trio, and we didn't see how the diabetics versus non-diabetics responded. So if I could see that, that'd be great. Dr. Zuckerman and Dr. Wittes, the last words.

Dr. Zuckerman: Yes. I believe Dr. Kirtane made a statement that crossover was at 12 months. I want to clarify that. That's for the Radiance trial, Solo and Trio had crossover at six months, further emphasizing all the good panel questions about what's happening after six months. Thank you.

Dr. Lange: Thank you. And then Dr. Wittes?

Dr. Wittes: Yes. I just want to clarify that I'm interested in the ITT, not only at six months, but also at 12 months. And that refers also to the number of anti-hypertensive medications. Not only at six, but also at 12.

Dr. Lange: Okay. Thank you, Dr. Wittes. So to our response, Helen, do you feel like you understand what the panel's asking for?

Dr. Reeve-Stoffer: Yes. I believe we do. Thank you, Dr. Lange.

Dr. Lange: Great. We're about to take a break here for 15 minutes. I want to again thank the sponsor for a really terrific presentation, being responsive to the questions, and for offering to get the additional data that we can talk about after lunch. So thank you very much to ReCor.

At this point, we're going to take a 15 minute break, and we're going to reconvene promptly at 11:15. So if you'd like to turn your videos off at this time, we'll have a timer on the screen, I believe, if I'm not mistaken. And we'll reconvene promptly at 11:15 Eastern Standard Time. Thank you.

Dr. Lange: I should have mentioned to the public observers that during the break, the panel members do not discuss any of the meeting topics either with any other panel members or anybody attending virtually. So, I just want to make that statement public. We'll now proceed to the FDA presentation. I would like to invite the FDA representative Dr. Paul Warren to begin. The FDA representative will have 75 minutes to present. Please begin your presentation now.

FDA Presentation

Dr. Warren: Good morning, everyone. This is the FDA's presentation regarding ReCor Medical's Pre-Market Approval application, or PMA for the Paradise Ultrasound Renal Denervation System. We appreciate the panel's time today and the opportunity to discuss this novel device. My name is Paul Warren. I'm a biomedical engineer and the lead reviewer for this PMA and I'll be starting the FDA's presentation with a brief description of relevant clinical and device background information.

You'll hear from a few members of our review team today. We're grateful for the expertise and feedback provided by our entire clinical and statistical review team who are listed on this slide. This is an outline of the topics on which we'll be presenting. I'll begin by going over background information on hypertension and the subject device, as well as a short overview of the designs of the clinical studies. You'll then hear from Dr. Wei-Chen Chen on statistical methods for analyzing the clinical data. Dr. Doug Silverstein on clinical study results and Dr. Dave Gebben regarding the patient preference study. Then to close, I'll discuss the potential post-approval study design and summarize FDA's conclusions.

The proposed device aims to treat patients with hypertension, a condition that is a major public health problem, In the US, the National Health and Nutrition Examination Survey or NHANES estimated that between 2017 and 2018, hypertension impacted about 45% of all adults with a higher prevalence in Black Americans at 57% than Caucasian or Hispanic Americans, both

at about 44%. The link between hypertension and an increased risk of serious conditions including stroke, heart disease, heart failure, vascular disease, and renal disease is well established. To date, anti-hypertensive medications remain the mainstay of hypertension therapy. Still, blood pressure medication adherence is present in only about 60% of patients, and attainment of target blood pressure goals occurs in less than 50% of patients.

For a formal definition of hypertension, the 2017 guidelines published by the American College of Cardiology, American Heart Association, and other organizations set thresholds for categories of hypertension. Stage one, hypertension is defined as a systolic pressure of 130 to 139 mmHg, or a diastolic pressure of 80 to 89 mmHg. Stage two, hypertension is defined as a systolic pressure at or above 140 mmHg or a diastolic pressure at or above 90 mmHg. A patient is considered to have uncontrolled hypertension if their blood pressure remains above goal, either because of non-adherence to treatment or despite treatment adherence. Finally, treatment-resistant hypertension is present if a patient has an above-goal blood pressure, despite the use of three anti-hypertensive medications with complementary mechanisms of action, one of which is a diuretic. These definitions will be important when considering the specific patient populations evaluated in the clinical studies and for which populations the device should be indicated.

While various physiological mechanisms are associated with blood pressure regulation and consequently hypertension, renal physiology plays a key role. As shown in the figure on the right, the renal vasculature is innervated mainly by efferent sympathetic nerves. Efferent nerve stimulation leads to increased reabsorption of sodium and water, increased vasoconstriction, which reduces renal blood flow and the renal filtration rate, and increased activity of the renin-angiotensin-aldosterone system, all of which ultimately increases blood pressure. Thus, renal nerves are a therapeutic target for modulating sympathetic activity, to reduce blood pressure. The

subject device delivers energy bilaterally in the proximal branch of the main renal artery and/or an accessory renal artery.

Renal denervation or RDN is an approach that aims to reduce sympathetic activity by ablating the nerves surrounding the renal artery. This is achieved by delivering controlled emissions of radio frequency or ultrasound energy, or delivering chemical neurotoxins such as ethanol to the renal arteries. Early single-arm clinical studies of percutaneous RDN technologies were promising showing large decreases in blood pressure. However, subsequent Sham-controlled studies did not show the same degree of blood pressure reduction, nor was a significant difference found between the RDN treatment and Sham groups. Furthermore, some animal studies have shown evidence of partial re-innervation following the denervation treatment, which may have implications for the durability of blood pressure reduction via RDN in humans.

Because of the uncertainty surrounding RDN technologies, the FDA convened an advisory committee meeting in 2018 to discuss clinical trial design and scientifically sound ways to evaluate the safety and effectiveness of hypertension devices. The panel's key recommendations included the use of a Sham-controlled study arm to help isolate device treatment effects; the use of two trial designs, one in which patients are taken off their blood pressure medications to demonstrate proof of concept and one in which medication is standardized for patients to minimize the confounding effect of medication use and study the effect in real-world hypertension patient populations; the use of ambulatory blood pressure as the primary measure of effectiveness to avoid limitations of other metrics such as office blood pressure; the definition of a between-group difference in blood pressure reduction of at least five mmHg as being clinically significant, although it wasn't specified if this should be 24-hour, daytime, or nighttime ambulatory systolic blood pressure; and finally, the value of patient preference information in weighing benefits versus risks.

With these recommendations in mind, ReCor worked with the FDA to design clinical studies to evaluate their Paradise Ultrasound Renal Denervation System. The Paradise uRDN System consists of a percutaneous catheter used to deliver ultrasound energy bilaterally to the renal arteries, to generate heat and ablate the surrounding nerves, with sterile water circulated through the balloon to provide cooling and prevent excessive ablation in the surrounding tissue.

Typically, at least two ultrasound emissions at an operating frequency of about nine megahertz are administered per renal artery. The Paradise System's proposed indication for use is to reduce blood pressure in patients with uncontrolled hypertension who may be inadequately responsive to or who are intolerant to anti-hypertensive medications.

The Paradise uRDN System was designated as a breakthrough device by the FDA in 2020 based on its potential to provide benefits to patients with resistant or uncontrolled hypertension. FDA's breakthrough device program is for devices that may provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions. This program is intended to provide the American public with timely access to new devices with the potential for significant impact by expediting their development, assessment, and review.

This program offers several benefits as listed here and is intended to help bring these devices to market more quickly. However, it's important to note that a breakthrough device designation does not alter or reduce the statutory requirements for device approval. For approval, the FDA still requires that a breakthrough device demonstrates a reasonable assurance of safety and effectiveness. For breakthrough devices, the FDA may be willing to accept greater uncertainty for a pre-market submission along with timely post-market data collection if uncertainty in the benefit-risk profile can be balanced by other factors such as the probable benefit to patients from earlier access to the device versus the probable risk of harm, should additional data reveal the device to be ineffective or unsafe.

In addition to the clinical assessment you'll be hearing about today, the Paradise System has also undergone numerous non-clinical and pre-clinical evaluations as listed here. Based on the FDA review, there are no outstanding non-clinical concerns.

I'll now provide a brief overview of the study designs for the trials ReCor conducted to evaluate the Paradise uRDN System. ReCor conducted three independent studies: Solo and Radiance-II were studies of patients off medication, while Trio was a study of patients on standardized medication, which consisted of a triple blood pressure pill. For all studies, potential subjects were first screened by measuring office blood pressure. Those meeting a pre-specified blood pressure threshold and other initial criteria were enrolled. Solo and Radiance-II subjects then discontinued their blood pressure medications and underwent a four-week washout period. Trio subjects had their blood pressure medications replaced with a single, fixed-dose triple combination pill, then underwent a four-week stabilization period on the triple pill. Finally, subjects who met the criteria for daytime ambulatory blood pressure levels as shown here were randomized. In FDA slides, uRDN stands for ultrasound renal denervation and denotes the treatment group, while Sham refers to the control group. You'll hear about study endpoints later on in our presentation. Finally, some additional key design elements include a pre-specified medication escalation plan between two and six months to achieve blood pressure goals. Study blinding through six months for Solo and Trio, through 12 months for Radiance-II, and Sham patients being permitted to cross over to the uRDN group after six months in Solo and Trio and after 12 months in Radiance-II.

Key study enrollment criteria included patients being between 18 and 75 years old, having a history of hypertension, and having suitable proximal or accessory renal artery diameter and length for uRDN treatment, as well as no renal artery stenosis greater than 30% as confirmed by CTA or MRA. Generally, having an office blood pressure greater than 140 over 90 mmHg at the initial screening step, allowed a patient to proceed in the study with the exact criteria listed in the

first row of this table. Similarly, a daytime ambulatory blood pressure greater than 135 over 85 mmHg, after washout or stabilization, allowed a patient to be randomized. Lastly, Solo and Trio had a one-to-one uRDN to Sham control randomization scheme, while Radiance-II had a two-to-one randomization scheme.

Now, I'll turn FDA's presentation over to Dr. Wei-Chen Chen to discuss statistical methods.

Dr. Chen: Thank you, Dr. Warren. I'm Wei-Chen Chen, a statistician in the CDRH Office of Clinical Evidence and Analysis. First, I will describe the main differences in statistical analysis plans for the primary safety and the effectiveness endpoints. In Solo and Trio, there was no pre-specified primary safety endpoints and the primary effectiveness endpoint was pre-specified and tested. In Radiance-II, the primary safety endpoint was pre-specified and tested, and the primary effectiveness endpoint was pre-specified and tested. Next, I will briefly go through the evaluation of primary and secondary endpoints.

For the primary safety endpoint, the analysis population was the uRDN-treated subjects in the Radiance-II trial. The primary safety endpoint was defined as the occurrence of at least one of these major adverse events (MAE) at 30 days post-procedure or new hemodynamically significant artery stenosis at six months. Additional analyses were performed using data pooled from the Solo, Trio, and the Radiance-II trials.

The safety event rate performance goal or PG was set at 9.8%, which was based on a literature review. The hypothesis for the primary safety endpoint was a comparison of the proportion of subjects who had at least one safety endpoint event to the PG. The success of the primary safety endpoint was determined from the upper limit of a one-sided 95% confidence interval around the observed safety event rate.

Turning to the primary effectiveness endpoint for each of the three individual trials, Solo, Trio, and Radiance-II, the primary effectiveness endpoint was defined as the change in daytime

ASBP from baseline to two months. Daytime was defined as 7:00 AM to 10:00 PM. The statistical hypotheses were formulated as the superiority test comparing uRDN to Sham. In statistical notation, it was to test whether the parameter β_{txt} was equal to zero or not, where β_{txt} was the regression coefficient from the Analysis of Covariance model or ANCOVA. The model is shown in this slide. I want to point out two important terms highlighted in this model. First, β_{txt} was the parameter of interest associated with treatment effect for the primary effectiveness endpoint. Second, X_{bl} was the baseline BP, which was the covariate to be adjusted. Because of X_{bl}, we call this model a baseline-adjusted ANCOVA model.

The primary analysis is based on the Intention-to-Treat ITT population. The goal was to test this β_{txt} at the two-sided 0.05 alpha level. The sponsor also pre-specified an additional analysis for the primary effectiveness endpoint. When the assumption of normality for the ANCOVA model may be in question, an ANCOVA on the ranks analysis was performed. This on-the-ranks analysis is a non-parametric version of the baseline-adjusted ANCOVA model, but it does not provide a treatment effect or a confidence interval. The sponsor reported a descriptive summary based on the median for treatment effect using the Hodges-Lehmann estimate without adjusting for baseline BP and this summary is not associated with the ANCOVA or ANCOVA on the ranks p-values.

In the ITT analysis, missing data were imputed as follows: in Solo, Trio, and Radiance-II, for subjects who met the protocol defined "High BP Action" as escape criteria, the last BP measurement before medication change was used; in Solo and Trio, subjects with missing data for BP, a value of zero was used for the BP reduction. It is questionable whether this imputation approach is reasonable or not for estimating the treatment effect because the zero value may be in favor of or against the BP reduction trend. In Radiance-II, the sponsor proposed a multiple imputation approach, which may be a reasonable alternative. The imputation model included age, sex, and baseline ambulatory SBP that generated 20 imputed data sets. Then, the results were

combined via Rubin's Rules to derive the p-value for testing the hypothesis and derive the confidence interval for the treatment effect.

Several secondary effectiveness endpoints were analyzed to compare the reduction in average BP between uRDN and Sham from baseline to two months, as shown on this slide. Similar to the primary effectiveness endpoint, the ANCOVA adjustment with baseline BP was used to analyze these secondary endpoints. Several additional endpoints include the instance of BP reduction at five, 10, 15, and greater than 20 mmHg. A responder analysis baseline proportion of subjects with BP control was defined as less than 135 over 85 mmHg. Medication burden was analyzed by the number of anti-hypertensive medications and the medication load index, which was defined as the weighted average of the prescribed dose over the standard dose. Our clinical reviewer, Dr. Silverstein, will discuss the medication burden in detail.

Prespecified subgroup analysis included the evaluation of 14 baseline covariates individually. Subgroup indicator and treatment by subgroup interaction terms were included in the baseline-adjusted ANCOVA model. In the analysis, the interaction term was then used to evaluate whether or not the BP reduction results were different by subgroup.

There are two important statistical considerations to keep in mind in interpreting the result of secondary and additional endpoints. 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. Now, I would like to turn over our presentation to Dr. Doug Silverstein, who will go over the clinical results.

Dr. Silverstein: Thank you, Dr. Chen. My name is Doug Silverstein. I'm a nephrologist in the FDA's Office of Gastro-renal, ObGyn, General Hospital, and Urology Devices. I'll start with a brief recap of the three separate trials. Solo and Radiance-II were off-med trials while the Trio trial

was an on-med trial. Solo and Radiance-II enrolled patients with mild to moderate or stage 2 hypertension, whereas Trio Trial patients had resistant hypertension. Initial screening was based on office blood pressure. Subjects in Solo and Radiance-II had their blood pressure meds discontinued, followed by a four-week washout, while Trio subjects had their current blood pressure meds replaced by a triple pill containing a calcium channel blocker, angiotensin receptor blocker, and a diuretic with blood pressure stabilization established over the next four weeks. Final eligibility was dependent on daytime ambulatory systolic blood pressure. Randomization for Solo and Trio were one-to-one and randomization was two-to-one RDN to Sham for Radiance-II. The final sample size of randomized subjects was 146 for Solo, 224 for Radiance-II, and 136 for Trio. Blinding was required until six months for Solo and Trio and 12 months for Radiance-II. Crossover was permitted at six months for Solo and Trio and 12 months for Radiance-II. 142 Solo subjects reached 12 months follow-up and 94 reached 36 months follow-up. A total of 37 Solo subjects crossed over from the Sham group to the RDN group. In Radiance-II, 215 subjects reached 12 months follow-up and 19 Sham subjects crossed over to RDN. 131 Trio subjects reached 12 months follow-up, 106 reached 24 months and 21 Sham subjects crossed over. There was a limited number of subjects in all three trials who withdrew before the primary safety and efficacy endpoint analysis time points. All three studies included multiple crossover subjects, which reduced the number of control subjects for longer-term analysis.

Turning to baseline study subject characteristics, randomization resulted in an equal distribution between RDN and Sham for all major criteria. There was about a two to greater than threefold higher proportion of males randomized in all three trials, and the mean age was 52 to 54 years. There was an equal number of US and OUS subjects in Solo with more OUS subjects in the Trio and Radiance-II trials. Caucasians accounted for 66% to 81% of subjects with black or African-American subjects accounting for 16% to 21%. Mean BMI and abdominal circumference

were high in all studies. Baseline office systolic blood pressure and diastolic blood pressure were lowest in Solo and highest in Trio, and the results were balanced between RDN and Sham subjects.

Before the procedure, Solo subjects were taking zero to two blood pressure meds with the vast majority receiving one or two meds. Similarly, Radiance-II subjects were taking zero to two blood pressure meds with a somewhat higher proportion of no blood pressure meds at screening versus Solo subjects. Trio subjects were taking more blood pressure meds at screening than Solo and Radiance-II, three to four meds in the vast majority, consistent with the Trio eligibility criterion of resistant hypertension. In Solo, Radiance-II, and Trio, the number of blood pressure meds at baseline and screening was generally similar between RDN and Sham subjects.

I will now discuss the major safety results for the three trials. We recall that the primary safety endpoint was limited to the Radiance-II trial and consisted of a composite of the 30-day post-procedure incidence of major adverse events or MAEs, or new artery renal artery stenosis defined as a greater than 70% diameter stenosis within six months of randomization. The types of MAE events are listed on this slide. An additional pooled analysis was pre-specified for all RDN-treated subjects in the three trials.

Here are the primary safety endpoint results. Among 150 Radiance-II subjects, the safety event rate was 0% with a confidence interval of zero to 1.63%, which met the pre-specified performance goal 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%.

Here are the observed safety events for the three studies. The overall percentage of events was low in all three trials. There was one hospitalization for a major cardiovascular or hemodynamic event in the Solo trial. In the Trio trial, there were two deaths. One death was due to an unknown cause that occurred 21 days after the RDN procedure. This subject had prostate cancer, was found dead at home and an autopsy was not performed, and another death occurred in

a subject before the two-month visit after crossover into the RDN group and the RDN procedure. The cause of death in that subject is unknown. There were two major vascular complications, a pseudo aneurysm and dissection, and one blood pressure-related hospitalization in the Trio trial. There were no cases of hemodynamically significant renal artery stenosis.

Next, we turn to renal arterial responses to RDN treatment. The rate of renal artery narrowing was determined by CTA/MRA imaging at six and 12 months in all three trials. Here are the six- and 12-month CTA/MRA data for Radiance-II, RDN, and Sham subjects, excluding crossovers. The highest rate of stenosis, 31% to 50% in RDN subjects was 2.7% at 12 months. No RDN subject developed renal artery stenosis defined as a greater than 70% diameter stenosis through 12 months.

Renal function was assessed by estimated glomerular filtration rate or eGFR, which was calculated from serum creatinine at various time points in all three trials. 12-month eGFR data and serum creatine are available for the Solo and Trio trials. On this slide are the Solo trial data, which are similar to the Trio results. The mean change in GFR at 12 months in RDN subjects was -0.99 milliliters per minute and 3.40 in Sham subjects with a mean difference between the two groups at 12 months of 3.79. This numerical difference was statistically significant, but FDA believes the differences are not clinically significant. Importantly, GFR, which naturally slowly declines with aging, was stable in RDN subjects. Similarly, serum creatinine changes were statistically but not clinically significant between the RDN and Sham groups and creatinine levels remain stable in RDN subjects through 12 months.

I will now discuss the major effectiveness results for the three trials. Recall that the primary effectiveness endpoint was the mean difference in change of daytime 7:00 AM to 10:00 PM ambulatory systolic blood pressure, or ASBP, between treatment and Sham groups from baseline

to two months after RDN or the Sham procedure. The primary analysis population was the ITT cohort.

Up until two months, in all three trials, additions or changes in blood pressure medications were permitted only for emergent situations such as a hypertensive crisis. Both the Solo and Radiance-II off-med trials met the primary effectiveness endpoint based on the ANCOVA model with a baseline blood pressure adjusted treatment effect, or the delta of 6.3 mmHg for blood pressure reduction favoring RDN. In the on-med Trio trial, the 4.5-mmHg blood pressure reduction difference in favor of RDN did not reach statistical significance. In other words, the effectiveness endpoint was not met based on the ANCOVA model. Therefore, ANCOVA on the ranks was also conducted.

The results of the ANCOVA on the ranks were significant. Due to possible outliers, the data may not follow a normal distribution. The median blood pressure reduction, therefore, was also reported. The results of the median indicated the treatment effect between RDN and Sham, or the delta, was below five.

In a previous slide, we showed the primary efficacy endpoint was met for daytime systolic blood pressure. On this slide, please focus on the results for 24-hour systolic blood pressure, the left plots in the figure, and office systolic blood pressure, the right plots in the figures, in the Solo and Radiance-II for ITT subjects at two months. In both Solo shown here and Radiance-II shown here, the mean difference in the reduction in 24-hour systolic blood pressure and office systolic blood pressure were significant in favor of the RDN Group in both the Solo and Radiance-II subjects.

In Trio, please focus on the results for mean 24-hour systolic blood pressure, the left plot in the figure, and office systolic blood pressure, the right plot in the figure. The mean blood

pressure reduction difference between RDN and Sham for 24-hour systolic blood pressure and office systolic blood pressure did not reach statistical significance.

2018 guidelines included the methods for determining the average change in blood pressure after device therapy for hypertension. The agency believes a proportion of subjects achieving at least a five-mmHg reduction in systolic blood pressure is clinically meaningful. In Solo at two months, a significantly greater proportion of RDN subjects achieved at least a five-, 10, or 15-mmHg decline in daytime systolic blood pressure, the primary effectiveness endpoint, than Sham subjects. Similarly, in Radiance-II or two months, a significantly greater proportion of RDN subjects achieved at least a five-, 10, or 15-mmHg decline in daytime systolic blood pressure versus Sham subjects. Finally, in Trio at two months, a significantly greater proportion of RDN subjects achieved at least a five-, 10, or 15-millimeter decline in daytime systolic blood pressure versus Sham subjects. Please note that the p-values were not adjusted for multiplicity.

Achieving a target blood pressure is associated with reduced cardiovascular risk and is important to patients and clinicians. The top figures show the rate of achieving an ambulatory systolic blood pressure or ASBP of less than or equal to 135 mmHg in two months and the bottom figures show the ASBP change as a function of baseline blood pressure. In the top figures, in Solo and Radiance-II, we see that more RDN subjects achieved the target of less than or equal to 135 systolic blood pressure regardless of baseline blood pressure. On the bottom figure, we see that ambulatory systolic blood pressure reduction at two months was greater in RDN subjects in both Solo and Radiance-II, regardless of baseline blood pressure tier.

In the On Standardized Medication Trio Study, except for the patients where the baseline ambulatory systolic blood pressure was greater than 153 mmHg, more RDN subjects achieved ambulatory systolic blood pressure of less than equal to 135 mmHg at two months compared to the Sham. In the bottom figure, we see that the ambulatory systolic blood pressure reduction at

two months was greater in RDN subjects versus Sham subjects, regardless of baseline ambulatory systolic blood pressure.

Subgroup analyses were performed to determine if the blood pressure changes were impacted by various clinical parameters. In both Solo, the farthest plot on the left, and Radiance-II, the plot on the right, ambulatory systolic blood pressure results were in favor of RDN and were generally consistent across all subgroups that included race, age, gender, location of study site (US versus OUS), baseline daytime ambulatory systolic blood pressure, and office systolic blood pressure.

In the On Standardized Medication Trio trial, there was a trend towards a greater response to RDN in the US versus OUS subjects. While all the results favored RDN, there were no differences based on these parameters in the results favoring RDN.

I will now discuss the durability of blood pressure reduction for all three studies. The agency believes that meeting the two-month primary effectiveness at this endpoint is important. The durability of blood pressure reduction is also essential. These figures show hourly systolic blood pressure at baseline, two months, and six months for the Radiance-II off-med trial. RDN is on the left and Sham is on the right. In general, for both treatment groups, blood pressures are higher during awake hours and lower overnight. For RDN subjects, on the left, compared to the baseline shown by the top light blue curve, at two months, shown by the dark blue curve in the middle, there is a reduction in blood pressure throughout the day. After two months, blood pressure medications could be restarted and at six months shown by the black curve at the bottom, there was a further reduction in blood pressure throughout the day. For Sham subjects, on the right, compared to the baseline shown by the top, light-gray curve, at two months shown by the dark-gray curve, there was no reduction in blood pressure. The curves appear superimposable. After two months, blood pressure meds could be restarted and at six months shown by the black curve at the

bottom, there is now marked blood pressure reduction throughout the day. Please, also note that at six months when all RDN and Sham subjects could have been back on blood pressure meds for several months, the RDN and Sham blood pressure curves appear to be similar, indicating similar levels of blood pressure control.

The next two slides look at absolute and relative changes in blood pressure for the RDN and Sham groups. As a reminder, in the off-med studies, anti-hypertensive medication use was only permitted during the first two months for hypertensive emergencies. Whereas thereafter, medication changes were permitted to optimize blood pressure control. In Solo, the graphs on the left, at two months, shown with the red arrows, RDN subjects had a significantly greater decline in daytime ambulatory systolic blood pressure, 6.3 mmHg and office systolic blood pressure, 6.9 mmHg compared to Sham subjects. After two months, blood pressures continued to decline in both treatment groups with a greater relative decline in Sham subjects as at six months, the daytime ambulatory systolic blood pressure reduction difference between RDN and Sham was 2.5 mmHg, and at 12 months, the daytime ambulatory systolic blood pressure reduction difference between RDN and Sham narrowed further to less than one-mmHg. For office blood pressure at six- and 12-months, narrow treatment difference was observed that was far less pronounced compared to daytime ambulatory systolic blood pressure. In Radiance-II, the graphs on the right show that, at two months, RDN subjects had a significantly greater decline in daytime ambulatory systolic blood pressure, six mmHg, and office systolic blood pressure of 5.52-mmHg compared to Sham subjects. After two months, blood pressure continued to decline in both treatment groups with a greater relative decline in Sham subjects such that at six months, the daytime ambulatory systolic blood pressure and office blood pressure reduction difference between RDN - Sham was less than one-mmHg.

In summary, in both off-med trials, RDN was associated with an early significant blood pressure reduction while Sham subjects were off blood pressure meds. Blood pressure reduction during the follow-up six- and 12-month periods, continued in the RDN group. However, the reintroduction of blood pressure meds resulted in similar blood pressures in the two following treatment groups, in the longer term.

In the On Standardized Meds Trio trial, changes in blood pressure medications were permitted after two months, to optimize blood pressure control. At two months, shown with the red arrows, there was a trend towards a greater decline in daytime ambulatory systolic blood pressure and office systolic blood pressure in RDN versus Sham subjects. After two months, blood pressures continued to decline in both treatment groups with a greater relative blood pressure reduction in Sham subjects such that at six months, the ambulatory systolic blood pressure and office systolic blood pressure reduction difference between RDN and Sham was less than 1 mmHg. At 12 months, the daytime ambulatory systolic blood pressure reduction was 1.1 mmHg in favor of the RDN group. The office blood pressure reduction difference was 6.2 mmHg in favor of the RDN group.

In summary, in the On Standardized Meds Trio trial, daytime ambulatory systolic blood pressure reduction during available follow-up continued in the RDN group, but similar ambulatory systolic blood pressures were observed between the RDN group and the Sham group at six and 12 months. Blood pressure trends at 12 months were discordant between daytime ambulatory systolic blood pressure and office blood pressure.

Medication burden was determined by two criteria: the number of prescribed anti-hypertensive medications and the anti-hypertensive medication load index (the latter, a composite based on medication dosages). Calculations were performed by the formula shown.

In Solo, the table shows the change in daytime ambulatory systolic blood pressure, and office systolic blood pressure during the first 12 months. At two months, RDN subjects had larger daytime ambulatory systolic blood pressure and office systolic blood pressure reductions versus Sham subjects, while receiving a similar number of anti-hypertensive medications. At six and 12 months, the daytime ambulatory systolic blood pressure and office systolic blood pressure reduction differences narrowed between treatment groups versus baseline. However, the RDN group is receiving a numerically lower number of medications by 0.3 medications and has a 0.2 lower med load index. The figure on the right shows the proportion of subjects on zero to three or more anti-hypertensive medications. At two months, the vast majority of RDN and Sham subjects were receiving zero to one meds. At six and 12 months, numerically more RDN subjects were taking no medications versus Sham and a greater proportion of Sham subjects were receiving one to two meds.

In Radiance-II, at two months, RDN subjects had larger daytime ambulatory systolic blood pressure and office systolic blood pressure reductions versus Sham subjects while receiving a similar number of anti-hypertensive medications. At six months, the daytime ambulatory systolic blood pressure and office systolic blood pressure reductions were generally similar in the two groups with a 0.2 greater number of blood pressure meds and a 0.1 higher med load index, in Sham subjects. The figure on the right shows similar medication use at two months between treatment groups and no significant difference in medication use between the two groups, at six months.

In Trio, at two months, RDN subjects had larger median daytime ambulatory systolic blood pressure, and mean office systolic blood pressure reductions versus Sham subjects, while receiving a similar number of anti-hypertensive medications and having a similar med load index. At six and 12 months for daytime ambulatory systolic blood pressure reduction and at six months for office systolic blood pressure reduction the differences narrow between treatment groups versus baseline.

There was a 0.3 greater number of anti-hypertensive meds in the Sham group at six and 12 months, whereas the higher med load index in the Sham group of 0.1 and 0.2 at six, and 12 months, respectively. The figure on the right shows no significant difference in the tiers in the number of meds at two, six, and 12 months.

Blinding was performed with the Bang Blinding and James Indices. Blinding was generally maintained across all three trials using both indices. In the off-med trials, more Sham subjects were able to identify their assignment at six months, compared to the ability to do so at baseline.

Now I'll turn the presentation over to Dr. David Gebben, who will discuss the patient preference study.

Dr. Gebben: Hi, I am David Gebben. I am a Health Economist with the Patient Science and Engagement team in the Office of Strategic Partnerships and Technology Innovation.

For over a decade, CDRH has been committed to bringing the patient perspective and experience into our regulatory efforts. In 2016, CDRH issued a guidance document on the role that voluntary Patient Preference Information (PPI) can play in the regulatory decision. PPI is defined in the guidance as 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. Patient preferences are not the same as other clinical trial data information. A patient preference study does not replace clinical data, but instead assesses the relative value that patients place on a treatment profile or its alternatives. Patient preferences can help evaluate how patients view trade-offs between the benefits and risks of various treatment options.

The FDA has published guidance regarding what factors should be considered in benefit-risk determinations. CDRH recognizes patient preference information can supplement the assessment of benefits and risks. Patient preference studies can help inform how treatment options

would be considered by reasonable patients as they consider their health choices. Patient preference assessments consider both patients' willingness and unwillingness to accept the benefits and risks of the subject device of a PMA relative to alternatives.

To be included in the FDA's benefit-risk assessment, patient preference studies need to be designed, conducted, and analyzed in a way that allows for useful evidence to be generated. The CDRH PPI guidance lays out features that can assist in the determination of whether a study is of high quality to generate all scientific evidence. Well-designed and conducted patient preference studies include features such as the use of established good research practices, effective communication of the benefits and risks with minimal cognitive bias, and the features or attributes relevant to the treatment options.

The sponsor conducted a patient preference study engaging 258 respondents to ascertain preferences for the uRDN procedure compared to standard-of-care medication therapy through a survey. In the actual survey, a respondent saw educational material on each of the attributes, and characteristics of the treatment options shown on the left side of the figure, along with the levels associated with the attribute and the columns labeled treatment A and treatment B. The educational material defined the attributes an levels that respondents saw in the survey. The respondent then faced a series of choices similar to the one shown here. This created a panel data set, which allowed estimation of how much the various attributes influenced the decision or how the respondent would trade off the various attributes and levels, also known as preference rates. The study was conducted following ethical research practices. The survey was understandable to respondents and the analysis was performed consistent with widely accepted methods described in the published literature. At an early stage in the development of the study, the sponsor discussed with the FDA the general approach. However, the sponsor did not confer with the FDA on the final level of the attributes before conducting the PPI study and submitting the results in the PMA. A few attribute

levels do not correspond to levels supported by the evidence, which may have tilted the patient preference study results toward the uRDN procedure.

The preference weight results are shown in the bar graph. On the left side of the bar graph are listed each of the attributes in bold text with its associated levels. The results of the study were generally what would be expected. The attributes and levels that we would expect to be preferred were given greater importance. The bars to the right of the zero indicate attributes that were generally viewed positively by respondents. The bars to the left of the zero indicate that the procedure and additional treatment were not preferred by respondents. In other words, in general, respondents preferred to avoid surgery and an additional treatment. The longer the bar length, the greater the preference for that level. The greatest bar lengths to the right in the figure are for the absolute reduction in 10 years of CV risk. Therefore, this attribute was the most important attribute to respondents. The greatest weight was placed on it by respondents in the survey with a 30% decrease in risk, preferred over a 15% decrease in risk, on average. This was more important to respondents than the side effects and risks of the treatments.

While not in the FDA executive summary, based on the panel data set of preference weight, the sponsor estimated that 42% of respondents would choose the uRDN procedure overtaking an additional pill when all other attribute levels are held constant. The limitation of the data is that for one attribute, the risk of mild to moderate side effects requiring more doctor visits, while the levels were reflective of the procedure risks, the mild to moderate pill risks were not consistent with the published literature. The expected mild to moderate risk associated with pills would be expected to be between zero and 10%, based on the literature. The sponsor presented the lowest risk at 20%. Also, for another attribute in treatment durability, respondents were presented with a level of an additional procedure in seven years, which is longer than currently available clinical data.

Therefore, this may be an inaccurate treatment characterization. Those attribute levels could have potentially tilted respondents' preferences toward the uRDN procedure.

Now, I'll turn it back to Dr. Warren.

Dr. Warren: Thanks, Dr. Gebben. I'll now close the FDA's presentation with a discussion of the proposed post-approval study and a summary of the FDA's conclusions.

If the Paradise System is approved for marketing, ReCor plans to conduct a post-approval study in which they will continue to follow Solo and Trio subjects for three years and Radiance-II subjects through five years. In addition, they'll initiate a US arm of the Global Paradise System Registry enrolling up to 500 new subjects at 100 sites in line with the approved indications for use.

In the new enrollment post-approval study, the primary safety endpoint will be generally similar to what was evaluated in the pre-market studies, with serious events such as death and major vascular complications through 30 days of renal artery stenosis, and decline in renal function through six months and beyond. Primary effectiveness will be assessed via changes in home and office blood pressure at three months. As the study design has not been finalized, the FDA would appreciate the panel's feedback on key aspects of the post-approval study, such as whether the sample size is sufficient, the value of a single arm study design, how to assess the durability of blood pressure reduction, and whether hospitals and staff should receive specialized training for optimal use of the Paradise uRDN System. Also, should the post-approval study focus enrollment on diverse patient subgroups, considering the small enrollment of African-American and female patients in the pre-market studies? FDA would appreciate any panel input on post-approval study subgroup analysis.

In the next two slides, we'd like to present a summary of our conclusions. The primary safety endpoint for the largest study, Radiance-II, was met with a safety event rate of 0% and a 1.1% safety event rate in the pooled analysis of uRDN subjects across Solo, Radiance-II, and Trio.

The primary effectiveness endpoint was met for Solo and Radiance-II, which both had a statistically significant between-group difference in mean daytime ASBP reduction of 6.3 mmHg at two months. Although the Trio analysis using ANCOVA was not significant, the analysis using ANCOVA on the ranks was, and the median treatment effect at two months was 4.5 mmHg.

The strengths of the clinical investigation plan include three Sham-controlled randomized trials that were independently powered for effectiveness. Limitations include a 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 the durability of blood pressure reduction due to blood pressure medication changes after two months, the subject unblinding, and Sham subject crossover to uRDN, which reduced the control group sample size.

Lastly, the patient preference study found that some patients may prefer uRDN treatment to taking an additional pill, all else being considered equal. Thank you all for your time and attention. We look forward to the panel's discussion and recommendations.

Questions to FDA

Dr. Lange: Great. I would also like to thank the FDA for an excellent presentation. For the next 30 to 35 minutes, the panel can ask brief, clarifying questions for the FDA. I'll ask you to raise your hand. Dr. Somberg, you have the first question.

Dr. Somberg: Thank you. Does the FDA think that the analysis using covariances, which was pre-specified is not significant, but using covariant rank is significant? It seems a difference is due to a lack of a normal distribution. So, if you don't find significance with your pre-specified, is it or is it not appropriate to use the covariant rank method that then gave them significance?

Dr. Malone: Hi, this is Misti Malone and I'm the Assistant Director of the Peripheral Interventional Devices Team. I will pass this on to our statistician. Dr. Chen, did you want to address this question?

Dr. Chen: Thank you. This is Wei-Chen Chen, FDA. Regarding the ANCOVA and ANCOVA on the rank test, both were pre-specified in the IDE stage. So, both provide information on the treatment effect of this device, whether significant or not. However, I want to point out that the two methods were not tested in the same hypothesis. The ANCOVA on the ranks is for the distribution of the entire blood pressure reduction. However, ANCOVA is still for the primary effectiveness endpoint which is for the mean blood pressure change between two treatment arms. Does this answer the question?

Dr. Zuckerman: Dr. Wei-Chen Chen, can you then indicate why for the median difference, an additional technique was used to assess that?

Dr. Chen: For the ANCOVA model, the residuals were not normally distributed. The sponsor may have the diagnosis for that result and because there were some outliers. Ideally, we would look at other statistical methods to summarize the data, and the median is one of them. So, that is why both were reported, but both have the same value of negative 4.5-mmHg. So, both stand for the consistent result.

Dr. Somber: Am I understanding you correctly, that both ANCOVA and ANCOVA on the ranks were pre-specified? Thus, if you didn't have a normal distribution and you used ANCOVA ranks, you still had significance with a pre-specified analysis tool.

Dr. Chen: Yes, that was correct. Both are pre-specified.

Dr. Lange: I've got Dr. Hirshfeld, Dr. Wittes, Dr. Saville, Dr. Bates, and Dr. Dan Luzi. So, Dr. Hirshfeld.

Dr. Hirshfeld: Yes, I'd like to ask, what I think is a relatively simpleminded statistical question. The question is: are we looking at the analysis in the right way? Is the entire analysis based on root mean differences? When you look at the data such as in FDA executive summary table 20, you see that even in the treated groups, there are 35 to 40% of the subjects who were treated with the uRDN

procedure that had essentially no effect in terms of having a blood pressure response of less than five mmHg. This was briefly asked in the previous session with the sponsor, but it seems that we're dealing with something where there's a very heterogeneous response to this treatment. Some subjects seem to respond very dramatically to 15-mmHg and greater drops. There are more of them in the treated group than in the untreated group. I'm wondering whether we're overstating the efficacy of this, particularly from the standpoint of taking care of the patient. If I want to recommend this procedure to a patient, I want the procedure to work for the patient. If the patient has, for example, a 40% chance that it will not work, does it matter that the group's mean values are different? So, I'd like to hear some thoughts about this in terms of how the analysis is done.

Dr. Lange: Dr. Hirshfeld, that is an excellent thought. Since this is not a clarifying question for the FDA, I want you to pose that same question during our deliberations after lunch. Are you comfortable with that, John?

Dr. Hirshfeld: Yes. I posed it now because I was interested to hear the FDA's take on this. The FDA agreed with a sponsor about the analysis plan and the sponsor completely ignored this aspect of the analysis in their presentation.

Dr. Lange: Since this is a question directed toward the FDA, I'll let that stand. Misti, who would you like to direct that to?

Dr. Malone: Thank you. Dr. Silverstein will take this one.

Dr. Lange: Thank you, Douglas.

Dr. Silverstein: Yes. In our original slide deck, we showed a slide looking at the percentage of patients who achieved an ambulatory systolic blood pressure of less than or equal to 135 to two months, as a function of their baseline blood pressure. So, to your point, the data shows that depending upon your initial systolic blood pressure, you might have a differential response. So, patients who started with a lower blood pressure tended to achieve that target greater than those

who started with a higher blood pressure. We showed that on one of our slides already. I can flash that up if need be. So, to the questioner's point, I think that's very valid. I think there was a differential effect depending on the patients' baseline blood pressure. It would suggest to us that patients who start with a higher blood pressure might be those who are more resistant to response to any type of therapy, whether it be RDN, Sham, or medication. So, the original baseline blood pressure does seem to determine the response. Now, why does that occur? Again, it might be that these are patients who are more resistant to any therapy. It may mark patients who may have had longer-standing hypertension, which was less likely to respond to any type of therapy. But I agree that we should discuss this as a group, after lunch, to include the sponsor in that discussion.

Dr. Zuckerman: Dr. Hirshfeld, could I answer your question, simply? It's important to recognize that this is a breakthrough designation device and to appreciate the role of pre-post market balance. I think what you're pointing to is that the predictors of success remain uncertain here. The question that we need for independent advisory panel input, in the afternoon is: in a PAS study, should we be looking more closely at the questions that you've raised, predictors of success? Is this important? This is more of a panel question that you're raising.

Dr. Lange: I think this will be a great discussion after lunchtime. Dr. Wittes?

Dr. Wittes: Thank you. So, I have a bunch of questions, but I'll limit them. Let me first start with the mean / median issue with the two different p-values. Interestingly, as everybody's noticed, the mean and the median are the same. But I have a couple of questions about that. So, it sounded to me from the briefing document and also from what the FDA said, that the process the company used was to look at whether the parent distribution was normal or not. And if the parent distribution, that means the distribution of the data, was not normal, then switch to ranks. Let me ask you whether that's correct, because if it is correct, then I have a comment about that. Was that the process?

Dr. Malone: Dr. Chen can answer that.

Dr. Chen: That was correct, but I want to point out one point. The normal distribution is on the residual of the ANCOVA model.

Dr. Wittes: Okay. All right. That wasn't clear. So, you looked at the residuals for the ANCOVA, the residuals were not normally distributed and you switched to ranks. That's what happened?

Dr. Chen: Yes.

Dr. Wittes: All right. That's not how it was written. It wasn't written clearly in the briefing document. The thing that has to be normal is the distribution of the mean, not the distribution of the parent. In some ways, it doesn't matter much because the real question is: Is the effect big enough? And, the effect is less than five in both groups. But, how big were the outliers that made this difference? So, that's my first question. The second question is, for the Solo and Trio, did you use multiple imputations there or did you just use the imputation to zero? And my third question, and that's all I'll ask, is on slide 34. Why in Radiance-II was almost a full third of the patients on no anti-hypertensive medication before they entered the study? That doesn't sound right. They must have had a hint. How did you decide that they couldn't respond to medications?

Dr. Lange: So, to the sponsor, I'm going to ask them to show the distribution because Dr. Wittes asked how far out the outliers were. So, if you could show the distribution, that would be great. I think the sponsor should probably also address the imputation about Solo and Trio.

Dr. Reeve-Stoffer: Do you want to see that now or would you like to see that after the break?

Dr. Lange: What would you prefer, Dr. Wittes?

Dr. Wittes: I don't care. But, I'm interested in whether or not the sponsor did the multiple imputations. I don't think they did because they didn't cite that. But also, whether the FDA said, "We don't really like this imputation to zero, but we use multiple imputations for Trio". I'm asking if they tried multiple imputations for the other two.

Dr. Reeve-Stoffer: I can respond to that from the sponsor's side of things. For Solo and Trio, initially, we did impute zero, but we also did multiple imputations, and for Radiance-II, we did multiple imputations.

Dr. Malone: And it may help to mention which ones of those were pre-specified. I believe the multiple imputations for Radiance-II were pre-specified.

Dr. Reeve-Stoffer: That's correct, yes.

Dr. Wittes: And were the results the same?

Dr. Reeve-Stoffer: So, the results with multiple imputations are better. We showed a difference between groups of over five with multiple imputations. Our way of measuring using the zero was the most conservative way of looking at it. The multiple imputations give us a larger group difference. I can show you that data if it's helpful.

Dr. Lange: Sure. If you show that after lunch, that'd be great. Also, if you can show the distribution, after lunch, that would be terrific.

Dr. Reeve-Stoffer: Absolutely.

Dr. Lange: Great. On slide 34, why were a significant portion of the Radiance-II patients not receiving any medication?

Dr. Reeve-Stoffer: So that's actually part of the study design. The patients for Radiance-II that were coming into the study could be on zero, one, or two meds. They had to be uncontrolled, but they could be on zero, one, or two meds because the idea is that they can safely come off medications, to be able to assess the primary endpoint.

Dr. Lange: So, I'm unclear. How could they be uncontrolled if they're not on any medication?

Dr. Reeve-Stoffer: They had to have a history of prior prescription to medications, inferring that those patients would be intolerant to medications and remain on zero. But their blood pressure is uncontrolled.

Dr. Lange: Okay. Thank you. Dr. Wittes, does that address your question?

Dr. Wittes: Yes. That's helpful. Thank you.

Dr. Lange: Great. Dr. Saville.

Dr. Saville: Yes, thank you. Dr. Wittes answered a couple of my questions, or at least asked a couple of them. But just to clarify: the criterion that was used to decide if it was normal or not, was based on the residuals. But was that based on a test? Was that a p-value? How did that work?

Dr. Malone: Dr. Chen is going to take this one again.

Dr. Chen: It was based on a Shapiro-Wilk test. There were also other tests that the sponsor can provide and most of them are significant in some way.

Dr. Saville: Okay. So, if you had a significant p-value, you say, that's not normal.

Dr. Chen: That was the criteria provided by the sponsor, and in other tests as well.

Dr. Saville: Okay. My point is that normality assessment could be pretty subjective. It sounds like there was a very clear rule that says it's either normal or not normal. I've seen a lot of data in my life and I don't think I've ever seen anything that looks exactly normal. So, this goes back to my questions to the sponsor about trying to understand more about the data. I was really after those box plots, trying to understand where the data points are, and trying to figure out the influence of outliers. The method used for has a linear regression and ANCOVA on the ranks. I know that's based on a paper back from the sixties or seventies. It's pretty outdated. And I know this is pre-specified, but you're doing ANCOVA assumptions about all those ranks being independent, which clearly can't be independent. So, I have some issues with that analysis. I was curious if either the FDA or the sponsor had explored more contemporary methods such as the proportional odds model, on an outcome that is continuous but not normally distributed. I'm just curious if someone had explored that, which I would also like to adjust for the baseline ambulatory systolic blood pressure?

Dr. Malone: I think this would be a good question to ask the sponsor. They did additional analysis looking at the per protocol population and those with complete ABPM. There are several analyses on this patient population beyond just looking at the normality. So, this may be a question they can address.

Dr. Reeve-Stoffer: Yes. I would like to ask Chris Mullin to respond to this.

Dr. Mullin: Chris Mullin, Biostatistician with NAMSA. I'm sorry, could you just clarify something? You mentioned a technique that I didn't hear the name of it. Dr. Saville, you were asking for a more modern technique.

Dr. Saville: Sure. A proportional odds model.

Dr. Mullin: Proportional odds model. Got it. Okay.

Dr. Saville: For points not normally distributed, often I would do these proportional odds and adjust for the baseline value you're interested in adjusting for.

Dr. Mullin: Okay. I'll see if we can get something like that. I think the original paper we referenced is replicated a little bit later by, I think it's Conover several years later. Generally, we find that it seems to be a well-accepted method, but no matter what method we used, in all the different analyses, we generally see very similar effects. I think some of the nuances that we're talking about (means versus medians, imputation) are very important. Overall, we do see very similar results. Concerning the normality tests, whether it's Shapiro-Wilk, Kolmogorov–Smirnov, Cramer-von Mises, or Anderson-Darling, those tests are almost all significant indicating a lack of normality, not necessarily due to outliers per se, but after the break, we'll show you the distribution of the data so that you can get a sense of it.

Dr. Saville: Great, thank you. One additional question for the FDA. On slide 54 of the presentation, I didn't understand why I didn't see 12-month data for the Radiance-II on those graphs. I'm guessing there's a reason, but if someone could clarify that, it would be helpful.

Dr. Malone: There's limited data available beyond six months for this study. This study is the most recent of the three studies, so there's limited data available. We didn't show that but if you'd like to ask the sponsor to provide additional information, recognizing it would be a limited number of subjects.

Dr. Saville: Is it limited because you have a follow-up, ongoing and they haven't reached the 12 months, yet?

Dr. Malone: Yes.

Dr. Saville: Okay. Thank you.

Dr. Lange: Doug, do you have 12-month data that you can share?

Dr. Reeve-Stoffer: We do not have the 12-month data that the patients are still in follow-up.

Dr. Lange: Okay. Thank you. Thank you, Dr. Bates.

Dr. Bates: I would appreciate some clarification on the direction of how we're supposed to evaluate today's meeting. We're having a statistical, academic regulatory discussion and I wish to know if that's how we're supposed to limit our evaluation. It sounds like the FDA and ReCor got together five years ago and decided to do a Sham controlled study in which 293 patients were treated with the catheter therapy. It looks like ReCor has fulfilled all the obligations that the FDA put on them and they have some safety and some efficacy data that we can debate on. But my question is, it seems that this is a proof of concept design and is this how we're only supposed to evaluate today's presentations or are we to think about a more general application of this in patients who come to us? From a clinician standpoint, three-drug hypertension is not resistant hypertension, to me. All my patients are on β blockers because they have anxiety, arrhythmia, or heart failure, and they aren't great hypertension drugs. Is this an add-on to a β blocker or is this just a substitute for a β blocker? All my patients are on Spironolactone for several reasons. Should this be considered as a treatment after five drugs or a treatment after two drugs? So, I'm trying to get some

direction, if we're supposed to limit it to the trial design and the proof of concept under this application or after lunch, if we're supposed to have a more general clinical discussion on clinical safety and efficacy?

Dr. Zuckerman: Let me try to very briefly answer your excellent question, Dr. Bates. And the key point will be after lunch after you've had something to eat. But, here's the bottom line. As you saw, this is a breakthrough designation device with a pre-post market balance that you as an independent advisory committee member, and an expert clinician, need to provide advice to the FDA. The bottom line is that the sponsor did follow the FDA requests regarding trial design, trying to demonstrate proof of principle. But there are important considerations regarding how this technology can diffuse out into the real USA, with your patients. What we need to discuss this afternoon is if there is safety and effectiveness, what are the reasonable indications and PAS requirements to logically approach some of the real clinical questions that you've asked. So, please keep your clinical hat on. Do not get dismayed by the statistics, but this is an after-lunch conversation.

Dr. Bates: So, this is a two-level evaluation, not just a single-level evaluation.

Dr. Zuckerman: That's right. I would remember that this is a breakthrough device designation.

Dr. Bates: That's why I asked the question. Thank you.

Dr. Lange: Thank you, Eric. Great question. More to come after lunch. Dr. Damluji.

Dr. Damluji: Yes. Thank you so much for the excellent presentation. I'm keeping it brief because it was addressed previously. Is there an effect measure modification in Solo by abdominal obesity? Is there a subgroup analysis at six months for interactions?

Dr. Zuckerman: Those are great questions for the sponsor to answer after lunch.

Dr. Lange: Okay. So again, subgroup analysis at six months.

Dr. Damluji: Yes. On slide 50, I don't know if there's a signal for abdominal obesity, that there are super responders to catheter-based therapies versus Sham.

Dr. Malone: Dr. Silverstein can take this very briefly.

Dr. Silverstein: Yes, exactly. The last speaker mentioned slide 50. Looking at it, there's a significant effect of abdominal obesity on the response which favors the RDN group. The p-value is 0.02, so it does favor that. My apologies for not pointing that out, but that data was shown on the slide for the Solo ITT group, it was not true for the Radiance-II group.

Dr. Lange: Dr. Damluji, did you see additional information?

Dr. Damluji: Yes, that's perfect. Thank you. And I don't know if there is an interaction data at six months. Maybe that's a question for the sponsors. Thank you.

Dr. Lange: Okay. If you could dig deep and see the interaction for the Radiance-II and Solo ITT data at six months, that would be great. Dr. Corriere.

Dr. Corriere: I just had a couple of real quick questions about the patient preference study. There was a mention of bias and attribute levels that favored RDN. I was wondering if you could give some elaboration on exactly what that was. It sounds like a hint of forging ahead without the FDA's input or oversight with that study and I was curious about the nature of how that happened. Finally, were those participants in that study, patients with resistant hypertension? Were they candidates for the current study or were they a sampled population with similar characteristics?

Dr. Malone: Okay, thanks. And I'll let David get it. Dr. Gebben, if you want to address this one.

Dr. Gebben: Sure. So, I'm going to take your third question first because I believe that'll be the fastest one to answer, which is the subjects in the patient preference study. They were to be as closely aligned with the rest of the clinical trials as possible. So, that is essentially what the patient population was. Now, I'll jump back to the first one regarding the question of bias or the impact of the level of mild to moderate side effects would be. As we stated, the lowest level was the

interventional treatment and so, within that, when conducting a patient preference study, the preferences are then going to, in a sense, be impacted by the levels that are presented. In the results that are shown, everything is relative to what is contained within the DCE chart that we showed. So, if you think the lowest possible risk level is 20%, if there are, from the literature shown, indications that the moderate to mild risks for pill medications would be 10%, that would then, therefore, impact what you might be willing to accept as a risk. I apologize, could you repeat your second question because I want to make sure I answered it correctly or that might be better answered by ReCor?

Dr. Corriere: You had just mentioned the study launched ahead without an expected amount of involvement in the FDA's input, and I was curious if that should affect how we look at those results.

Dr. Gebben: I'll take the first pass and if ReCor would like to expand, of course, I would respect their position on that. The patient preference information is voluntary for submission. ReCor did interact with the agency at the beginning of the study and we proceeded with them forward. I don't know why they didn't hand us the final attribute table. Again, that was within their purview, and again, this was voluntary information for them to submit, as they saw fit.

Dr. Corriere: Thank you.

Dr. Lange: The sponsor, the attribute table was not evaluated by the FDA before being submitted. Do you want to address that?

Dr. Reeve-Stoffer: So firstly, I just wanted to clarify that we had discussions with the FDA on two occasions, and then I'll ask Dr. Marsh to speak to the actual attribute table and the final discussions.

Dr. Marsh: Kevin Marsh, at EVIDERA. As just noted, we did engage twice with the FDA on the design of the study. The latter time that we engaged in the design of the study, if my memory serves me right, I think was on the lower end of the mild to moderate adverse event range, as it is

in the final design. It was updated after that second engagement with the FDA. However, it was increased upward to make sure that the range was aligned with the final set of data in the submission. So, I think that the lower end of the range was consulted on, but I'd need to go and double-check the exact parameters that were included in that submission to the FDA, at the time. To the broader question about the potential bias introduced by this design —

Dr. Lange: I'm sorry, sir. With all due respect, I've got four more questions in the next five or six minutes. So, if you'll hold that comment to after lunch, that'd be great.

Dr. Marsh: — No problem.

Dr. Lange: I do want to get your comment in, but I want to get the other questions in. Dr. Allen?

Dr. Allen: Yeah. Thank you. Great presentation by the FDA. I need some clarification from the FDA because maybe I'm the only one that was struck by Dr. Silverstein's slides on how they meet their primary efficacy endpoint but when you look at the absolute difference in blood pressures at longer-term follow-up, and when you go back and look at the ReCor data out to 24 and 36 months, there's not a lot of bang for your buck. At least that's from a simple surgeon's looking at this. And so, can Dr. Silverstein clarify what he was trying to say in that they seem to meet their primary endpoint? But did I read his slides correctly in that there's very little difference, less than three mmHg at longer-term follow-up? It's as if you picked your endpoint differently, you would have a completely different outcome.

Dr. Silverstein: I think that's a question that is probably best presented to the sponsor, but let me give you our thoughts on that. Remember that blood pressure medications were withheld for the first two months unless the patient had a hypertensive emergency. Thereafter, blood pressure medications were introduced in all three studies to optimize blood pressure. So, the reason that the two-month period was selected to withhold medications was to allow us to assess the effect of the device by itself. Thereafter, you are seeing a constellation of factors that might be affecting

the achievement of blood pressure after that time. So, yes, we note, as we showed on slides, I think 54 and 55, that the durability is maintained in the RDN group. But then you see a greater response occurring after two months in the Sham group because again, they are receiving medications to optimize their blood pressure. So, it was not an unexpected finding. Again, I think the sponsor can respond to the significance of that. And I think that Dr. Farb may also want to make a comment.

Dr. Lange: Okay. I'll let Andy. Go ahead, Dr. Farb.

Dr. Farb: I'll keep it very brief, Dr. Lange. I think that's the gist of the question, right? What is the clinical significance when you go out longer? Compared to a finding at two months, as it turns out, blood pressure medications work right when we introduce them. Whether the clinical significance of that treatment difference versus Sham, considering all the other factors including medication changes and how the clinical importance of that for patients and the clinical significance of those medication differences turns out, at the later time points.

Dr. Lange: Keith, I think this is going to be part of the thing that we're going to sit on, after lunch, part of our deliberations.

Dr. Allen: I just want to follow up on one other question to the FDA. Once again, as a surgeon, I'm not a hypertensive specialist, but I look at blood pressure improvement as a surrogate and Dr. Zuckerman's beaten in me over the last 15 years that surrogates are poor endpoints. I don't really see any clinical endpoints in these trials. We seem to take for granted that we're going to reduce stroke, reduce death, and reduce hospitalizations from cardiovascular mortality. But is the FDA concerned that we don't have any “meat” to this data other than the surrogate of blood pressure decrease?

Dr. Zuckerman: Okay, Dr. Allen, excellent question. Since you referenced my name, I'll simply answer it. The FDA accepts a few surrogate endpoints, but one of them is blood pressure because the strictest criteria for demonstrating that blood pressure is an adequate statistical

surrogate endpoint has been supplied to the agency. So, that particular question is not under discussion today.

Dr. Lange: Thank you, Dr. Lewis, and then Deneen.

Dr. Lewis: Thank you. I think that the FDA document, and I agree with it, says that the durability is definitely based on non-clinical and clinical data open to discussion and not proven. I have a concern and a question for the FDA. There are numerous examples, and I'll use some renal examples of IDNT, RENAAL, Captopril trial where patients are given an antihypertensive versus a placebo. The investigators are blinded, they have a blood pressure goal, and they are allowed to use whatever medicines they want to achieve that blood pressure goal. And that's exactly what was happening between two and six months. There was no crossover and there was no unblinding, and we proved that there was really no unblinding. In all those studies, there is a significant difference in lower blood pressure in the group that received the anti-hypertensive study in a blinded fashion, compared to the placebo. That had to be handled with proportional hazard regression modeling to make sure it didn't account for the positive results on the renal outcomes. Did the FDA assume that would be true at six months or were they unconcerned about the durability at six months? Did they assume that there would be a lower blood pressure if the nerves had not re-innervated?

Dr. Malone: This is Misti Malone. I don't believe we assumed any of the results here. We were interested in looking at the durability, recognizing that there are some potential confounders here and that the doctors treated these patients to the goal. There was protocol-driven medication escalation between two and six months. So, we were interested in looking at the results for durability at six and 12 months and seeing what the outcomes were between the two groups.

Dr. Farb: I could just add that I think there are two issues. One is the durability of the blood pressure reduction provided by RDN and the other is the durability of the treatment difference. We

were, of course, interested in both of those. We are very interested in hearing the panel's, interpretation and the clinical significance of those two results.

Dr. Lange: Yes, that's going to be a great discussion. So, I'll ask you to lead that, by the way. All right. I've got Deneen, and Dr. Seville, and that should take us to our lunch break. Deneen Hesser?

Mrs. Hesser: Two quick questions that I think ReCor can address. Was there any drug testing done to monitor adherence to the drug regimens?

Dr. Silverstein: It sounded like you were directing that question toward ReCor, but they did do drug testing. I will let them elaborate on those results, but there was drug testing done to test for adherence.

Mrs. Hesser: Okay. Where along the trial trajectory was the patient preference study conducted? Did it inform the trial design or was it done as an independent study separate of the three trials?

Dr. Gebben: This is David Gebben. I'll take that. As I understood it, it was conducted independently so the participants in the patient preference study, were not also members of the clinical trial, is my understanding. It was done in parallel, which is an acceptable way to do it.

Mrs. Hesser: Okay. Thank you.

Dr. Lange: Dr. Saville and then Dr. Zuckerman.

Dr. Saville: Just to follow up on my other question. I don't know who's better to answer this question, but when will the 12-month data be available or when would we have follow-up available on everyone in the Radiance-II? I feel that’s important data and I feel that there must be a reason why we're having this panel meeting now, as opposed to waiting for that 12-month data on ReCor.

Dr. Reeve-Stoffer: We are in the final stages of collecting the 12-month data, so it should be available reasonably soon.

Dr. Lange: You're talking to physicians. Reasonably soon. Now, what does that mean?

Dr. Reeve-Stoffer: We're talking about probably one to two months.

Dr. Lange: One to two months. Okay. Great. Thank you. And Dr. Zuckerman?

Dr. Zuckerman: Yes. So, this Q&A has followed along the same lines as the ReCor Q&A, where significant questions and concerns have been noted about the durability of device therapy. In your summary, Dr. Lange, I would ask you again to really emphasize to the sponsor that they should come back after lunch prepared to discuss this question, as well as practical problems with taking anti-hypertensive medications long-term. The FDA is really looking for independent advisory panel comments on this topic.

Dr. Lange: I'm not sure I could have said that any better. Thank you, Bram. So, between now and lunch here are the things that need to be provided. Dr. Wittes asked for the distribution curve, so we could see how far the outliers are and also asked for the results of the multiple imputation, rather than just saying it looked the same. Dr. Saville asked about more contemporary methods to analyze the data, the proportional odds model, or whatever else the sponsor can provide. Dr. Damluji asked about a subgroup analysis at six months. As Dr. Zuckerman said, the absolute change in blood pressure that looked apparent for two months is gone by six months. And what is the clinical significance? That's wrapped around both of the durability issues. If this doesn't provide any additional thing than medications, why would we suggest using it on a patient? And what are the practical problems either with medications or with this as well? I'm trying to put it again in the clinical context. I really do feel that the FDA is wrestling with these significant issues and that's why they've assembled this expert panel and are willing to hear from everybody on the panel and also from the sponsor as well.

So, with that, I'm going to close again. I'll remind all the panel members not to discuss among anybody on the panel or virtually or really with anybody. Have a wonderful lunch. We're going to convene, promptly, at 1:30 for our Open Public Hearing. And with that, I'll ask everybody

to have a wonderful lunch, stretch your legs, and then come back for a very robust discussion. Thank you.

Open Public Hearing

Dr. Lange: It's now just a couple of minutes after 1:30. I'd like to call this meeting back to order. At this time, we'll proceed with the Open Public Hearing portion of the meeting. Public attendees are given an opportunity to address the panel, to present data, information, or views relevant to the meeting agenda. Mr. Collier will now read the Open Public Hearing disclosure process statement.

Mr. Collier: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee Meeting, the FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the committee of any financial relationship that you may have with any company or group that may be affected by the topic of this meeting. For example, this financial information may include a company's or a group's payment of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking. At this time, I will now turn the meeting back over to Dr. Lange. Thank you.

Dr. Lange: Thank you, Mr. Collier. Prior to the final date published in the Federal Register, the FDA received seven requests to speak. The first six speakers will be pre-recorded presentations, followed by one live presentation. Each speaker has no more than five minutes allotted for their

comments. The first speaker is Dr. Jay Giri from the Catheterization Laboratories at the Hospital of the University of Pennsylvania. Dr. Giri, you may begin.

Dr. Giri: Thanks so much for this opportunity to discuss both hypertension and a potential novel treatment for it, renal denervation, which really affects a lot of my patients as a practicing cardiologist. By way of background, my name is Jay Giri and I'm an Interventional Cardiologist practicing at the University of Pennsylvania in Philadelphia. I've been in active practice for a little more than 10 years. But if you go back to training, I've been doing this for about 20 years, taking care of many patients who suffer from hypertension.

I think hypertension in general is the most important comorbidity that currently affects our cardiovascular populace. And this is for a couple of reasons. First, is its ubiquity, especially as the population ages. The scourge of hypertension is something that really affects more and more of the patients we encounter. And you all probably know the literature that would state that it's estimated that maybe 40% of patients, over 40 to 50 years old have some degree of hypertension. The second issue is the relative contribution of hypertension to cardiovascular disease, kidney disease, and stroke. All three super important issues create tremendous problems for individual patients and their quality of life. And then, also from a population standpoint, I think for healthcare and the country at large. So, the question becomes there are a lot of medicines for hypertension. How are they doing? And the bottom line is, from what I see in my patients, they can struggle a little bit. Even with all of these potential oral medical therapies available, they still tend to struggle with their hypertension.

There are a few different reasons for this. One is it can be difficult to get on these multi-medicine regimens, to keep them straight, and to take them as directed. That's something that patients find difficult and burdensome. Secondly, is naturally the cost associated with keeping all of this going, if you're on multiple medicines for hypertension. And third, is side effects that

sometimes can be associated with one or more of the medicines, either in individuality or in combination with one another. For all these reasons, we're at a place where we need a better solution, at least as an adjunct to what we're doing, to help patients deal with hypertension, which is causing all these terrible outcomes down the line for our population. And I've been really impressed, at being in the field of researching renal denervation over the last decade to see the potential impact that it could have on patients.

The biggest issue that you want to tackle if you're looking at a potential procedural solution for hypertension first and foremost: Is that procedure safe? Naturally, while drug therapies can have side effects, they very rarely have any side effects that are so serious that you can't stop the drug and get better from it. So, naturally, we have to hold something like renal denervation to a very high standard. And the good news is it has been held to quite a high standard. It seems to have passed it with flying colors. Specifically, some of the issues that we worry about with procedural solutions like renal denervation is, are the kidney arteries being damaged in any way when we're doing the cases. Are there major vascular complications happening when we're doing the cases? And, are there potential late-term effects when you're examining these kidney arteries down the line, that might demonstrate that you somehow damaged them by doing the denervation procedure? The answer to all three of those questions, in study after study, appears to be “no”, which is great news. Additionally, as the field evolves, and I think we really are at the nascency of the technological achievements around renal denervation, this procedure is going to get even simpler from the standpoint of being able to perform it with even more efficiency and even lower potential risks of any of the complications I mentioned. But right where we stand right now, we're in a really good place for being able to offer this therapy to folks who are suffering from hypertension.

The second issue with renal denervation is that we want to also consider if it is efficacious and if it is actually lowering blood pressure in our patients. And I've been really happy to see that the standard for how renal denervation has been evaluated has been one that's been extremely rigorous. The thanks go to clinical researchers, industry, and regulators for demanding this very high standard for considering this device and the folks. And, specifically, that standard has been Sham controlled randomized trials, the highest bar of evidence that has ever been sought for procedural therapies. It's been really gratifying to see that the Sham-controlled by randomized trials with pre-specified endpoints looking at blood pressures have been positive, as I mentioned, even when being held to such a high standard.

So, when you put this together, I think we're looking at a therapy that is addressing an absolute public health need. It is something that patients certainly desire in the sense that a single procedure can allow them, hopefully, to come off one or maybe two of their medicines, which they find complex and burdensome to take. And most importantly, I think it has the potential to provide sustained benefits to patients over time, in terms of reducing the risks of myocardial infarction, stroke, kidney disease, and heart failure, four of the major disease processes I deal with, frankly, on a daily basis as a practicing cardiologist. So, I do hope that everybody looks favorably upon the data as it's been presented thus far. I definitely think we need this tool in our armamentarium to treat patients nowadays. Thank you.

Dr. Rader: My name is Dr. Florian Rader. I'm a Non-invasive Cardiologist and Hypertension Expert and direct the Hypertension Center of Excellence at Cedar-Sinai Medical Center in Los Angeles, California. I appreciate the opportunity to be able to speak on renal denervation in clinical practice and just for information, I'm not being paid for my time here today.

So, I've been treating difficult hypertension for over a decade now, and therefore, I'm well aware of the many reasons why hypertension remains uncontrolled in so many Americans. And

unfortunately, those hypertensive individuals continue to be at a preventable risk for cardiovascular complications. Some of the reasons that lead to years of exposure to unhealthy blood pressure are patients not taking their anti-hypertensive medications or taking only a portion of them, cutting out those that either cause side effects or are thought of as drugs. Patients just simply don't want to put them in their bodies. Although we have many tricks to get around this problem, current solutions remain imperfect, and hypertension control also remains a significant challenge even in the hands of an expert like myself.

I was fortunate enough to witness the evolution of renal denervation, including ultrasound renal denervation, what we're talking about here today, as a possible, new tool to improve blood pressure control without the need for additional medications. While 10 years ago, we couldn't be quite so sure if renal denervation works, now, after several large and adequately powered Sham controlled randomized clinical trials, I believe, we unequivocally can say that renal denervation not only lowers blood pressure but also does so in a meaningful way. With about five-mmHg reduction in ambulatory blood pressure and about 10-mmHg of office blood pressure, such a blood pressure reduction will translate into a significant reduction in cardiovascular risk improvement of overall control rates, and importantly, a reduction in medication burden for many patients who currently have uncontrolled hypertension and are being treated with multiple agents. I've seen many patients in whom renal denervation really made the difference in getting their blood pressure into a healthy range, and although not the norm, I've even seen patients not requiring blood pressure medications anymore after renal denervation.

Don’t forget, that the procedure is easy to perform, has a stellar safety track record, and therefore, is quite easily incorporated into clinical practice. I also want to mention that the European Society of Hypertension released a position paper in 2021 stating that renal denervation represents an evidence-based option to treat hypertension, in addition to lifestyle changes and

blood pressure-lowering drugs. Similar position papers have also been published in the United States and I was part of one of them.

So, we are now at an inflection point. We either say that we continue on the same path and accept that some patients will have uncontrolled hypertension and will have poor cardiovascular outcomes or we add renal denervation to the armamentarium of hypertension management to improve the lives of many patients. Again, renal denervation works. It is safe. So, in my mind, the right choice is obvious. And just to be clear, by no means do I think that every hypertension patient should undergo renal denervation. They won't. But especially for those with high cardiovascular risk and those who had several efforts in controlling their severe hypertension and just were unsuccessful in lowering blood pressure, overall, the impact of renal denervation I believe will be meaningful. And that's it for me. And with that, I want to thank you for the time and I'm sending my best wishes from Los Angeles.

Mrs. Anderson: My name is Candyce Anderson. I'm 73 years old and live in Minneapolis, Minnesota. I've had hypertension for 20-plus years, starting in my early fifties. I've been on one medication during that time, although the medication has varied, depending on the recommendation of my physician. I wasn't surprised to develop hypertension as it runs in my family; both of my parents had hypertension. I try to always take my medication at the same time of day, and I keep it in the same place in the kitchen. I also take vitamins and other supplements. It is easier for me to remember to take them all at the same time.

While I don't think about it every day, I am concerned about my hypertension and overall health. I discuss the medications, supplements, and any other issues at my annual physical, and I heed my physician's recommendations, though I've always preferred fewer medications, when possible. It was frustrating to understand that I would be on medication for hypertension for the remainder of my life, not only to try and remember to take a medication daily, especially when

first starting, but to make sure that it's part of a daily routine. I admit that I wasn't always compliant at first, refusing to believe that I really had hypertension and there wasn't an option other than medication, and I saw my siblings struggle with the same concerns.

I was very interested in the study for the Paradise procedure when I learned about it as I was hoping it was a better way to control my hypertension. My sister and I were on vacation when she spotted the information on Facebook, in 2019, and we both applied for the study. We were accepted as was our brother. Following my procedure, my hypertension was better controlled. I'm now on Losartan, 25 milligrams once per day, which is controlling my hypertension well. Knowing that I have to be only on one low-dose medication is very important to me, as is maintaining my health in the best way possible to prevent any issues from arising unexpectedly. I can say that my siblings feel the same way.

As you think about your decision today for the Paradise procedure, I just ask that you remember all the other patients out there today who are like me, people who are listening to their doctors, trying their best, taking their medications as directed, and still not able to control their hypertension. I hope you can help them and their doctors with another option. Thank you for your time.

Mr. Gray: Hello, my name is Gerard Gray and my friends call me Jerry. I'm 73 years old. I live in Ravenel, South Carolina, which is just south of Charleston. I've been married for over 50 years and I have two grown children, Alexis and Josh, who have blessed us with two grandchildren each: James, age 17; Gray, age 15; Madeline, age 12; and Jackson, 18 months. Currently, I'm retired, but I was a Manufacturing Operations Manager and Director as well as a Management Systems and Leadership Consultant. This was my career after university and four years in the Army, as a Commissioned Officer. On an interesting note, my last Commanding General was

General George Patton. No, I'm not that old. It was his son who commanded the Second Armor Division, the same as his dad, who was an army first.

My hypertension has been a chronic issue for over 30 years. I've been on multiple medications and tried numerous ones who achieve better control. It was first noted, however, but not chronic, in 1972 during an insurance physical when I graduated from college, got married, and was commissioned in the army, all in the same month. Obviously, enough to drive up my blood pressure.

I've been on up to seven medications. While never an issue to remember my meds, I've had multiple discussions with my personal physicians who achieved uniform control over the years. Overall, the issue of not achieving long-term control has always been a mental burden for myself and my wife. My family history is not favorable in cardiac and hypertension issues, with my dad dying at 45 when I was nine years old, and my mom experiencing a stroke at 60. My oldest brother died at 43, after a heart transplant. I became aware of the study for the Paradise procedure you are reviewing today, through a Facebook posting and after initial screening, I entered the program. The overall experience was excellent with knowledgeable and caring professionals at MUSC, truly concerned for my well-being and the integrity of the study. While I'm still taking medications, only three now, less than half from the previous experience, my peace of mind is much improved with the current excellent control of my blood pressure. I consider it truly a gift of good medical science and the application of scientific learning.

I'm very thankful for the opportunity to participate in this study. I'd also like to thank you for letting me share my story with you today. There are so many other people out there like me, who need an option like this to help them get better control of their blood pressure and have peace of mind about their future wellbeing. Thank you.

Mr. Barnett: Hello. My name is Jean Barnett and I'm 62 years old. I have no financial disclosures. I have been happily married for 41 years to my wife, Susie. We have two daughters and five grandchildren, ranging from ages 18 to 11 years old. We live in Alvin, a small rural community in Berkeley County, South Carolina, on property that's been in our family for five generations.

I retired in February of 2022 from a paper mill where I worked as a millwright for 37 years. Since retiring, and I've been trying to catch up on chores around the farm and helping out at our Volunteer Fire Department. We also try to travel as much as our grandkids' sports activities allow us to. I joined the ROTC while in college, so the Army could help pay my tuition, and they sent me to Fort Knox for the ROTC version of boot camp. About three weeks in, they did random blood pressure tests and mine tested high. I don't remember what the numbers were, but it was higher than what was allowed. They pulled me out of training and checked my blood pressure for the next two days. It stayed high, so they sent me home. I have been on blood pressure medicine ever since, and after a while, I was taking two medications daily.

One of the side effects was frequent trips to the bathroom. So, I didn't want to take the medication at bedtime, but I had an hour's commute to work in the morning, so I didn't want to take it in the morning either. On the days that I chose not to take the medication, I would get a headache around 2:00 PM, like clockwork.

Other small things that you may not have to think about would have a big impact on your life or trying to find over-the-counter medication for coughing and colds. It's frustrating and when you do, it's usually not very effective. And when I went to the dentist, they would check my blood pressure before administering Novocaine, and sometimes they weren't able to.

One day, I was playing around on Facebook and saw an advertisement about a blood pressure study at MUSC, and here we are. I went to MUSC to be screened and was accepted into

the program. A year later, I found out that I was one of the blessed ones that got the procedure. It worked. My blood pressure isn't perfect, but it's low enough now that I'm only taking a very low dose of one medication. The best part is the small things that it's brought to my life. Small things in the grand scope of life, but big things when they are happening to you. Like now I can take my medication at bedtime and have no more frequent bathroom visits and no more 2:00 PM headaches. I ask that you think about my story today as you consider your decision, and all the others like me who are out there struggling to manage their blood pressure and want to have the small things in life back that make life better. Thank you.

Mrs. Brown: My name is Cynthia Brown. I live in Gardena, California. I am 51 years old. I have one son and one granddaughter. I am currently employed as a Social Worker for the county of Los Angeles. I am a Veteran of the United States Navy. I am an active member of Zeta Phi Beta Sorority Incorporated, Alpha Psi Zeta Chapter.

I have had hypertension for over 20 years. I tried to lower it using dietary measures such as juicing and taking herbs. People would tell me that I did not look right and in truth, I did not feel right. I finally filled the prescription for Benazepril that was given to me by my primary physician. My blood pressure was often high, but I did not take my medication. I have a medicine routine, so I often do not miss medication unless I'm away from home. My problem is eating the wrong foods and failing to exercise.

I'm aware that high blood pressure is viewed as a silent killer. I have lost friends to strokes that were related to uncontrolled blood pressure. I know people with kidney and heart issues that are directly related to uncontrolled blood pressure. I understand how serious the condition is. I was in my forties when I was diagnosed with high hypertension. I know that I need to address the issue or I would not live a long, healthy life. I also know that hypertension is high in my community, partly due to genetics or failure to eat healthy foods.

I saw an ad on Facebook about the trial. I clicked on the ad and sent in my information. I was accepted into the trial. After the trial was unblinded, I was told that I was given a placebo. I accepted the chance to crossover. Throughout the trial, the staff was considerate and kept me informed. I received phone calls and/or emails to see how I was doing. The blood pressure logs helped a lot because I did not take my blood pressure daily. I had the surgery and my blood pressure dropped right away. I felt amazing. I do have to continue to watch my diet and exercise. I noticed that foods such as pork will cause my blood pressure to increase. I was switched to a low dose of blood pressure medication instead of a higher dose of the previous pill. I also do not have the issue of thinning hair, which was a side effect of the other medication. Most importantly, I have peace of mind that my hypertension is under control. I would like to thank Dr. Rader and the staff at Cedars-Sinai for accepting me into the trial.

Dr. Lange: Thank you. At this point, we'll hear from Jessica Copeland, a live speaker. Jessica?

Dr. Copeland: Hi. I'm Dr. Jessica Copeland. I'm a Senior Fellow, speaking on behalf of the National Center for Health Research, which is a nonprofit think tank that focuses on the safety and effectiveness of medical products. And it's important to note that we do not accept funding from any companies that make medical products and I don't have any personal financial disclosures.

So, I really wanted to talk about the evidence that's been presented today. This is my most important slide. And what I have here is a chart that shows the anti-hypertensive efficacy of the Paradise System compared to other anti-hypertensive medications. On the right, you have the treatment modality, so ARBs, ACE inhibitors, beta-blockers, calcium channel blockers, hydrochlorothiazide, and then you have the Paradise System at 60 days, and then the Paradise System at 12 months. A lot of this information regarding the medications came from this study right here. Then on the left-hand side, this is the mean ambulatory systolic blood pressure lowering effect at 60 days. I think the most important thing to take away from this slide is that the 24-hour

ambulatory mean systolic blood pressure lowering effect of the Paradise System is less than every other single anti-hypertension medication, with the exception of the hydrochlorothiazide. The other very important thing to take away from this slide is that at 12 months, the mean ambulatory systolic blood pressure lowering effect was 2.4. And this came directly from the Radiance-Solo study.

It's important to consider whether or not the results that have been presented today are actually clinically meaningful. So prior studies have defined non-response for renal denervation systems in general as a reduction of ambulatory systolic blood pressure of 10 or less at six months. Then in 2018, the FDA advisory panel agreed that a reduction in ambulatory systolic blood pressure of five to seven or more was clinically meaningful within effectiveness and durability of 12 months. But as you can see from the Radiance-Solo, and the Radiance-II and the Radiance-Trio Trials, none of them have met that threshold. I think there is a larger concern that the magnitude of blood pressure reduction from renal denervation systems in general is thought to decrease over time. And there is a sympathetic reinnervation mechanism that's thought to maybe be a potential driver of the diminished long-term effects.

It is really important to consider the fact that none of the data that's been presented shows that reducing blood pressure with ultrasound, or renal denervation system reduces cardiovascular events or improves cardiovascular disease, as do some anti-hypertension medications.

It's important to consider whether or not these data can actually be applied to the target patient population. So, we know that hypertension frequently occurs in patients with other sympathetic-mediated pathologic states. These patients were not well represented in the Radiance trials, as you can see from the slide. Then across the Radiance-II and the Solo Paradise treatment groups, 67% were male, 78% were white, 3.6% had an estimated eGFR of less than 60, and 4.9% had type 2 diabetes. So, although this data comes from multicenter international institutions, the

results have limited generalizability and the study population is not representative of the US population with hypertension.

We have talked about the long-term consequences, but I think overall the follow-up has been too short to thoroughly assess the long-term risks of the Paradise system. I think the long-term risks of the Paradise ultrasound renal denervation system at six months are based on very limited data and the effects after 12 months are relatively unknown including cardiovascular risk, renal function, and renal artery stenosis.

In summary, I think we're all aware that hypertension is a major public health burden that results in morbidity and mortality, but I think it needs a sound evidence-based solution. The 60-day effect on a 24-hour ambulatory systemic blood pressure is less than nearly all the other anti-hypertensive drug classes, with the exception of hydrochlorothiazide. The mean reduction in 24-hour ambulatory systolic blood pressure at 12 months was 2.4 mmHg in the Radiance-Solo trial. And there's no data that's been presented that suggests that lowering blood pressure with this device will actually improve cardiovascular disease or reduce cardiovascular events. There's another thing to consider about the patient and procedural factors that actually predict success. And that is largely unknown at this point. Just to conclude, the data on the potential long-term risks of the Paradise uRDN system are very limited. That is all that I have. Thank you so much.

Dr. Lange: Thank you, Dr. Copeland. Before I close the Open Public Hearing, officially, I want to thank Dr. Giri, Dr. Rader, Mrs. Anderson, Mrs. Brown, Mr. Gray, and Mr. Barnett for participating and providing your perspectives and opinions. So, thank you very much. I'll pronounce the Open Public Hearing to be officially closed and we'll now proceed with today's agenda.

We'll move to the panel deliberation and specifically during this part, there were a number of additional either slides and/or information that was requested from the sponsor or from the FDA that will help in our deliberations later when we begin to answer the FDA questions.

Panel Deliberation

Dr. Lange: So, I'll first turn to the sponsor. Helen, Dr. Lewis had asked about the number of uncontrolled patients with uncontrolled hypertension in the Sham group and how many proceeded to crossover and how many did not.

Dr. Reeve-Stoffer: We have that data. I just wanted to give one point of clarification, Dr. Lange, if it's okay. Because there were a number of questions that kind of fell into the same categories, we have grouped them, so it does follow pretty much in line with your list, but there are a number of statistical questions, for example, that we've put together. Would that be okay?

Dr. Lange: Sure.

Dr. Reeve-Stoffer: Okay, thank you.

Dr. Lange: So, I'll ask those that have asked questions and if they weren't answered at the end of your presentation, we'll address those. Thank you.

Dr. Reeve-Stoffer: Okay, thank you. And also, we thought for clarification, it might be helpful, since there was a number of questions about when crossovers could occur, that I just clarify how the protocols were written.

As indicated, for Radiance HTN, the crossover could occur after six months. The Radiance HTN contains both the Trio and the Solo cohorts. Per protocol, patients were allowed to crossover at six months. But there was a caveat, and that caveat was the primary efficacy endpoint had to have been met, which in reality meant that patients weren't crossing over before 12 months. And we'll show you the data for that.

For Radiance-II, which was the pivotal study, and therefore, already based on the primary effectiveness being demonstrated, patients could cross over at 12 months. So, I just wanted to make sure that was clear.

Dr. Lange: I'm sorry, let me go back to that. So, before they could crossover, they had to meet the primary endpoint and that is a…

Dr. Reeve-Stoffer: The study had to meet the primary endpoint. Yes. So, for both Trio and Solo, we had to have met the primary endpoint before we allowed the crossovers.

Dr. Lange: Thank you.

Dr. Saville: And by met, you mean that you actually achieved physical significance on the primary point, is that what you mean?

Dr. Reeve-Stoffer: Exactly, yes. We had provided the data to the FDA at that point, and also the DSMB had to agree that it was safe for the patients to cross over, and that drove the time.

In terms of the number of Sham patients that crossed over in both Solo and Trio, we haven't included Radiance-II because the study is ongoing. So, the total number of Sham patients with ABPM data available at 12 months in Solo was 67, and in Trio was 59. 54% of Solo, so 36 of those patients, actually underwent crossover. Our numbers are slightly more than what was presented in the FDA presentation because the crossover was ongoing. For Trio, 32%, so 19 of those patients. You can see the time and I wanted to make sure that was clear because the median time and the earliest time seemed long based on the fact that they could have crossed over at six months. There were 31 patients in Solo and then 40 patients in Trio who did not crossover. Of the 31 in Solo that did not crossover, 20 of those were eligible to crossover. So, you can infer that the remaining chose not to crossover, were lost to follow-up, or had completed their follow-up by that time. In terms of the Trio patients, we had 40 patients that did not cross over. Again, 21 of those would have been

eligible but they either chose not to cross over or they've been lost to follow-up or they had withdrawn concerns.

Dr. Lange: So, by the 12-month period, none of these patients in Solo or Trio had been crossed over?

Dr. Reeve-Stoffer: That's correct, yes.

Dr. Lange: Okay. Dr. Lewis, does this answer your question?

Dr. Lewis: Yes, it does. Thank you very much. This was helpful.

Dr. Lange: All right.

Dr. Reeve-Stoffer: Okay. The next question that we had was requesting ambulatory blood pressure ITT analysis, including the crossover population for both Solo and Trio over 12 months, so, including six and 12 months. I can show you that data here. So, on the left side of the panel, we have Solo from baseline through 12 months, and Trio baseline through 12 months. You can see the blood pressure reductions and also you can see the number of medications. This is very much in line with the data that was previously presented.

Dr. Lange: Do you have this with the Sham as well?

Dr. Reeve-Stoffer: We have a subsequent slide that has the Sham included.

Dr. Lange: Okay.

Dr. Reeve-Stoffer: We have a copy of the FDA data, which shows the Sham analysis. I'm going to pass it on to Dr. Kirtane. He will cover a number of different questions that he will reference.

Dr. Lange: So again, just to make clear, even though ITT includes a core of crossover patients at 12 months, none of them had been crossed over.

Dr. Reeve-Stoffer: Exactly.

Dr. Lange: Thank you.

Dr. Kirtane: Thanks so much. This is Ajay Kirtane. One of the things that I wanted to talk about a little bit is about the unique study designs that were employed for these three trials. These trials had a primary endpoint assessed at two months, where there was a comparison between renal denervation versus Sham. Personally, I have never been involved with a study that actively titrated medications and actively titrated treatments after randomization from the two to six-month time points and beyond. Here's an example of what actually occurred within these studies. The FDA presentation said they were permitted to add medications but it wasn't a permission. Investigators for both groups - and remember, the investigators and the patients were blinded - were required to try to control blood pressure in both groups. This is just an example of the protocol that was used in Radiance-II and Solo, active titration of these medications with either a new drug or an increase in dosage. In Trio, it typically started with the addition of an aldosterone antagonist. As such, although as a clinician, we would love to be able to compare the denervation group versus the Sham group, it becomes very difficult to actually determine between group differences because both groups are being titrated with the exact same goal for blood pressure under blinded circumstances. So, this gets to the question of why are the pressures similar at six months? Why are the pressures similar at 12 months? We entirely expected that to be the case. In fact, we told our investigators that the goal should be to lower blood pressure in both groups. So, that's the response to that specific question.

I'll also just show you data where we look for ways to discern if there was actually a difference between these groups. So, we pooled the data from the three trials together and there was no statistical heterogeneity between groups. Looking at slide B, on top is daytime ambulatory systolic blood pressure, and on the bottom is home blood pressure. If you use a mixed method model and look at the six-month difference between blood pressures adjusting for the differences in medications (recall the control group, the Sham group had more medications added back), one

can see that at each time point, for instance, with home blood pressure and even at two and six-months with daytime ambulatory systolic blood pressure, you require all three studies together to get the power to discern this. There is an actual difference in blood pressure. So, despite the fact that we tried to control blood pressure equally in both groups, you see some persistence of effect.

Dr. Zuckerman: Dr. Kirtane, could I interrupt you? Has this been shown to the FDA in the PMA?

Dr. Reeve-Stoffer: It was provided to the FDA just recently and it's been accepted for presentation.

Dr. Zuckerman: Was it provided to the FDA after the PMA was submitted?

Dr. Reeve-Stoffer: It was. The home blood pressure differences were part of the PMA and the ambulatory blood pressures were provided more recently.

Dr. Zuckerman: Okay. The panel needs to understand that this mixed model has not been independently verified by FDA statistics and we'll need to take it for what it is.

Dr. Lange: Great. I've got Dr. Lewis and Dr. Saville who want to follow up on what's been talked about so far. Julia, you first.

Dr. Lewis: With all due respect, you own lack of experience with doctors having the same goal. Being able to use anti-hypertensives with a forest, or at least a recommended sequence, has been done in many studies: IDNT, Captoprill, RENAAL, and Entresto. The cardiologists on the panel could probably come up with several more. Indeed, the group that has the anti-hypertensive drug effect compared to the placebo group, typically, in the majority of studies, has a significantly lower blood pressure than the placebo group, presumably because of the effect of the fact that one group is receiving a drug that lowers blood pressure and one is receiving a placebo. This would suggest that this might be happening here. But again, this is unverified data.

Dr. Lange: We're going to use this time primarily to gather data that we requested and then to get clarification on it. Julie, I want you to maintain that comment because we'll talk about that during deliberation.

Dr. Saville: If we just go back to that last graph, we were just looking at, the one with the linear mixed model. I just want to make sure I understand this, but that mixed model is adjusting for the number of medications that visit.

Dr. Kirtane: That's correct.

Dr. Saville: Okay. So that's a post-randomization value that you're adjusting for in the model, correct?

Dr. Kirtane: Correct.

Dr. Saville: Okay. There are issues with that. Usually, you adjust for things that are observed at baseline. But that's something you're trying to get at after you count for an outcome of medications. With all things being equal, what is the difference in systolic blood pressure?

Dr. Kirtane: This is definitely an exploratory analysis and, of course, these are post-randomization covariates. We did feel that with the mixed model and the fact that medications were differentially asymmetric between the two groups, and I can show you the distribution of medications in a second, that this was one way of adjusting or accounting for the fact that medications were different between the two groups. A more conventional way of illustrating that is to see what the medications were at baseline and screening. This was another question that was asked. I think what one can appreciate is that at six months, there are double the number of patients in the denervation group that are on zero meds compared to Sham. The proportion of patients in three or more meds is greater in the Sham group compared to the denervation group. Certainly, small differences, but there are differences between these two study groups.

Dr. Lange: Dr. Wittes, you had asked about this slide.

Dr. Wittes: Yes, this does not answer my question because I asked what happened to those that were on zero and what happened to those who were on one. This just gives the total, it doesn't give the changes.

Dr. Lange: Can ReCor provide that information?

Dr. Kirtane: We'll see if we can provide that. Thank you.

Dr. Lange: Okay. Thank you.

Dr. Kirtane: But just to point out the longer-term effects as this was another question about the ITT analysis specifically. These are data from the FDA briefing document, examining the longer-term effects, 12 months, and 24 months in both Solo on the left, and Trio on the right. While the numbers are small, there was active medical titration between groups, and there was a crossover that occurred after 12 months, I think one can appreciate that the denervation blood pressures are lower than the Sham group blood pressures, in an ITT analysis, and this was what several of the panelists asked for, from 12 to 24 months.

Dr. Lange: That's the office blood pressure. Does the home blood pressure look like that?

Dr. Kirtane: Unfortunately, we don't have daytime ambulatory systolic blood pressure beyond 12 months or home blood pressure.

Dr. Wittes: Can I say something? This is Janet Wittes. This is not really ITT because it's missing all types of data. It's very hard for me to understand graphs like this when there's selection going on that we don't know about. It's pretty good for the first six months, but then there's missing information. There isn’t an imputation.

Dr. Kirtane: The FDA generated this graph. My understanding is it does include the crossover patients and it includes all the valuable data for the follow-up time points that the FDA had.

Dr. Wittes: But it's missing the 24 months, which is about one-third of the patients. So, it's only really relevant for up to 12 months. Is that right? And even 12 months is missing 10% of the patients.

Dr. Saville: Have you done any analyses comparing those who have missing data versus those who don't have missing data? I'm talking not necessarily only about those who crossover. You have for 12 months, 52 with observed data points on the Sham versus 67 which you had to start with. So, you're missing 15. How do those 15 compare to those who have observed data? And same thing, when you look at 24 months. Have you done any analysis to look at that?

Dr. Kirtane: We can certainly conduct those.

Dr. Lange: Dr. Nachman?

Dr. Nachman: Yes, thank you. We should be careful not to assume that office-based systolic blood pressure changes, especially at 12 months. For example, it is similar or equivalent to a reduction in ambulatory blood pressure, especially when we're considering what we think is the mechanism of action of the denervation. My understanding is that office-based systolic blood pressure is much more likely to be affected by adrenergic stimulation and that this would not necessarily translate into a true benefit if we were to look at ambulatory blood pressure monitoring.

Dr. Lange: Thank you, Dr. Starling. We're going to have deliberations in a moment. I just want to make sure that the sponsor and the FDA get to answer our questions before we start deliberations. Randall?

Dr. Starling: Rick, tell me if this is the wrong time, but going back to slide 55 which was just shown in the FDA presentation. I remain troubled by all the different measurements. I'm trying to understand why a Trio daytime systolic blood pressure at 12 months shows little difference between the ambulatory, the office, and the home blood pressure. We were told by Dr. Weber at

the beginning of this meeting, that ambulatory blood pressure was the gold standard and you didn't even need a control group.

Dr. Kirtane: I'd like to answer that.

Dr. Lange: I'm sorry. Randall, we'll talk about slides 54 and 55 as that's one of the questions the FDA has in terms of measuring those. I'm sorry, sir. Go ahead.

Dr. Kirtane: I wanted to say that one of the challenges with the specific protocol was that the patients had directly observed therapy of their prescribed antihypertensive regimen, right before taking the ABPM home. I fully agree with Michael's points that during the prior FDA panel meeting, we all agreed in consensus that ABPM was a very valid and accurate measurement. However, I will state that because of the way the protocol was constructed, there is a greater likelihood of adherence to the medications because they were taking it under directly observed therapy with ABPM compared to some of the other endpoints. That's of course speculative, but it's certainly plausible given the way that the study turned out.

Dr. Lange: All right. There were some additional things that were asked.

Dr. Kirtane: We can go to slide EF-24 as there was some discussion with regard to the various ways that we calculated the endpoint in conjunction or aligned with the FDA's data. As the FDA demonstrated, whether the data is depicted as means or medians, the effect size is very similar. If we use ABPM data in all patients that had it, the effect is perhaps greater. Looking at slide 47, this is the ITT analysis, the second is all the patients that had their ABPMs, and the third is ITT with multiple imputations because we did this after the fact, in both Radiance-Solo and Trio. One other thing I'd like to point out is that there were six patients who had missing ABPM data, all of which, in the Radiance Trio study, were in the denervation arm. Some of those patients had drops in blood pressure as ascertained by home and office measures. However, we imputed a zero change for those patients because we didn't have the ABPM. On the other hand, there were four patients in

the study, all of whom were in the Sham group that actually had spikes in their blood pressure to greater than 180 mmHg. They needed rescue medications and we couldn't put an ABPM on them before giving them those rescue medications because their blood pressures were over 180. They all occurred in the Sham group and rather than giving them a plus 20, plus 25, plus 30, we imputed a zero change for those patients. So, I would actually posit that if we account for those 10 ABPMs differently, we might've actually observed a greater treatment effect than the five mmHg, or so, that was observed irrespective of how this was done. Those data are consistent with both Solo and Radiance-II, with no heterogeneity between trials.

Dr. Lange: Dr. Saville, any comments?

Dr. Saville: Yes, I understand the second part about the Shams. Can you explain again, those who are on treatment?

Dr. Kirtane: Yes. In Radiance-Trio were six patients that had baseline ABPMs that did not have ABPMs at two months. In conventional standards, today, we would do multiple imputations for those patients. At the time the trial was designed, the way this data was handled was we simply imputed a zero change as if denervation had no effect whatsoever on those patient's blood pressure. As a result, as you can see in this slide, the ITT analysis actually favors Sham more than the complete ABPM analysis, which is completely matched between zero and two months. I hope that explains it.

Dr. Saville: Yes, that's helpful. I heard the terminology used, “the most conservative.” I wouldn't say that necessarily because computing zeros on those assume they're not getting increased blood pressure, which is possible, maybe not likely, but it is possible. I see your point. Thanks.

Dr. Kirtane: I think that the key thing that you had asked for was the distributions themselves, and that also helps to analyze and assess some of these questions. On this slide, I have each of the

three trials and the distribution, the waterfall plots. On the left is the denervation group and on the right is the Sham group. I will caution in Radiance-II, there was two-to-one randomization. So, if you count the bars, there will be twice as many on the left as there will be on the right. First, one can appreciate that the distribution is not normally distributed. Chris Mullin will be able to show you some other detailed testing that you asked for. Additionally, you can see if you cut the decrease at five mmHg or 10 mmHg, irrespective of categories, there are more patients that have a drop in blood pressure with denervation compared to Sham. I don't think you have to do multiplicity testing or adjustment for that because you're just basically cutting the data at whatever cut point you want. Overall, the distribution favors denervation. Radiance-Solo has very similar results and that will be shown in the next slide as it comes up. This is Radiance Solo, similarly demonstrating greater reductions with denervation versus Sham. Every patient in the analysis is shown here, in this slide: at five mmHg it's 66% versus 33% and at 10 millimeters it's 43% versus 18%. Finally, I'll show you Radiance-Trio, which also shows essentially the exact same thing. More patients in the denervation arm achieved blood pressure drops compared to the Sham arm with various cut points shown in the slide. This is again, to one-to-one randomization.

Dr. Saville: Yes, that's helpful. So, you can see on this graph, for example, there's a really large increase. If I'm reading this right, on the Sham procedure, you have the data point all the way to the right with a change from baseline of 40. So those are influential outliers that are pulling the mean in a certain direction in favor of renal denervation. You have similar kinds of influential data points on the left-hand side for both Sham and the treatment group. So yes, this is helpful. Thank you.

Mr. Mullin: Chris Mullin. You also asked about the proportional odds model. My colleagues were able to run that during the break, so we could bring that up. This is post-hoc and the FDA has not had a chance to review the model with all the caveats that need to be provided. We looked at a

proportional odds model based on reductions of less than five, reduction of five to 10, or greater than 10. We 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. This is from a model adjusting for a baseline that is similar to the primary analysis model. It also uses the same imputing zero for the appropriate patients, as we did in the other model. Not adjusting for baselines was very similar and there was no evidence from these models that the proportional odds assumption was violated.

Dr. Saville: That's helpful. And that's a two-sided p-value.

Mr. Mullin: Correct.

Dr. Saville: I think the analysis I really wanted was where you didn't dichotomize the five, 10, and 15 and instead you left it essentially as continuous as possible.

Mr. Mullin: My apologies. Okay.

Dr. Saville: No worries.

Mr. Mullin: The magnitude of the p-value from the rank ANCOVA is about 0.02. So, I would expect very similar results across these different models, like we've said.

Dr. Saville: I'm not expecting different answers there, but that's the analysis that I would propose if I had been involved in this analysis plan from the beginning. Thank you.

Dr. Lange: Chris. Two things: one, thanks for providing this data, especially on the fly. I don't know that anybody but a statistician could come up with this in less than a month, let alone in a couple of hours.

Mr. Mullin: I have to thank Lisa and Candace, my colleagues, for being able to do it so quickly.

Dr. Lange: But I also want to thank you on the fact that you were honest about it and acknowledged that the FDA hasn't had the chance to see this review. I appreciate that, thank you.

Dr. Saville: Just a quick follow-up. That model adjusted for the baseline systolic blood pressure. Is that accurate?

Mr. Mullin: The one I showed you, did adjust but the one not adjusting for the baseline was very similar.

Dr. Saville: Okay. Thanks.

Dr. Reeve-Stoffer: Dr. Lange, the next question that we have answered, I'm not sure that you had captured. There was a question regarding what happens to the energy from the device in the presence of calcification. I'm going to have Dr. Coleman respond to that.

Dr. Coleman: Thank you. To clarify and to address the question from this morning, if energy is delivered potentially at locations of calcification within the arterial wall, we do recognize that there's a theoretical potential for deflection of energy towards the arterial wall. However, because of the cooling mechanism within the Paradise System where we're actively cooling and protecting the arterial wall for thermal injury, we do not anticipate that there would be any safety concerns.

Dr. Lange: All right. Thank you.

Dr. Reeve-Stoffer: Dr. Lange, the next question I have is how many patients we had with an eGFR less than 60. We were able to demonstrate that and we provided the ambulatory data. On slide eight, you can take a look at the actual efficacy. As I indicated, we had a small number of patients with a GFR of less than 60: there were 14 in the treatment group and 13 in the Sham. But you can also see that, and again, with the caveat that these are very small numbers, there was an effective decrease in ambulatory blood pressure in those patients, independent of whether they had a GFR less than 60 or greater than 60.

Dr. Lange: Yes, Dr. Nachman asked about this and also about the number of meds in Trio, in the intervention, in Sham. The FDA showed that data. Did you see that Patrick?

Dr. Nachman: No, thank you very much.

Dr. Reeve-Stoffer: Then I'm going to ask Dr. Kirtane to discuss the antihypertension regimen, and blood pressure decrease that he would like to share.

Dr. Kirtane: Just one point about the medication burden. Specifically, in Trio, the first line agent to be used when blood pressure was uncontrolled was an aldosterone antagonist. There was a difference in the aldosterone antagonist usage in Trio between the two study groups, both at six months and 12 months. While the DDD, which is a way of accounting for both dose and number of pills, was nominally not that different and one of the reasons for that is that the dose of spironolactone necessary to achieve a one increase in the DDD is 75 milligrams. In this trial, most patients were on lower doses than that, so that's one of the reasons why we separated out aldosterone antagonist usage as a fourth-line agent for these types of patients.

Dr. Lange: I appreciate the explanation although I'm not sure it's as valid. The question is regarding the med load index and the number of meds in Trio. I guess it looks similar at six months and 12 months.

Dr. Reeve-Stoffer: Correct. Yes.

Dr. Lange: Okay. Okay. Thank you.

Dr. Reeve-Stoffer: The next question that we have is: What was the blood pressure response in diabetic versus non-diabetic patients? On slide 21, you can see the forest plot for the patients who had diabetes versus those who didn't. Again, caveating that we had a very small number of patients who actually had diabetes. But there's no statistical significance.

Dr. Lange: Great. Thank you. And for the record, uncontrolled diabetes, elevated hemoglobin A1C, or type 2 diabetes were in exclusion criteria, that's why the numbers are small. Thank you very much for pulling this out. Thank you.

Dr. Reeve-Stoffer: That's correct. Thank you. We had a question regarding the interaction with abdominal obesity at six months. There was no interaction and I can show you that data on slide A.

Dr. Lange: That looks like at two months.

Dr. Reeve-Stoffer: Yes, it's a two months data. We can provide you with the six-month data, we do have it. The last question came from the discussion with the FDA panel about the clinical implication of the six-month durability data. I would ask Dr. Fisher to discuss that. Is that okay to discuss now or would you like to wait until later?

Dr. Lange: Let’s continue if that will help frame our discussion. Just so that the sponsor and FDA are aware, when we get into the deliberative process, neither the sponsor nor the FDA will be giving presentations or contributing, unless invited to do so. Now would be a great time.

Dr. Fisher: Speaking about the importance of durability, as a quick reminder, the primary outcome in these studies was at two months. Again, they were not designed to look at results at six months and beyond anything, all later results were considered observational. A speaker brought up before break that we have to distinguish between durability of effect and durability of differences between groups. And I think that's really important. Data show the durability of effect. We have 24-month data out in Trio, we have 36-month data in Solo. What we do not have, is evidence of a large between-group difference, and again, due to mandated trial design, titrated medications, and again, this was our goal, I'd like to remind us all the durability in a blood pressure trial, comparing to Sham, untreated patients out many months in a blood pressure trial is really unprecedented to ask, for data like that. Longer hypertension trials have not run against placebo for many months, for ethical reasons. Let's not forget the clinical message: patients in whom we're discussing renal denervation and considering it, are patients who are looking for a lasting effect. These are patients who are considering renal denervation because they've tried lifestyle modifications, and

medications, and have failed. Their blood pressure's uncontrolled and they're looking for lasting treatment. Ultrasound renal denervation represents an important treatment option for these patients who are uncontrolled.

Dr. Reeve-Stoffer: Dr. Lange, we have managed to pull together one shift table for the Solo trial. Would you like us to present that?

Dr. Lange: Please. Thank you very much.

Dr. Reeve-Stoffer: I'll have Dr. Kirtane speak to it.

Dr. Kirtane: Sorry for the delay in getting this to you. It's complicated: up on top is the denervation group, on the bottom is the Sham group, green are patients that had lower medicines, light-colored is no change and red is an escalation of medicines. One thing that I'd like to point out, as you recall when patients at screening came into the Solo trial, they were uncontrolled. When they subsequently followed up, they had better levels of blood pressure control with lower blood pressure as a whole. So, overall, one can somewhat appreciate on this complicated slide that there are more patients in the green than the other groups, and in the denervation group compared to the Sham group. Of course, these analyses are somewhat difficult because they're dosage dependent but this is what we could pull together. I'm sorry, we couldn't pull the other ones.

Dr. Lange: Let's leave it there for just a second and so people can digest it. Dr. Wittes?

Dr. Wittes: Yes, this is very useful. I wish we had it before because I was trying to get a sense of what happens long-term. What is the relationship between where you were at baseline and what happens afterward, in the two different groups? So, thank you for pulling it together.

Dr. Kirtane: No problem. I think from a clinical standpoint, and this gets back to Dr. Fisher's question. For many patients, if their blood pressures are high, it's unlikely that they're going to be lowering, getting control, or coming off of their medications, but their blood pressure will hopefully be controlled. And if you start off closer to levels of control, then you're more likely to

be controlled and may be able to keep your medicines constant or come off of them. I think that's probably the clinical message that can segue into the next segment. Thanks so much.

Dr. Wittes: I didn't understand something and now I do. So, I don't have a question.

Dr. Lange: I've gone through and I think most of the issues have been addressed either by the sponsor or in the FDA's presentation. Were there any other clarifying questions to the sponsor that we were expecting that haven't been provided? Dr. Saville?

Dr. Saville: Yes. I just had one follow-up. I asked the question earlier on why we don't have the 12-month data from the Radiance study. The answer that I got was that we haven't finished follow-up, yet. I'm looking at FDA, slide 32 which says 185 completed visits. So, I'm confused. Do we have some people who still haven't finished the 12-month visit?

Dr. Reeve-Stoffer: We actually do. We have two patients that are still waiting for the final visit.

Dr. Saville: Okay. That's helpful. Thank you. And that's why you're going to have that data closed out pretty soon and locked.

Dr. Reeve-Stoffer: Exactly.

Dr. Lange: Anything else directed towards the sponsor in terms of clarifications? I'm not seeing any other hands up and I'm going to move to the FDA. There were several requests but it looks like the sponsor did most of these. FDA, are there any outstanding data that you need to present?

Dr. Zuckerman: No, Dr. Lange, but I would like to underline the point that Dr. Fisher made in the last presentation. While durability will certainly be a focus of the panel's discussion, the sponsor, in collaboration with the FDA, had to come up with a length of time that was ethical and scientifically justified. And that's why the two to three-month endpoint was there. Certainly, from the FDA perspective, we did not feel that the medication titration protocol could be delayed beyond that point.

Dr. Lange: Thank you for that. All right. If there isn't anything else to bring to the sponsor, I'm going to call for a 15-minute break and then we'll come back for the FDA Questions to the panel. We'll use that as a framework to talk about the issues that we've already begun. Dr. Lewis, you have your hand up. Do you have a comment before we go?

Dr. Lewis: Yes, I just have a comment. I'm wearing my hat as having been two-term chair of the FDA Cardiorenal, but, our job as the advisory committee is to decide whether this is safe and efficacious for the public. Whether the FDA agreed or didn't agree to the plan or believes in it, we're not trying to line it up and say it's okay. Everybody's fallible. We're here to make an independent advice to the FDA, with all due respect.

Dr. Zuckerman: That's an excellent comment, Dr. Lewis. But sometimes the panel becomes confused regarding what did FDA recommended and is the FDA in agreement with the trial design. That's the only point that I made. We welcome independent comments, certainly, and that's the whole point of this advisory panel proceeding.

Dr. Lewis: Agree. Thanks.

Dr. Lange: Thanks, Julie. Dr. Somberg.

Dr. Somberg: I must say, I strongly disagree with that statement you made, Dr. Lewis. I think what the protocol is set out to do and the agreement between the sponsor and the FDA is very critical for the determination of a panel. I've been on this panel for a very long time, over 25 years. I think it's very important for us to understand that if you agree on a study with the agency, that goes a long way in setting the parameters for our evaluation of it. And it's nice to ask for other things, but in the real world, nothing would ever get approved.

Dr. Zuckerman: So, right now, we don't want to get into a discussion between CDRH and CDER rules. I think it's very important today to understand that we're operating in the CDRH context. I'll be glad as the discussion ensues to continue to explain that, especially in light of the

fact that this device has a breakthrough therapy designation. There's a specific reason why devices are regulated differently from drugs, and that's what Dr. Somberg is alluding to. This is why we have our panel education, but we have important work to do in terms of just looking at the questions. So, let's proceed under Dr. Lange's guidance.

Dr. Lange: All right. Dr. Lewis, you're right. In the end, we're going to decide whether it's safe and efficacious, I totally agree. With that, we're ahead of schedule, which is great because it gives us a lot of time to get into, what I'm going to call, a robust and meaningful discussion. We're going to take a 15-minute break, which means we're going to reconvene, promptly, at three o'clock. That's actually 18 minutes, so, promptly, at three o'clock. FDA, be prepared to present your questions, panel, let's get into it! Thanks.

FDA Questions

Dr. Lange: It's now 3:00 PM Eastern Standard Time. I'd like to call this meeting back to order. At this time, let's focus our discussion on the FDA questions to the panel. Panel members, copies of the questions have been sent to you electronically and posted online for the public. I would ask that each panel member identify herself or himself each time she or he speaks to facilitate transcription. I will turn it over to Dr. Paul Warren to read the FDA questions in just a moment. But before doing so, we have eight questions with some sub-questions. In essence, there are about 11 questions to cover and some of the meatier ones occur a little bit later on. I'm going to take the chair's prerogative and if I think that we discussed these earlier questions, if we've provided sufficient direction to the FDA, we'll spend less time on those and more time on the latter. At any point, if the FDA feels that we haven't discussed it fully, please make that known to me and we'll continue the discussion. With that, let me hand it over to Paul Warren, to read the FDA questions to the panel. Dr. Warren, question number one.

Question One

Dr. Warren: Thanks, Dr. Lange. Question number one is related to safety. As a reminder, the primary safety endpoint was a composite of the rate of 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 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 is not associated with a functional reduction in renal blood flow, please note that the long-term follow-up data are limited and it's not clear if renal artery lesions will change over time. So, please discuss the acute and midterm procedural and device safety profile of uRDN and the clinical significance of renal artery responses to uRDN treatment.

Dr. Lange: All right, open for discussion. I'm going to call John Hirshfeld. Your thoughts?

Dr. Hirshfeld: From everything that we can see so far, I don't think that safety is an identifiable issue, at this point. I do agree with the caveat in the FDA question that long-term follow-up is still appropriate because it's possible that a later problem with renal stenoses could emerge. But, at the moment, I don't see any signal of any problem.

Dr. Lange: Okay. Eric, you're an Interventionalist, as well. Any concerns?

Dr. Bates: Thanks. I would suggest that as long as this remains the femoral artery approach procedure, I suspect the complications from the access site are undercounted in this very carefully conducted study. And then, when it gets out into the community, with a broader range of operators, with different support staff, and different cath labs, there might be a small incidence of access sites complications, as they are with all of our interventions. Although I don't see a major safety endpoint, I would think this may be a little too "rosy" to say there are no safety outcome problems.

Dr. Lange: And of course, those complications, Eric, would not happen in our labs. Those would be in other people's labs.

Dr. Bates: And they're not related to the catheter. They're related to procedural access.

Dr. Lange: Are there any dissenting views? Jim and Keith?

Dr. Blankenship: Yes, I agree. At one point it was mentioned, that there was an arterial dissection and an aneurysm. Looking at the data, those were access complications and the complication rate was actually quite low for femoral access and it may be undercounted. I suspect that when it gets added to the community, that radial access will become the default access route. I was concerned about the renal artery stenosis. I'm reading from the BMJ, the British Medical Journal, volume 320, in the year 2000. It says with respect to progression, most studies over a variable follow-up period, estimate the risk of radiologic progression of atheromatous renal artery stenosis to be 50%. The rate of occlusion of renal arteries with greater than 60% stenosis is about 5% per year. So, to me, that is reassuringly pretty low. In summary, I don't have any significant safety concerns.

Dr. Lange: All right. Dr. Allen, anything to add to that?

Dr. Allen: No. From a vascular surgery standpoint, I think this is all relatively low risk. I don't think the issue here is safety.

Dr. Lange: Okay. Dr. William Vaughan?

Dr. Vaughan: Just to note that the company's last month press release, noted how the European hypertension societies said this is a source of treatment. And they quote a prominent, heart physician out of Paris. The recommendations state that renal denervation should be performed in experienced specialized centers and that the process of patient selection should be done by a multi-disciplinary team. That might be something that we would want to talk about later, in terms of warning labels.

Dr. Lange: Keep that thought. Great thought. All right. Dr. Zuckerman, with regard to question one, the panel generally believes that the procedural risks are related to vascular access and very little if any, risk assigned to the ultrasound renal denervation. Is this adequate for you?

Dr. Zuckerman: This is very helpful. Thank you. May I ask that our other vascular surgeon, Dr. Corriere, also comment on safety, if he is inclined?

Dr. Corriere: Yes, I agree with the previous comments. The reason I asked whether there was protocolized access is that the event rates in this study are much lower than we usually see with six French access, particularly, if they're all femoral. Certainly, if you experienced higher rates of access complications, it would have a drastic effect on the benefit versus risk for this intervention.

Dr. Zuckerman: Thank you.

Dr. Lange: All right. Let's move to question number two.

Question Two

Dr. Warren: Question number two is related to effectiveness. Data have been presented using both ambulatory blood pressure and office blood pressure measurements. Most prior hypertension trials have used office blood pressure measurements. However, ambulatory blood pressure measurement 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 blood pressure assessments made for ambulatory blood pressure that are free from potential biases, for example, the white coat effect.

FDA presented these figures earlier, in our morning presentation. These show blood pressure reduction in the treatment, in sham groups, at two months for all three studies. They also show 24-hour ambulatory blood pressure reduction, daytime ambulatory blood pressure reduction, and office blood pressure reduction side-by-side. You'll see that in Solo and Radiance-II, the office blood pressure reduction is greater than the ambulatory blood pressure reductions for both treatment and Sham. However, in Trio, the office blood pressure reduction is comparable to the 24-hour and daytime ambulatory blood pressure reductions in the treatment group. For the Sham group, the office blood pressure reduction is actually smaller than either of the ambulatory blood pressure reductions. Please 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. Lange: I've got Dr. Allen, Dr. Somberg.

Dr. Allen: Sorry, Richard. I don't have a strong opinion on this topic.

Dr. Lange: Okay. Then will you yield to Dr. Somberg and then Dr. Hirshfeld.

Dr. Somberg: I think they're both useful. I remember the meeting five years ago where ABPM was advocated and the same thing was discussed. Certainly, ABPM gives you more data points and that's very useful. It's most accurate, at night, which is important for especially non-dippers and blood pressure. But I'm always worried about the patient who presents for a visit and the blood pressure's outrageous. The patient says the blood pressure's much lower at home, you put on an ABPM machine, and it's someplace in between. So, I think there's definitely a value to measuring both, and it's very important to point out here. All three studies met their primary endpoint using ABPM, which is probably tougher than office blood pressure. But office blood pressure was also significant. The other thing about ABPM is that it correlates very well with left ventricular hypertrophy, the total burden, the heart deals with. So that's another consideration that adds value

to ABPM that is probably related. You lower it and it'll reduce left ventricular hypertrophy. You don't and that's going to be a problem. I think it's great that they looked at both ("they" being the sponsor). It was very successful in all three studies at that two-month endpoint.

Dr. Lange: Okay. Thank you, Dr. Somberg. Dr. Starling?

Dr. Starling: Yes, thank you. I consider the ambulatory as the gold standard, based on my knowledge of how it works. It hasn't been discussed a lot, but there was marked diurnal variation referred to as dipping. As Dr. Somberg mentioned, the diurnal drop is associated with cardiovascular outcomes, so that's reassuring. I'm very intrigued as to the disparity though, and trying to understand if there's something here that maybe the hypertension experts know that I don't know, whether somebody is more likely to take their medication before going to a doctor's visit versus a random ambulatory blood pressure measurement. But I'm perfectly comfortable with ambulatory blood pressure monitoring.

Dr. Lange: Okay. Dr. Blankenship?

Dr. Blankenship: Yes, I just noted that the paper circulation from the Hypertension Academic Research Consortium endorses the ambulatory and says, as a practical matter, all randomized trials may use two or more of these measures, for instance, office-based and ambulatory. But the ambulatory blood pressure is specified as the primary effectiveness outcome measure, so that's their endorsement.

Dr. Lange: Can I have the FDA put up slides 54 and 55 for just a second? We're going first to slide 54. Let's focus on the left-hand side: Solo daytime ambulatory blood pressure, and Solo office. The bottom one goes out to 24 months. Let's just look at the 12-month. That's halfway down on the bottom, and you can see there's a marked discrepancy in the office systolic blood pressure. At the same time, for the ambulatory daytime blood pressure, there's no difference. Now, let's go to slide 55 and you'll see the same thing with Trio. Again, let's look at the 12 months. That is the

ambulatory systolic blood pressure, at daytime, without difference. And then a huge difference. Just looking at the 12 months, it should be fairly comparable. So, I have concerns that the office blood pressure really represents what's going on. When I see a big discrepancy like that, I tell my patients to spend less time in the office because it changes their blood pressure. Like many of you, I still see patients clinically, and I can say that about half the patients that have hypertension when they come into the office on medications, when you send them home, they record 40 or 50 blood pressures that are oftentimes normal. So, I don't trust an office reading. There's an intermediary home blood pressure measurement that doesn't necessarily have to be an ambulatory. There's a home blood pressure measurement that, in my opinion, is more likely to represent what's going on throughout the day than an office. Are there any other comments from our hypertension experts? I don't want to leave this because this has less to do with whether they meet the endpoints of the study and more to do with how we're going to follow people in the post-approval study. That's why I think the FDA really wants to nail this down.

Dr. Zuckerman: Yes. Dr. Lange, could I ask that we go back to question slide seven? Your points about ambulatory blood pressure are very important, but question slide seven shows that there are two types of ambulatory blood pressure: the daytime average that the sponsor used and the 24-hour. When one goes to the Solo trial, again, you'll see a difference in the mean difference. So, it would be very helpful for the hypertension experts on this panel to further define what is meant by ABPM and if there is an optimal one.

Dr. Lange: Okay. John Somberg.

Dr. Somberg: It's certainly important to look at the full 24-hour because we know that patients who have nocturnal hypertension are most at risk for cardiovascular events. And we know that the point of great cardiovascular vulnerability is just before and when you wake up. That was all critical in terms of ABPM measurements, not to criticize that the primary was daytime ABPM. But

I think it is important, in future studies, to try to look at both daytime and nighttime. I just want to comment on Richard. When you see your patients and you frighten them, and some of them get very high elevations of blood pressure, I think that has consequences. For someone who spends most of their time, and I'm somewhat serious about this, someone spends most of their time at home and has a less stressful life, that is fine. But, if you're one who has to deal with all of us all the time, all the sponsors, and has a situation like that, I think labile hypertension is a concern. So, I wouldn't throw any of this stuff out. And it's very nice in this particular trial that many things go in parallel. It works on most measurements and in fact, it works in all situations. So, I'm very optimistic that there's some benefit and we see an important signal here.

Dr. Lange: All right. I was laughing earlier as I couldn't say that their high blood pressure was in response to being in an office or being in my office, in particular. Dr. Lewis, Dr. Yeh, and Dr. Wittes.

Dr. Lewis: I want to say that I think that the ambulatory blood pressure monitoring was a really important choice in this trial because of the limited sample size compared to a sprint that had 10,000 patients so that there could be a balance in the noise of the things that affect the office blood pressure. I will tell you a trick: you can turn the lights off, tell them not to talk for five minutes, and keep their feet on the floor then do their blood pressure the way it’s done in studies. When our nurses check them in, they're talking away with them. That might help your office blood pressure. But I do want to say that given that they had a limitation in their sample size, understandably, this was the better choice for sure.

Dr. Lange: Let me follow up, again, to help with the FDA. If we're going to do a post-approval study that has hundreds of patients, not thousands, Julia, would you recommend an ambulatory blood pressure or do you feel comfortable with the office?

Dr. Lewis: I think ambulatory blood pressure, although may be prohibitively expensive would be, as it was in this study, the better choice. It may be prohibitive.

Dr. Lange: All right. Thank you, Julia. Dr. Yeh, Dr. Wittes, Dr. Starling, and then we'll summarize.

Dr. Yeh: I was just going to say that when I look at the different blood pressure measurements, I think it's really important to focus on the two-month data and the consistency across each of these measurements. The small differences in the magnitude of the effect size are probably not even statistically different from one another. The consistency, the directionality, and the approximate magnitude are all comparable. In thinking about that for the long term, the sponsor has proposed a patient home trans-telephonic mechanism of measurement, which, for all the feasibility reasons, in a much larger sample, would seem to be appropriate to me based on the consistency of what we're seeing at two months between all these measurements.

Dr. Lange: Thank you, Bob. Dr. Wittes, Dr. Starling, and then I'll summarize.

Dr. Wittes: Just a quick request for the FDA: It would be so much better and easier for us if you presented these as box plots so we could see the variability. Right now, the only way we can look at the variability is to look at the means and then the p-values to realize that this measure is less variable than the other. It would not take any more space and it would be so much more valuable.

Dr. Saville: I second that.

Dr. Lange: All right, so noted. Thank you. And I'm sorry I didn't ask for that earlier. Janet and Ben, I should have. All right. Dr. Starling, you got the last word.

Dr. Starling: Yes. I strongly favor the ABPM and the sponsor plan for the telemetric. The one sidebar I'll make is that I haven't heard or read during these proceedings what the standardization was for office-based blood pressure. As was just mentioned, at many places, there's a device known

as Blood Pressure TRU that takes five blood pressures because of the well-known phenomenon of office hypertension, as you've described in your practice, Dr. Lange.

Dr. Lange: Yes. By the way, every time patients see me, their blood pressure goes up.

To summarize, everybody feels that ambulatory blood pressure is the gold standard, especially, if one's going to look for relative differences in small sample sizes. There wasn't a person who said office blood pressure alone was sufficient. There were some that said they would like to have both. Then the medium, as Dr. Yeh mentioned, is the home trans-telephonic. With this, patients are not going into the office, but they're recording multiple pressures at home, which is in fact what they did, in the study, over a three-day period, to document whether they needed to adjust medications. Bram, does this provide you with sufficient opinions and direction?

Dr. Zuckerman: This was an excellent discussion including the suggestions from Dr. Wittes and Saville regarding the presentation of data.

Dr. Lange: All right, thank you. Let's move on to question number three, Dr. Warren.

Question Three

Dr. Warren: Okay, question three is also related to effectiveness. The FDA and ReCor reviewed the discussions during the 2018 Circulatory System Devices Advisory Panel and there is 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, we considered a five mmHg difference in systolic blood pressure reduction measured by ABPM between treatment groups 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.

The ITT population results, which I think will be shown in a figure on the following slide, showed a between-group difference of 6.3 mmHg in favor of uRDN for the off-blood pressure

medication studies, Solo and Radiance-II, and 4.5 mmHg difference in favor of uRDN for the on standardized medication study Trio. Please discuss the clinical significance of the absolute blood pressure reduction in uRDN subjects versus the difference in blood pressure reduction between uRDN and Sham groups in evaluating the treatment effect for Solo, Trio, and Radiance-II.

Dr. Lange: All right. I've got Dr. Lewis, Dr. Somberg, and Dr. Yeh. Dr. Lewis, first.

Dr. Lewis: I have a similar comment. I was much more impressed with the table that showed the percent of patients in the two groups that achieved a greater than five-mmHg, or greater than 10. With a continuous variable like blood pressure, you could have many zeros and the means could mask a more clinically impressive effect, which I think actually was the case here. There was about 60% with greater than five in the denervation, and 30% in the Sham. I was more impressed with that than the means. I didn't know that the person from that organization was going to do the blood pressure work for me because I did review the expected maximum dose of blood pressure reduction and I believe that slightly less than one med is probably the right equation. I still think it's impressive that Trio for reasons that they gave is slightly below the five-millimeter mark. But is still, an impressive result or a significant result.

Dr. Lange: Okay. Looking in terms of 5, 10, 15, 20, in certain categories, to find out the percentage is more meaningful to you.

Dr. Lewis: Right. I'm sorry I didn't pull up the table quickly. It’s the table we looked at earlier, that's in both briefing documents, about the percent of patients who achieve that goal. It shows how many people had an MI versus rating the angina. Or how many people went on dialysis versus how many people's GFR slope changed. It's just a better way to get a feel for how many people had a clinically significant thing when there can be a wide variability in responses.

Dr. Lange: Is this the one you're referring to?

Dr. Lewis: No, it's the one where it's actually just a number, where it says 60% of this and 30% did this with the Sham versus the denervation. What percent of patients achieved greater than five millimeters in each group? What percent of patients achieved 10 in each group? That table tells you more than the means.

Dr. Lange: Okay. The one that was just up was a bar graph, and I'm wondering if it's the same information just presented in a different way.

Dr. Lewis: I'm sorry. Yes. I think that's a better way to think about how it's impacting a number of patients.

Dr. Lange: Okay. Dr. Somberg?

Dr. Somberg: I certainly agree with Dr. Lewis. To answer the FDA's question, I think the absolute reduction is not the metric. It's the difference between the true Sham, which is a placebo in the first two months, compared to the intervention. I think that's the most critical. Also, the waterfall plot is very informative, too. How many people and to what extent they have a reduction in their blood pressure is very informative, as well. But I think the difference is going to be that you need one key metric in a study, the difference.

Dr. Lange: Okay. Dr. Yeh.

Dr. Yeh: I agree with both comments. It's the difference between the Sham control and the placebo that is the more important number at only the two-month mark. I would have that caveat, that subsequent to that number is probably not even interpretable based on all the limitations that we've seen with the crossover and the medication titration, et cetera. The other thing that I think both Dr. Somberg's and Dr. Lewis's comments highlight is just the vast amount of treatment effect heterogeneity there is in the trial, which I don't think we have a good accounting for of what might drive that treatment effect. Heterogeneity would be one of the very important goals of any

subsequent study, potentially in post-market, to understand the treatment effect. That's going to be really important to guide clinical practice.

Dr. Lange: Okay. Thank you, Dr. Hirshfeld. Dr. Saville, and back to Dr. Lewis.

Dr. Hirshfeld: Yes. I would like first of all to follow up on what Dr. Yeh said. I wonder if the sponsor can show the slide that they showed later on with the individual responses stratified by the directionality of the response. I thought that if they have access to it, and that can be put up, I think that would illustrate what we're confronting.

Dr. Zuckerman: For the record, you're referring to the waterfall plot that the sponsor has from one of the trials.

Dr. Hirshfeld: Yes. If we take a look at the waterfall plot, it's much more possible to see what's going on in the whole patient population than when we're looking at derived mean values and bar graphs.

Dr. Reeve-Stoffer: We can provide that to you if it's acceptable to bring up the Radiance-II waterfall plots.

Dr. Lange: Would you please? Thank you very much, Helen. While they're doing that, Dr. Saville?

Dr. Saville: Yeah, I just want to say that I agreed with the other panel members that it’s really the difference between the treatment and Sham groups that we care about. I know there was a comment made at the beginning of the sponsor presentation that the ambulatory systolic blood pressure essentially had zero placebo effect. Clearly, we see there's some placebo effect because the blood pressure's going down in the Sham group. I don't I think because there is reduction in both groups, you have to think about the difference between the two groups. I wouldn't get too hung up on the consensus committee recommendation of the five to seven mmHg. I think you're in the ballpark of that and I wouldn't worry about it being 4.5 or 5.5. I think you're seeing consistent

results across the three studies even though in one of those studies, the Trio was not seriously significant. Again, I wouldn't get hung up on that as you're seeing a consistent trend across the three studies. I think you're seeing some benefit that, from what I understand from a statistician's perspective, would be clinically meaningful.

Dr. Lange: Dr. Saville, let me put something back to you and Janet Wittes. The post-approval study is likely to be a single arm study. I've heard everybody say, and appropriately so, that we're looking for the difference between the Sham and the placebo. But it is likely that if it's a post-approval study with a single arm, there won't be a Sham group. So, let's give the FDA some direction on this. Dr. Yeh.

Dr. Yeh: I was going to say that the comparison between Sham and the active treatment at the two-month mark is an important one because the goal of the post-market assessment is not to confirm that the procedure works at the two-month mark, but rather to understand long-term safety, durability of treatment, et cetera. And they're there. I think that the ethics of doing a Sham control study in which you actually let people not be treated for their hypertension when they show up in the office to demonstrate that, is not feasible. So, in that situation over the long term, it's imperfect. But I do think that single arm difference compared to baseline over time or number of medications over time is the imperfect, but probably the most feasible mechanism to understand the long-term durability; short of other sort of physiologic assessments of reinnervation, et cetera. I don't know that it's feasible to do, a long-term follow-up that's appropriately powered for anything long-term.

Dr. Lage: Okay. Thank you, Dr. Yeh. Okay. So, let me go to John first, then to you, Dr. Wittes and Dr. Somberg. Dr. Hirshfeld?

Dr. Hirshfeld: I think this really emphasizes the heterogeneity of the patient population and the oversimplification that is derived from converting all of these kinds of data into a mean value with the standard deviation and a bar graph. It's clear that there's about a third of the treated patients

who derive no benefit. And then there's another third who seem to have derived considerable benefit. Concurrently, in the Sham group, there was a larger fraction, probably at least half, maybe two-thirds, who derive no benefit which you would expect. Nonetheless, there was another third that appeared to have derived benefit from the Sham procedure. This emphasizes the amount of noise in the data that I think will have implications for how this technique is applied to the general population of people with hypertension. It's pretty clear that there's a lot of different differences in these subgroups.

Dr. Lange: Okay. Thank you, John. Dr. Wittes?

Dr. Wittes: Yes. There's been a lot of discussion about how the study couldn't have been done with a Sham for many months. Of course, it couldn't be done, but that's not the question. To me, the question is on the long-term effect of this intervention compared to what would happen in real life when there would be changes of medication. So, there could have been really interesting questions asked about what the long-term effect is without having a Sham go on too long. In answer to your question about the post-marketing study, it would be very 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 antihypertensive medications in the population that has the intervention. It becomes a description of a population but not just the blood pressure.

Dr. Lange: Thank you, Dr. Wittes. Dr. Somberg, Dr. Saville, and Dr. Lewis.

Dr. Somberg: I think it's been established by the data that the duration of effect is persistent because the blood pressure goes down, at two months beats the Sham, which is the placebo, and then it continues to stay down. If it wasn't persistently effective, then it would come up. You don't need the Sham anymore because it's been contaminated with all these titrations of medications. In terms of the post-marketing study, if you don't have a control, it will be useful to show persistence of effect in larger numbers of patients, and it might even be able to tease out who responded and

who didn't. But they may be some populations, the Black Americans in particular, that I'm not sure the procedure is effective. That's been a signal in the earlier studies we saw years ago and I think we're seeing that signal again. It's confusing mainly because that population, saying Black Americans, they're a very heterogeneous group. It's not a genetic study, it's just a general identification. But there is something there and that might need a control group. Dr. Yeh, it's complicated and you bring up a good point that in some post-marketing areas, a single arm is appropriate, but others it may not be.

Dr. Lange: Okay. Thanks for the comments, John. Dr. Saville.

Dr. Saville: I agree with most of these comments. I think a post-marketing study is difficult, if your goal is to prove that renal denervation is beneficial relative to Sham. After that point, it will be very difficult to show that. If you have really good external data on hypertension patients in a registry somewhere, I don't know what's available in the field of hypertension with what is typically seen, then a single arm study can be helpful for helping you figure out long-term benefit and how this intervention compares relative to the standard practice. Otherwise, I think you're going to be limited to just showing bringing blood pressures down and keeping them sustained. Long term, it will be difficult to really show if that was really due to the denervation or if it was due to the meds. Unless you have good data for comparison, I think it's more about safety.

Dr. Lange: Okay. Thank you. Dr. Bates.

Dr. Bates: I was going to say something similar. It would be impossible to get efficacy data on a post-marketing study for 500 patients, selected over time, with all the confounding variables. That shows goodwill by the company to the FDA, no offense, but it will give you safety data. For instance, since a lot of these patients are on a beta-blocker, I would assume they might show no benefit, so that'll confound the results of an efficacy analysis. When we talk about labeling, I think

we need to address the question of whether this is a substitute for a patient who can't take a beta-blocker, or whether this is an additive therapy for a patient who tolerates a beta-blocker.

Dr. Lange: Dr. Zuckerman, I'm going to summarize and then let you ask the Panel for any clarifying questions. People are interested in absolute reduction and especially for certain goals, what percent achieve five, 10, or 15 millimeter or more than that drop. That will obviously depend on the starting blood pressure. People are interested in a waterfall plot. People are interested if we're going to look at its effect/durability after it's done and whether there's a long-term effect in terms of decreasing the number or amount of medication use. And everybody agrees it will be difficult to show a long-term effect or durability in a single-arm study. I think I've summarized all the prevailing opinions. Dr. Zuckerman, do you have any other clarifying questions that you want to ask any of the panel members?

Dr. Zuckerman: No, that's very helpful. Thank you.

Dr. Lange: Okay. All right. Let's talk about durability of blood pressure reduction. Dr. Warren, question number four.

Question Four

Dr. Warren: Okay, question number four. You have seen these figures before from FDA's morning presentation. The difference in daytime ASBP reduction favored uRDN over Sham 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 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 groups at two, six, and 12 months are shown in this table. In general, at six and 12 months, the Sham group took more medications and had a higher medication load index compared to uRDN, but the differences appear small. Challenges in interpreting longer-term blood pressure data include blood pressure medication

prescription following a pre-specified escalation protocol to attain a target blood pressure of less than or equal to 135 over 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; crossover from Sham to 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 for 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, and the clinical significance of blood pressure medication differences between uRDN and Sham subjects.

Dr. Lange: Dr. Somberg, you had your hand up first.

Dr. Somberg: A lot of this has been covered before, but the data you've just mentioned informs me that denervation is not superior to medications. And that's my take home message here. It lowers blood pressure, the denervation and is persistent, but when you do a titration with medications, you can take the Sham group to almost as good control as you do with denervation plus meds.

Dr. Lange: Okay. Thank you, John. Dr. Lewis.

Dr. Lewis: I actually agree with what Dr. Somberg said. At six months, we're seeing a relatively small difference in medications that are titrated between the two groups. I think it's important when we come to our labeling discussion to make sure we communicate what a clinician would expect to happen to a patient. And even more importantly, that needs to be explained to the patient.

Dr. Lange: Okay. Thank you, Dr. Lewis. Dr. Starling, Dr. Allen, Dr. Nachman.

Dr. Starling: I think it's very difficult to reach a conclusion for all the reasons that have already been discussed. Also, it raises the question if there are other factors at play that are undefined, including re-innervation. I'm comforted that the medication burden appears to be less in the renal denervation group.

Dr. Lange: Okay. Thank you, Randall. Dr. Allen.

Dr. Allen: Yes, I think it's hard when I look at the data and at what occurs at two months longer term. I grapple with approving a product that could be used in lieu of medications, and if it is reasonable to have an invasive procedure in lieu of non-invasive pills. If we're approving a product that allows patients to be more compliant, that may in and of itself be useful. I personally don't think that the denervation will be durable. I can't think of a single area where denervation has been used, whether it's lumbar sympathectomy or even cardiac transplantation where the organ is completely denervated that re-innervation doesn't typically or always occur. I don't think this is better than medicines at six months and certainly longer than six months. That's how I feel.

Dr. Lange: Thank you, Keith. Dr. Nachman.

Dr. Nachman: Yes. Thank you, Dr. Lange. At the risk of echoing what my colleagues have said if we ask the question differently, can the blood pressure reduction have been obtained without the procedure? The answer is yes. What has been said is that the difference in the number of medications is very small. But that graph that was shown previously, shows that there is a greater proportion of patients with the denervation that had a reduction in the number of medications, and that's meaningful. The big question in my mind and the big disappointment with the data for me is the Trio result study. These are the patients with the highest blood pressure, the highest risk of cardiovascular morbidity and mortality and the lowest chance that I could tell that they're going to have a very big difference in blood pressure or a reduction in the number of medications. And so the question that I think is raised here is who are the patients who are most likely to benefit from

the denervation? And I'm not sure about what I'm going to say here, but it seems to me that it's not the patient population with the highest risk. It may be the population with lower degree of severity of blood pressure that may see more benefits in terms of number of medications. That's the end of my comments. Thanks.

Dr. Lange: Thank you. Dr. Saville.

Dr. Saville: Yes. For me, there's clearly an acute short-term benefit here. You can clearly see some benefit of the denervation. It's unclear to me if there's long-term durable benefit from the procedure. But to be fair, I don't think this trial was designed to answer that question. I think we can look at the six-month data and at the 12-month data but these estimates are really close to each other in terms of the Sham versus the intervention group. From what I understand in the statistician's viewpoint, that's coming on a setting with some kind of strict protocol on this drug titration during that time period and maybe this is not the standard of care. For example, what usually happens, if you had some sort of comparative study comparing this intervention versus just doing whatever clinicians want to do then you could see if there is really long-term benefit. I think that makes it difficult. As well as the fact that you have really two endpoints. Really, you're interested in both a reduction in the blood pressure, as well as, the reduction in the meds and both those things are moving together. That's one reason why the sponsor presented this linear mixed model where they're adjusting for the number of meds. There're probably some better, more innovative ways to look at this. Talking as a Bayesian statistician here, you really have two endpoints instead of trying to adjust for one. Probably, there are ways we could try to model this multi-variate, because you have two outcomes that correlated with each other: how to move across time and how the missing data play into that. You have to think about missing data imputation if you have Bayesian multiple imputation strategy. Probably, there are ways to look at this but with

the data presented today, it's really difficult to say that we think there's durable benefit. I don't see it here in this data.

Dr. Lange: Okay. Dr. Blankenship.

Dr. Blankenship: One other way of looking at this in terms of durability is that the blood pressure goes down and it remains down and the gap between Sham and treatment closes. But we've seen data that there is a substantial minority of patients, perhaps 25 or 30%, who seem to get a very substantial reduction on the order of 15 millimeters or so, which is roughly equivalent to the anti-hypertensive effect you'd get from two different medications. Another way of looking at it, is that for a substantial minority of patients it may make a huge difference. Considering that we seem to agree that safety of this is pretty clear, that may be a trade-off worth taking. By comparison, something I do is close patent foramen ovales to prevent stroke, where the number needed to treat is about 10 patients closed per stroke prevented. And compared to that, this might look like a favorable trade-off.

Dr. Lange: Okay. All right. Dr. Wittes.

Dr. Wittes: I kind of disagree with Dr. Blankenship, who just spoke. When I look at six months and 12 months, the benefit with respect to average number of blood pressure meds and the median load index is very tiny. We know the safety looks fine. We're talking about a very small sample size, looking at safety over a short period. So, I don't see the benefit. I need to be convinced from you, practitioners, that if I were a patient wanting to decide that, on average, getting less than one drug difference in six months or 12 months, would make me want to have an intervention.

Dr. Lange: Janet, I just ran those numbers based on the shift that you asked for in each group. 26% of the patients treated with ultrasound and 26% of the Sham patients took one less medication, at six months. The numbers are identical.

Dr. Wittes: That's why we see those data because they tell the story.

Dr. Lange: I'm going to summarize what everybody has said today. A lot of people expressed their point of view that the intervention is really not superior to medication. If there is a reduction in medication, or medication load index, it's a relatively modest one. Is it clinically significant in terms of getting people off of medications? The numbers are exactly the same. There is some agreement that there is an acute decrease in blood pressure with the procedure. However, when one begins to add back medications, it's not clear that the procedure offers any benefit in terms of blood pressure reduction. Ben summed it up best in that, unfortunately, the studies weren't designed to answer durability and we really can't tell. If you wanted to, we could ask him to see what that would look like. But the general feeling is that if there is a benefit, it's a relatively modest benefit, at most. As Dr. Lewis mentioned, that needs to be mentioned in the labeling. In fact, Dr. Nachman said he's concerned that the patients that are at the highest risk are not likely to develop the benefit from it. Are there any other dissenting comments? Have I captured people's comments accurately?

Dr. Somberg: Yes, I dissent, Richard from what you've just said, because I don't think the question is the benefit of this procedure over alternative approaches to hypertension.

Dr. Zuckerman: Dr. Somberg, can I just interrupt a moment just for the sake of time? Dr. Lange, this has been a great discussion, but the question really refers to the durability of blood pressure reduction, and what I heard was that there 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. Would that be a fair summary, Dr. Lange?

Dr. Lange: I think that's an excellent summary.

Dr. Zuckerman: Thank you, sir.

Dr. Lange: Great. Bram, would you like us to move on to the next question?

Dr. Zuckerman: Yes, please.

Question Five

Dr. Lange: This has to do with the patient preference study.

Dr. Warren: Question five. ReCor conducted a patient preference study with 258 patients to ascertain preferences for the uRDN procedure compared to blood pressure 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 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. Lange: Dr. Lewis and then William Vaughan.

Dr. Lewis: One of the issues is that the patients are being asked to compare something that they've never experienced and don't have much insight into. So, I didn't find this very reassuring. Having catheterized a lot of femoral arteries and, in full disclosure, I had my own femoral catheterized many times and although there were no complications, it's still an unpleasant experience, for a couple days. I don't think these patients knew that. But in the data that they showed us, that I had asked for, the large number of patients, about 50%, if I recall correctly, of the Sham patients who had experienced the procedure, were willing to go back again. In some ways, I think that's more of a testimony to the patients' preference. I don't know if it was disclosed to them the effect size when they made that decision, but at least it says a comment about their willingness to undergo the procedure.

Dr. Lange: Okay. Mr. Vaughan.

Dr. Vaughan: I just wanted to note that their study showed about 42% of patients willing to do this and, tomorrow, in a very similar device, and a very similar set of questions, they found 15 to

31% preference. And I was wondering, did that company go along with the FDA's recommendations or did they do some of the variations that you encountered here?

Dr. Lange: Mr. Vaughan, that would be a great question for tomorrow. I'm sorry.

Dr. Vaughan: Can I ask a second question? This is just to the FDA.

Dr. Lange: Yes, sir.

Dr. Vaughan: American consumers are most concerned about the cost of healthcare. And to have one of these patient preference studies without any discussion of cost and cost-benefit is useless. That's just to the FDA. I hope you lobby to change the law.

Dr. Lange: I appreciate that comment, Mr. Vaughan. Thank you. Deneen.

Mrs. Hesser: I think that in looking at a high level of what we were provided from this patient preference study, overall, we saw that patients asked for a long-term reduction in their cardiovascular risk. They asked for as few drugs as possible, and they were willing to accept some amount of risk to do that. And there was a reference, just a couple of minutes ago, to the use of patient education to help make some of that benefit-risk decision for them. In a post-market study to require a good patient education program so that a patient can accept whatever risk level they're interested in, I have no problem with. Another piece that would've been particularly helpful in this study that can be added to the PAS, would be patient-reported outcomes. That would help us ascertain how happy people were and if they really lost only one drug out of their regimen. For some patients, that may be very valuable and they may be willing to go through the risk of a procedure to do that if it buys them a year or if it buys them perhaps two years. So, I would encourage a PRO to be done to complement this information.

Dr. Lange: Thank you, Deneen, for those comments. Dr. Corriere?

Dr. Corriere: Thanks. I just wanted to say that I thought the discussion was good. I think if this was an optional submission, it was really great to see a patient preference study included for us to

look at. The only other concern I had about that study was that we had a 10-year cardiovascular mortality rejection endpoint. We had one and three and I think a longer-term hypertension endpoint. I thought it was a little bit of a stretch cognitively for those respondents, given the timeline and the endpoints we saw today. I also just wanted to say that, as someone who does this kind of work, I've not seen, for device studies, that patients are very cost-sensitive at all, to the point where we've introduced that, to make sure we're not missing it. So, I would rebut that assumption might not be a given one just for the sake of interest. Thank you.

Dr. Lange: Thank you, Matt. Dr. Blankenship.

Dr. Blankenship: I think it's striking that in this kind of situation, patients will consistently opt for an invasive procedure with some risk over ongoing medical therapy. I'm looking at an article from Circulation from 2019, where they did a study, similar to the one that we're discussing right now. Three out of four people would prefer to have their coronary artery stented, a procedure which can be fatal over just taking medications. And to some extent, that's the tradeoff that people make with left atrial appendage occlusion: medication versus a procedure. So, it's not surprising that, as we see here, opted for the invasive procedure.

Dr. Lange: Thank you, James. Dr. Damluji?

Dr. Damluji: Yes, sir. I just wanted to emphasize the importance of adherence and compliance for these patients. We enroll older adults, above 75 years of age, in clinical trials here at Innova, and they are mostly concerned about compliance and adherence. That's probably driving some of these patient preferences towards the procedure and against taking more medications, at more frequent intervals. So, I think it should be weighted in the decision-making. That's my personal opinion.

Dr. Lange: Thank you. Dr. Saville?

Dr. Saville: Yes. The FDA question is, “Discuss the degree of importance that the patient preference study results should be given.” I think there's a disconnect between the patient preference study and the actual data we're seeing in the trial. For example, we see that 42% of respondents would choose the procedure over an additional pill. What does that mean? Does that mean over the long term? I think the question here might be, “Are patients willing to take the procedure for an acute reduction in the number of pills? Perhaps, an acute reduction in blood pressure? Maybe with the potential hope or promise that maybe I'll have some long-term benefit?” Maybe they are, but it's not clear to me that patient preference study, as it stands, really translates well to the data.

Dr. Lange: Okay. We’ve heard that, obviously, safety and efficacy, and patient desire and preference are of prime importance. Knowing what the effect size is, I would say have the sponsor work with the FDA to provide a reasonable patient preference. Also, as Deneen said, actually look at patient-reported outcomes, as well. I think everybody feels that there's a disconnect between this particular study and what you're trying to get to. I'm not sure anybody puts a lot of confidence in this particular study. Bram, does that answer your question?

Dr. Zuckerman: Thank you. That's very helpful, Dr. Lange. Certainly, we'll be seeing more patient preference studies, as we move forward. I think obtaining a better connection between the clinical questions faced by a patient and the patient preference study is paramount. That's what I heard the panel say. Is that correct, Dr. Lange?

Dr. Lange: I believe so.

Dr. Zuckerman: Thank you.

Dr. Langue: All right. Warren, question number six.

Question Six

Dr. Warren: Question number six is 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 indicated to reduce blood pressure in patients with uncontrolled hypertension, who may be inadequately responsive to, or who are 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. Lange: Dr. Hirshfeld.

Dr. Hirshfeld: I wasn't drawn so much to the "inadequately responsive: modifier as the word "may". Does this mean that if someone decides that you're inadequately responsive, therefore you're eligible according to these indications? I think that's a pretty fuzzy word, as opposed to "are", "who are".

Dr. Lange: Okay. These points are well-taken. Thank you, John. Dr. Somberg.

Dr. Somberg: I think Dr. Hirshfeld's suggestion is very important. But I also think that the indication for use should say that it's no more effective than pharmacologic therapy. This sort of suggests that if you are intolerant to medicines, or if medicines are ineffective, this will be effective. As we see, the higher the blood pressure, probably, the less effect size you see. So, I think it should say that it could be used for people who are, for instance, intolerant to medicines, as it says here, or who don't want to take medications. But it shouldn't give the impression, the indication that it is to be used because medications fail and therefore this will work. I think that's going too far.

Dr. Zuckerman: Dr. Somberg, could I specifically ask you a question? Your points are well taken. Are you suggesting that the first part of the indication states, "The Paradise uRDN System is indicated as an alternative to reduce blood pressure" so that you imply that's one potential tool in the toolbox? Can you be a little bit more specific?

Dr. Somberg: I'd have to think about the exact wording, but I don't want to say it's an alternative either. I want to say it's an alternative modality.

Dr. Zuckerman: Thank you

Dr. Lange: Dr. Wittes?

Dr. Wittes: There's a big difference between inadequately responsive because that sounds like people are on the drug and don't respond, and intolerant. I wonder whether in the non-Trio study, the other two studies, the Solo and the larger study, you actually collect information on whether the people had been inadequately responsive or intolerant? Is there any information on that?

Dr. Lewis: I asked that question and they said there wasn't.

Dr. Wittes: Then I don't know how this becomes operative without that information.

Dr. Lange: In fact, 20% of the people that were intolerant or inadequately responsive, were on no medications at the end of the study. Dr. Nachman?

Dr. Nachman: Yes. I want to echo what was discussed earlier, but the other thing that I am a little concerned about this indication for use is that it really is centered exclusively on blood pressure control, on hypertension. In fact, in the studies that have been done here, there is a large proportion of patients who have hypertension, severe hypertension, that were excluded from the studies and are arguably at greater risk of the procedure. So, we don't know how beneficial the procedure would be. I'm thinking about the very small number of patients who have a GFR of less than 60, they're going to be exposed to radiocontrast in a way that could decrease the safety. And there were very few patients with diabetes. So, I think that the labeling needs to be more granular than say,

"You have high blood pressure, therefore you qualify for this procedure." Really reflect who was studied in those studies and exclude patients for whom the safety and the benefit have not been proven.

Dr. Zuckerman: Okay. Dr. Nachman, in the warnings and precautions section of the labeling, certainly, your very important points need to be captured. But this question is really focusing on what is a general indication for use that is not entirely prescriptive, but somehow, captures the way this alternative modality should be considered. If subsequent panel members could first concentrate on the general indications for use before getting into some of the important specifics that Dr. Nachman mentioned, that would be very helpful.

Dr. Lange: Dr. Starling, Dr. Allen, Dr. Lewis, Deneen, Bill, and then Dr. Bates. So, Dr. Starling.

Dr. Starling: Yes, thank you. I view this as an option. Another point I would like to raise, one that Dr. Zuckerman is very familiar with who will be adjudicating this inadequately responsive or intolerant? In cardiology, we have many instances now, where a heart team is involved in decision-making. So, the question I raise is, as far as the labeling is concerned, would there be any language to indicate the process whereby this phrase in quotes would be adjudicated?

Dr. Zuckerman: Dr. Starling, that's a question for the Panel, similar to TAVR labeling, which recommends the use of a heart team. Is there a role for somehow placing a hypertension team evaluation in the indications for use? You'll need to confer with your other Panel members here.

Dr. Lange: Randy, before we start asking "yes" or "no", hypertension team?

Dr. Starling: Yes.

Dr. Lange: Okay. Thanks. Dr. Allen, I'm going to turn it to you and let you speak. Then, I'm going to ask you the same question.

Dr. Allen: I have a hard time with the fact that the studies that we've looked at, actually represent the IFU, as written here. In the Solo and Radiance-II trials, I don't see that these people

had uncontrolled hypertension. As Dr. Lange pointed out, 20 or 30% of them weren't on any blood pressure medicine at all. We've already had a robust discussion about the durability, and in fact, most of these patients are responsive to medications, as long as they take them at both six and 12 months. Bram is going to ask me, “How would I reword this?” I'm trying to think of that on the fly, but I don't think that the IFU is for uncontrolled hypertension or for inadequate response. So, in answer to Richard's question, if you need some type of blood pressure team to help decide that, probably you do. This is a lot like Watchman or generic LAA closure devices where someone really decides whether a patient can or can't take a blood thinner.

Dr. Lange: Thanks, Keith. Dr. Lewis, do you have a lot of experience with these?

Dr. Lewis: Yes. I actually agree with what the other panelists have said, that the way this is worded, implies information that wasn't collected and also that it's particularly effective in the population in which it was least effective, which was the Trio population. In Solo, by the way, included people that were well controlled, on zero, one, or two medicines. So, actually, the available data of efficacy is in people who don't look at all like this sentence. I don't know the exact wording, although I did think about this a lot over the weekend. But I think some metric of what this is going to do is more important to include in the communication to a physician. So that it's clear, that it will not take every patient on four drugs and have them require none. How that's done, whether it's done with a percent of people that achieve a certain goal or a mean, there has to be some communication of what would be expected in any basically hypertensive that receives this. Also, you did exclude people in Solo and Radiance who had any history of cardiovascular events. I know in Trio, it was a time-related one. That's an important consideration. I guess we don't know what removing the sympathetic tone would do in someone who had a history of heart failure or an MI. In fact, in heart failure, you could argue they might need their sympathetic tone,

down the road. So, I think a better way for the physician to know what he's offering a patient, is to indicate the magnitude of the effect.

Dr. Lange: In your opinion, Dr. Lewis, is that best handled with a hypertension team or in the absence of one?

Dr. Lewis: I'm sorry, say that again?

Dr. Lange: Is that best handled with a hypertension team, or in the absence of one?

Dr. Lewis: Do you mean who should determine the language or that you're recommending a hypertension team to determine if the procedure should be given to someone?

Dr. Lange: The latter.

Dr. Lewis: Yes. That's similar to a REMS, a type of requirement for something. I don't know what a hypertension team is at every institution. Is it somebody walking in and talking to their partner? Is it a real team? Do you require a REMS type of situation where some committee looks through, and knows the data well enough to determine it? I don't know, that seems to be a big hurdle.

Dr. Lange: Okay. Thank you. Deneen, William, Eric Bates, Robert Yeh, and John Somberg. Deneen Hesser.

Mrs. Hesser: In looking at the first sentence in the indication, I've repeatedly read to myself the words “as an adjunctive therapy is indicated to reduce blood pressure.” I'm getting concerned that we have totally left lifestyle modification out of this, and we need to let both physicians and patients understand that there is likely going to be a need for continued medication at some level. I just don't want to see this read “as a replacement for other therapies.”

Dr. Lange: Great. Thank you, Mr. Vaughan.

Dr. Vaughan: I like Deneen's comment, but also speaking for the over-75 crowd, I'm pretty sure nobody above 75 was included in these. I would hope, if this product is approved, that there'd be some monitoring of what it's like to be done on older people.

Dr. Lange: Okay. Thank you for that comment, Dr. Bates.

Dr. Bates: My concern is with definitions. We've got "uncontrolled hypertension", "inadequately responsive", and "intolerant", but we haven't defined any of those words. So, is "uncontrolled hypertension", 140, 135, or 130? Is "inadequately treated", three drugs, four drugs, five drugs? Is "intolerant anti-hypertensive medications", two out of seven, five out of 10? I might find this more compelling if we could somehow quantify or define what these terms are so that we could more precisely give direction on what a clinical indication might be.

Dr. Lange: Eric, I appreciate that and I share your comments and perspective. I realize this is not going to be in the label, but what would you label as "uncontrolled"?

Dr. Bates: That's probably what we need to debate because we're clinically still debating 120 versus 130 versus 140, especially in older patients and patients on polypharmacy. To me, clinically, I think the three-drug definition of resistance is historically a term that's not clinically useful because I can add a beta-blocker, add spironolactone, and then think about an alpha blocker before I have to ask a nephrologist or a hypertension doctor for assistance. Intolerance is subjective. For example, with statins, if you tell them they're going to have muscle pains, they're going to have muscle pains. You can tell them they're not going to have muscle pains, they don't. So, it's hard to define, but this clearly is not defined well enough to give clinical direction to a practitioner.

Dr. Lange: Okay. I've got two more comments, Dr. Yeh and Dr. Somberg. And then I'll try to summarize. Dr. Yeh.

Dr. Yeh: Thanks. My overall guiding principle for thinking about the wording is that the population that was studied and using the same criteria that were used to define the study

populations, for which we have evidence, should be reflected in the indication for use. In some ways, they've been more stringent here than they might even needed to be, based on the comment that was made before, which was that there were some patients in here who really were probably controlled on a medication. And the question in my mind is, "Should those patients who could be reasonably controlled medications be allowed the potential option of choosing a therapy like this or that be indicated for use?" Which it was, for example, in the Solo study. If we stick to that idea, that we should be faithful to the studies, then the other part of it is that the studies did not involve a hypertension team to evaluate those patients. Maybe I'm more of a minimalist in terms of what the FDA should be arbitrating here, but that's a decision for professional societies, or potentially a discussion for CMSs about reimbursement. But I don't think the discussion of efficacy and safety based on these studies should trigger our thinking about a hypertension group to make that decision when that's not what was studied and involved in the generation of these data. These are some of my thoughts.

Dr. Lange: Thank you, Dr. Yeh. Dr. Somberg and Dr. Lockhart.

Dr. Somberg: I wanted to say that the overwhelming majority of patients were treated for hypertension by general practitioners, then internists, and on occasion referred to cardiologists or nephrologists when they are most difficult to treat. So, I think there's already embedded in the practice of medicine, a heart team, and that has been shown with the recruitment here. The recruitment was very difficult because many professionals in the teaching hospitals where I think most of this was done or the referral centers, were satisfied with their therapeutic approaches and weren't referring hundreds of patients. They really had to scrounge for patients. So, I think with the community physicians and then the referral base in a hospital, the interventionalist is either going to have to advertise on Facebook or he's going to be part of a heart team, which will select the patients that he will receive.

Dr. Lange: Thank you, John. I appreciate those comments. Dr. Lockhart.

Dr. Lockhart: I was trying to take the wording into a different direction, just for consideration, because obviously what we're seeing here doesn't work. Something along the lines of "is indicated to reduce dose burden in patients with hypertension resistant to multi-drug therapy." I see Somberg is shaking his head, so I'll stop there then.

Dr. Lange: No, don't let him influence you. Keep going.

Dr. Somberg: I apologize. There are a lot of problems with the indication wording here, but if we just say, "It's people who were unresponsive to therapy" or "They had resistant hypertension", that wasn't what these studies that showed efficacy, which I believe showed efficacy, really evaluated. So, we can't really change because we only want to limit this to people who have markedly inadequate responses to medications or absolutely can't tolerate them. If we limit the indication to that, we're changing the interpretation of the studies, because that wasn't what the studies did. So, this is very difficult, but I just want to say, from hearing everybody, there's an unease with this indication, probably, because it's going to point people in a direction that the studies really haven't led. So there has to be a careful rethinking of how to word the indication.

Dr. Lockhart: I'm just trying to get to the point that this is not a replacement. This is an alternative as a supplement to medical therapy and the goal is to possibly reduce the amount of medications, as opposed to a permanent replacement.

Dr. Lange: Dr. Zuckerman, I'll summarize. I haven't heard from anybody who feels comfortable with this definition. I have heard, and I think Dr. Julia Lewis described it well, being able to describe the expectations or the magnitude of the benefits. People used the word "alternative" and the word "adjunctive", not leading people to believe that this, in and of itself is going to control their hypertension. You may end up convening another panel to walk you through this, but I don't think anybody who has spoken feels that this is the patient population they studied.

I'll take it even further. I know that somebody mentioned first who it didn't, and you tried to focus on who was enrolled, but who they excluded is incredibly important: congestive heart failure, cardiovascular disease, stroke, and diabetes. Without those caveats and adding this out here, then you include a bunch of people being treated that were really never a part of the study.

Dr. Zuckerman: Okay. Dr. Lange, let's try to summarize it in a series of steps on what we heard from the panel and correct me if I'm wrong. The first thing is that this "Indications for use" does not cut it. In the first sense, the Paradise uRDN System is indicated as a "possible adjunct" or "alternative" to reduce blood pressure in patients. The second part would be a better description of the patients in the Radiance-Solo and Trio trials. In the warnings and precautions section, there would be further elaboration of who was studied and where there is limited data, as Dr. Nachman pointed out, for patients who have GFRs less than 60 and many other important subpopulations. There could also be some mention that this needs to be a careful decision discussed with a patient. Does that cover the general gist of Panel comments or would you modify that?

Dr. Lange: To Dr. Lewis's point, you say "it may reduce blood pressure", in other words, "It may reduce medication usage."

Dr. Zuckerman: Okay.

Dr. Lange: Does anybody else want to comment about what Dr. Zuckerman has mentioned already? Something that you want to add?

Dr. Bates: Can I just ask a quick question again on how you define "indicated" from a regulatory standpoint? From a clinical guideline standpoint, that would be a word used to support a Class 1 recommendation, suggesting that you should do it. I assume in the regulatory language, that might have a different indication. Do you have to have that word in the package insert to justify the use of the procedure?

Dr. Zuckerman: Okay. It's a different indication. It does not imply Class 1 data. It's just a general construct suggesting where this particular device may be useful.

Dr. Bates: Do you have any optional words or does “indicated” have to be in there?

Dr. Zuckerman: What word would you substitute with, Dr. Bates?

Dr. Bates: I don't know what your rules are. I don't have 25 years for this. This is my first day on the committee.

Dr. Zuckerman: “Indicated” is usually the word that's used with no implications that it refers to AHA guidance documents.

Dr. Bates: Okay. That's what I assumed. Thank you.

Dr. Lange: Dr. Lewis?

Dr. Lewis: Two quick things. It would still be a benefit, in the indication, to include something about the magnitude of it. This isn't like someone with primary hyperaldosteronism, where you're going to take it out, and they'll never need another blood pressure medicine again. There should be some indication about that because a lot of practitioners aren't going to read past this sentence. I also want to say that I think there is a difference between patients who were excluded from the trial based on the exclusion criteria and patients who were poorly represented. About the excluded patients, we really know nothing about and for some reason, those were exclusion criteria. I assume that there was a concern about having those patients. I just would keep in the back of your mind that those are two different groups of people.

Dr. Zuckerman: Thank you.

Dr. Lange: Dr. Zuckerman, does that give you sufficient guidance or heartburn?

Dr. Zuckerman: No. It's very good guidance and it's something that the agency can really chew on. Thank you, Dr. Lange.

Dr. Lange: I wish we could've come away with some indications. Probably the best I can do is a proton pump inhibitor at this particular point. Dr. Corriere, Deneen Hesser, and Dr. Saville, and then we'll move on to the next question.

Dr. Corriere: I just wanted to briefly comment on what made me concerned with some of the public forum people who were patients. They really seemed to perceive that this was a substitute and come off medication and I think that's super relevant to the conversation we just had. I agree with the discussion.

Dr. Lange: Thank you. Thank you, Ms. Hesser.

Mrs. Hesser: I'd like to ask about a comment I just heard from Dr. Zuckerman, I believe, about approving this as a Class 1 drug device. Is that where this is headed instead of a Class 2 with special controls?

Dr. Zuckerman: No. Dr. Bates was referring to whether the word “indicated” in an FDA label implies that the data for FDA approval refers to the facts similar to an AHA guidance document, that there are Class 1 randomized trial data. The word “indication” used in FDA labels has nothing whatsoever to do with AHA guidance documents.

Mrs. Hesser: Okay. Thank you for that clarity. Okay. I appreciate that.

Dr. Lange: Dr. Saville, it looks like you have the last word here, sir.

Dr. Saville: Yes, thanks. With respect to the first part of this, that Dr. Zuckerman mentioned, this idea that this innovation may be helpful for reducing blood pressure and/or the number of medications, does there need to be something about the expectation of timing? Because when I read that, I think this is forever. I'm going to reduce these two things. The data support, the short-term benefit, and we don't really have any sort of evidence on the long-term benefit. Does there need to be something in the label that indicates that, or is that something that's handled somewhere else?

Dr. Zuckerman: No, that's a consideration that will be relevant and will also, if appropriate, push the sponsor to get us better, longer-term data if this device is approved. Thank you, Dr. Saville.

Dr. Lange: Question number seven.

Question Seven

Dr. Warren: 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. Lange: Dr. Corriere?

Dr. Corriere: I was surprised by the really low incidence of identifiable problems. I thought their imaging was pretty aggressive, and I really liked it. I was initially going to ask why they chose a 70% cut point, but I was impressed they had really low or even, 50% or less. I think it's difficult to make an imaging recommendation based on what they showed us.

Dr. Lange: Okay. Dr. Somberg?

Dr. Somberg: Right now, we have a small number of patients, not in the thousands. So, it would be appropriate to recommend ultrasound, which picks up 70%, I think, for a greater lesion, at 12 months, in patients who undergo this therapy. That might change over time.

Dr. Lange: Okay. Thank you. Dr. Allen.

Dr. Allen: I'm very comfortable with the data that shows no damage to the renal artery. And I would suggest if this device were approved, that imaging be part of the post-approval study. But I don't believe it needs to be in the labeling. As it's generalized, I don't think burdening practitioners with mandatory or recommended imaging is necessary.

Dr. Lange: Okay. Since this is a “yes” or “no” question, I'm going to ask for a show of hands. This is not necessarily a vote, but your particular opinion. Those of you who feel like routine MRI

or CT imaging should be done six to 12 months afterward, routinely, let me see your hands. Those of you who don't feel that's necessary, let me see your hands. Okay. I'll ask the same thing for the ultrasound. Do individuals feel that ultrasound should be performed six to 12 months later, routinely? Show of hands. Two. Three. Those of you who do not feel it needs to be done. 1, 2, 3, 4, 5, 6, 7. Okay. Bram, do you need any other clarification?

DR. Zuckerman: Yes, if you could just summarize for the record what the votes were so that we have ad infinitum.

Dr. Lange: Sure. When asked if a routine MRI or CT scan should be recommended, there was nobody in favor of that. With regard to routine ultrasound, the majority of individuals, that is about three-fourths, two-thirds, said that should not be recommended either.

Dr. Zuckerman: Thank you.

Dr. Lange: All right. Question number eight.

Dr. Warren: Question number eight.

Dr. Zuckerman: Excuse me, but we didn't do 7 B, which is "any other labeling recommendations." I think that Dr. Lewis, Nachman, and others have provided other suggestions that would be appropriate for warnings, and precautions, in a detailed discussion of the clinical trials and in the clinical trials section. But are there any other suggestions for what should be in the FDA label, if this product is approved?

Dr. Lange: Thank you. Dr. Corriere, then Mr. Vaughan.

Dr. Corriere: Was there going to be a pre-procedure imaging recommendation? And is duplex adequate for that, if the answer is "yes."

Dr. Lange: Matt, the answer would be "no." The anatomy needs to be defined ahead of time.

Dr. Corriere: Is that an imaging recommendation?

Dr. Lange: Yes. Matt, anything else you think should be on the label?

Dr. Corriere: No, I was just wondering without something very directive along those lines, if people were going to be just going with no imaging prior to an angio to do this procedure. Forgive me, this is my first panel, so I may be too much of a "Chicken Little" about that sort of thing.

Dr. Lange: No. In fact, Matt, I would follow the recommendations or the procedure in the studies, and that is obviously, anatomic definition beforehand, you need for sizing, accessory branches, and they already have site training that has been provided. The sponsor has recommended a post-approval study. Bram, I would say that a certain number of the training should be listed and a certain number of proctored cases as well. I would suggest that what the sponsor has offered would be adequate.

Dr. Zuckerman: Thank you.

Dr. Lange: Mr. Vaughan, you had your hand up, sir.

Dr. Vaughan: I mentioned earlier a press release from the company about how this should be done in specialized centers and so forth. I know this is just on renal imaging, but I would urge the FDA to maybe ask for a review of what some of the better OECD countries are doing in terms of labeling and see what's out there.

Dr. Lange: Okay. Thank you. Any other comments regarding anything else that needs to be added in terms of site training, expertise, imaging, or anything else in terms of FDA recommendations? Dr. Zuckerman, does that provide sufficient or is there additional information that you'd like?

Dr. Zuckerman: This is great. We can go on to the next question.

Dr. Lange: Okay. All right, Dr. Warren.

Question Eight

Dr. Warren: Sure. Dr. Lange, you had noted at the beginning that there were eight questions. We actually have nine. So sorry for misleading anyone into thinking we only had eight. Number eight.

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

Dr. Lange: Dr. Somberg.

Dr. Somberg: I'll break the ice by saying that I think the benefit-risk profile has been established that there's a benefit and the risk is very minimal. I think it's efficacious at two months, the studies weren't designed to show it's superior to drugs beyond that point. I believe the effect is durable because the blood pressure stays down over time, but I think it's important to note that the effect size is small. I remember when renal denervation was thought to be something that would cure resistant hypertension and one would need no therapies as follow-up. These very well-done studies show that's not the case, while it's another modality. It can be looked at like a drug. Just as other drugs, it probably has some side effect profile, like drugs do as well. So, it's not a Panacea, but it's certainly an option and I think it should be approved.

Dr. Lange: Okay. Dr. Allen.

Dr. Allen: Yes. I have a little different take on it. This is always a tough question on panels when the risk profile is, in my opinion, very low. I don't think this is a risky procedure and that always makes you lower your threshold for benefit. And while I agree there appears to be some acute benefit, I don't think that there is a durable benefit because the data is confounded by the up-titration of medications in both groups and there's very little difference; 0.2 or 0.3 drug differences between the two groups. So, the risk is very low, but I think the benefit, if there is any, is acute, it is not durable, and the benefit is marginal.

Dr. Lange: Okay. Thank you. Dr. Starling.

Dr. Starling: Thank you. Randall Starling. I'm personally comfortable with the risk-benefit. If this device becomes approved, I think there will be a niche in appropriate patients. Long-term surveillance is important as it has already been discussed.

Dr. Lange: Okay. Thank you. Dr. Yeh.

Dr. Yeh: I think the totality of the evidence does favor that there is an established positive benefit risk profile. As it has been said, the risk profile is extraordinarily low. The average treatment benefit might be modest, but I think it's highly variable and that's one thing. That's true also for the medication numbers that we're looking at. The average medication number won't capture the degree of potential benefit for maybe a smaller but significant number of individuals. I think we may be underestimating both the magnitude and durability benefit for some people. But I think that those will be important considerations in post-market evaluations to better understand the sort of heterogeneity of treatment benefit and who might benefit the most.

Dr. Lange: Okay. Thank you. Dr. Damluji.

Dr. Damluji: Yes, I agree with Dr. Yeh. There is evidence that this treatment is beneficial at two months. Now, you can disagree on the magnitude of this benefit, but there's a big space in defining super responders to this therapy. The safety profile of this therapy is favorable compared to all the treatments that are already approved. So, I think I'm in favor of this therapy.

Dr. Lange: Okay, Dr. Wittes?

Dr. Wittes: I'm ambivalent. I agree with everybody that the risk seems very low, but the benefit seems very low, too. So, there's my ambivalence. It's hard for me to judge risk-benefit when both seem very low.

Dr. Lange: Thank you, Dr. Lockhart, Dr. Lewis, and Dr. Saville.

Dr. Lockhart: As everyone's saying, it seems low risk and it seems that in the population, it's a low benefit. But I think until we have a larger number of patients being evaluated, we're not going to see that niche of the patients who are more responsive. Whether it's African American patients, age range, or obesity, we just don't know that from this small data size.

Dr. Lange: Thank you, sir. Dr. Lewis?

Dr. Lewis: Yes. I think the thing that really sways you is that the risk of the procedure, although it doesn't include the unpleasant parts of it, is very minimal. There is some, at least short-term, benefit. As long as that's well communicated in the indication, then the individual doctor can decide about presenting it to a patient, hopefully in the most informative way, that there are patients for whom this is going to be a beneficial option. I want to congratulate the company on the technology and the apparent safety of it.

Dr. Lange: Thank you, Dr. Lewis. Dr. Saville.

Dr. Saville: I agree with everything that's been said on both sides. I think that there are certainly no safety concerns, it's low risk, but also, as Dr. Wittes says, it's also low benefit. There is certainly a stronger benefit in the short term, and you've clearly proven that. To me, the questions are on how important the durability of effect is and how important it is that we have a long-term benefit. In the spirit of breakthrough devices, the pathway of timely access for patients with unmet needs, we're going to accept greater uncertainty in a pre-market submission in exchange for timely post-market data collection. So, I think all these questions go into that. It's not an easy decision, but a lot of this comes down to what's important clinically. Do we want to give timely access to something that will certainly provide some short-term benefit in hopes that there'll be long-term benefits? Or, do we want to wait until we know for sure that there's long-term benefit before we approve this or before we give this to patients?

Dr. Lange: Okay. Thank you, Dr. Saville. Dr. Cetnarowski, and then Dr. Hirshfeld. Go ahead, Dr. Cetnarowski.

Dr. Cetnarowski: Thank you. When we think about benefit-risk, we probably just migrate to safety and efficacy. I think it's important to bring in the totality of some of what we heard today, meaning, for example, the unmet medical need, the concerning trajectory of enhanced data of controlled hypertension, and also the patient preference data that we heard. So, when you look at

benefit-risk, the point for consideration of the voting panel is to really bring in the totality of the picture into play with other variables, like patient preference and overall need.

Dr. Lange: Okay. Dr. Hirshfeld and then Dr. Zuckerman.

Dr. Hirshfeld: I think I agree with what everybody else has said, that the small risk relationship gives somewhat of a pass on having a small effect size and heterogeneous effect on benefit. Nonetheless, I think this would be a good tool to have in the toolbox. I hope that the clinical community and the sponsor are going to be responsible for how they use it and how they promote it.

Dr. Lange: Okay. Thank you, Dr. Hirshfeld. Dr. Zuckerman.

Dr. Zuckerman: Okay. Dr. Hirshfeld's summary comments are extremely helpful, and I would bring us back again to the comments made by Dr. Saville and Dr. Cetnarowski. This is a breakthrough device, and by virtue of that designation, the agency could potentially live with greater uncertainty, with the caveat that important questions are quickly and largely resolved in the PAS setting. And that's why question number nine now becomes very important to see if we can focus on key questions, in key design, rather than a diffuse PAS that doesn't help us out here. Thank you.

Dr. Lange: So, to summarize question number eight. There is a very low risk, people believe there's a small, modest benefit, heterogeneity, and there are questions about durability. As you summarized, Dr. Zuckerman, the onus will be on the company, if it is approved, to be responsible in terms of both their promotion of the product and more importantly, conducting a rigorous, insightful, informational post-approval study. And we'll get to that with the next question. Does that summarize the comments to your satisfaction?

Dr. Zuckerman: Very well. Thank you, Dr. Lange.

Dr. Lange: All right. Oftentimes, with the post-approval study, we just wave our hands and let the FDA figure it out, but this isn't one of those times as the FDA's genuinely looking for us to provide some recommendations. So, let's read question number nine, and let's get about our business.

Question Nine

Dr. Warren: Number nine. ReCor proposed a post-market registry study that will incorporate uRDN subjects from <audio/video frozen> pressure, 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.

Dr. Lange: Great. I see several hands up. Dr. Hirshfeld, you first.

Dr. Hirshfeld: That's a legacy that didn't get canceled.

Dr. Lange: Okay. I'm aware that some people are about to be in a storm and one of those happens to be Dr. Saville. Ben, do you want to weigh in? You identified yourself and just in case you get knocked out, let's get you rolling, and then we'll move on to Dr. Lockhart and Dr. Wittes. Dr. Saville?

Dr. Saville: Sure, thank you. It would take some time to sit down and really think and talk through this. My first question is, what kind of data do we have that's available to compare it to? So, if we're going to do a single-arm study, what kind of data can we leverage to make some comparisons to what happens if we don't use this intervention? That's my first question. I don't have the answer right now, so I can't go through different options for that. I think there have been some arguments about using ambulatory systolic blood pressure, as the gold standard endpoint,

and for reasons I don't quite understand as a statistician, it seems like we're moving away from that, with the long-term collection of the Radiance-II studies. I feel that the post-marketing study should go back to that endpoint, if that, in fact, is the gold standard because you're going to, again, have this issue with the placebo effect that goes in there, if you look at the other endpoints. In terms of using more diverse patient subgroups, it's always a good thing if you can specify those. I don't have any great answers in terms of the best way to do that. In single-arm studies, it will be difficult to show that some patients may respond differentially to the intervention that's going to be best done, when in the context of the randomized trial and design. I'll leave the arterial imaging to the others, the clinicians, to discuss.

Dr. Lange: Okay. Dr. Lockhart.

Dr. Lockhart: As I mentioned before, I think the black population was underrepresented in the initial study. Coming from the South and seeing the health disparities that we face routinely down here, I do think we need to have better data on how this device helps the African-American population.

Dr. Lange: Thank you. Dr. Wittes?

Dr. Wittes: It seems, to me, that the first choice is whether it's controlled or not. If it's controlled, the only control is a randomized control, because otherwise, you're comparing people who choose to take blood pressure medicine versus those who choose to get this intervention. My guess is that a randomized study of this size is not in the cards. I don't see how a single-arm study can answer the question that we're all struggling with, which is, "What is the long-term durability?" The only thing it can ask reliably, or information that it can get reliably, is the description of what kind of medications and how many medications people need, to control their blood pressure, if their blood pressure can get controlled. And that should give some kind of insight into durability. The easy questions, yes, a more diverse patient subgroup would be good. I'm less worried about

office blood pressure in a study of this size. I think ABPM is probably not feasible, but a study of this size controls for office blood pressure. I don't know about renal arterial imaging.

Dr. Lange: Okay. Thank you, Dr. Wittes. Dr. Lewis?

Dr. Lewis: I think that the post-market study can tell us some important things. One of the answers will be that it's still safe. It will be the safety outside a PI-driven academic center safety group. The machine will be sitting there, five people will be scheduled, and the doctor who did the training might not be there. We'll get more safety information, but I think that will be a good thing. One of the things that I'm not sure I understand is who will collect the office blood pressure and the home-measured blood pressures. Is it going to be a telephonic device for home? I don't think that's what they mean, but I think it would be great if there could be at least some of this data collected by actual study coordinators. If that's their intent, that would be great. And if that's the case, then something we'll be able to see, outside of the study, is the durability of blood pressure control. Because, obviously, in the general population, our ability to succeed with just medicines is quite limited, due to costs, due to a million reasons. So, I think we'll see some durability information, as well. So, if there are things we could learn from a single-arm study, that could be quite helpful.

Dr. Lange: Okay, Dr. Lewis. Dr. Allen?

Dr. Allen: Yes. I don't think you're going to be able to do a randomized trial, but I think the important question that I would want to be answered from the post-market study would be exactly who is getting this therapy. And for me, the single-arm study would be relegated to patients who are on maximally tolerated blood pressure medicines. This device to me, should not be approved for those patients who simply don't want to take their blood pressure. And secondly then, to follow these patients and look at how their blood pressure is over time in relationship to their medication burden. What you might find is that their medication burden goes up as the kidneys reinnervate.

You might find the opposite, that over time it stays stable and the medication burden goes down. I think you will find that once you get out into the real world, where you're outside of the confines of a very rigid study, where people are really watching you, you may find that this has more "bang for the buck" than what I anticipate. But I think that's what you're going to learn from the post-market study.

Dr. Lange: Okay. Thank you. Dr. Nachman.

Dr. Nachman: Yes, thank you. So, we agree that the post-marketing study is not going to be a randomized control trial. The goal of blood pressure control is not to bring down the blood pressure, but to prevent cardiovascular mortality and morbidity. We agreed that the post-marketing study is not going to be a 9,000 SPRINT-like study where we can look at those hard endpoints. Dr. Zuckerman pointed out that blood pressure reduction is a surrogate endpoint. But I think that to answer the issue of proposed endpoints and blood pressure methods, it's important that we have confidence that what we're going to see is translatable into clinical benefit. There are precedents and data that gives us an idea of how much of a reduction in blood pressure in average ABPM, for example, is translatable into a meaningful reduction in cardiovascular morbidity and mortality. So, I would want the post-marketing study to be rigorous with respect to what kind of blood pressure we're measuring. I would suggest that it would have to be ABPM, not office measurement after Dr. Lange walked into the office and revved up the patient's adrenergic stimulus. I would propose that we have to stick to a threshold that is reasonably likely to translate into clinical benefit. I think that was presented before, somewhere around five to seven mmHg average ABPM is rigorous. It's also convincing that if it is attainable, it would translate into benefits. The other endpoint that I would be very interested in seeing is the proportion of patients, or the likelihood of patients reaching the target blood pressure, that my colleagues in cardiology can decide whether it's 135 or 140, but something that is fairly rigorous like that. Thank you.

Dr. Lange: Thank you, Dr. Nachman. Dr. Somberg.

Dr. Somber: From listening to my colleagues, I think there are two major areas of concern which I have, less about durability, but I certainly have in the Black American population. Just doing a single-arm open-label study is not going to get any more data than we currently have. I think right now the sponsors have shown that in terms of efficacy, at two months versus a Sham placebo, it's effective. But after that, we don't have that data. So, why don't they do a positive control, preferably randomized? You would get a lot of information even from a non-randomized study. You take patients who are on medical therapy and on denervation therapy without allowing any additional therapies until they have a breakthrough over a certain level. Then, they fail. If most of the patients that need the denervation arm fail at six months and at 12 months, then breakthrough therapy is no longer a breakthrough and needs to be withdrawn. But, if there is efficacy, then you would certainly have confirmation of what we have an inclination, at the moment, that it's going to be a valuable addition to therapeutics. So, I think just doing an open-label study as outlined here, is truly non-informative, and we need to have some sort of controlled, preferably randomized, but otherwise, non-randomized data, where there's a positive medical therapy control and people are considered failures if they need more medical therapy on the denervation arm.

Dr. Lange: Dr. Blankenship.

Dr. Blankenship: I agree with the majority of folks who feel that a single-arm study is really much more practical than doing a placebo arm. I think my major comment is that coming from a state where we have 42% of our population is Hispanic, and across the United States, 20% is Hispanic, as long as we're talking about subgroups, about 10% of Americans are black Americans and about 20% are Hispanic. So, we should make sure that we get representative enrollment from our Hispanic population, as well.

Dr. Lange: Okay. Thank you very much. Mr. Vaughan?

Dr. Vaughan: Yes, I'd like to make a plug, again, for including some seniors, in a subgroup. Also, and I haven't looked at this in 10 years, is the FDA Sentinel program still functioning? Would this be a good candidate for a sentinel study, Dr. Zuckerman?

Dr. Zuckerman: The Sentinel Program is a drug-related program, and generally, the Center for Devices runs PAS according to some of the guidelines we've been talking about. So, I don't think it would be applicable in this setting. Mr. Vaughan.

Dr. Vaughan: Thank you.

Dr. Lange: I've got four more hands showing: Dr. Yeh, Dr. Starling, Mrs. Hesser, and Dr. Nachman. So, Dr. Yeh.

Dr. Yeh: Thanks. There are a lot of things to be learned from a potential single-arm study. It’s not perfect, of course, but I think that sustained declines in measured blood pressures, over time, is going to be useful information to understand durability, even though it might not be what we would say is perfect information. There needs to be, probably, a separate on-label group and an off-label group. There have been a lot of comments about certain patients who weren't represented in the trials, and I suspect that those patients will be offered this therapy in the community. So, I think that a really careful attention to the understudied populations, the diabetics, et cetera, would be important, to capture a sufficient sample size. For the hard outcomes, I would say that there could be a different study design. Once you start introducing the blood pressure measurements, it's hard to power that sort of study for hard outcomes, because the sample size is so much larger. But hard outcomes can be generated with more pragmatic approaches, including linkage to claims, et cetera. So, that could be a separate study altogether, or a subgroup of another, to get more information on the hard outcomes. Finally, I don't think there are just randomized trials and then single-arm. There's a whole host of study designs that could be thought about. It would take more time to think about whether or not the opportunity for approval, or even the

dissemination of the device at different centers presents opportunities for designs like step wedge, rollouts, et cetera, that maybe not be randomized, but quasi-randomized, more able to get a control group to understand the effectiveness.

Dr. Lange: Thank you.

Dr. Zuckerman: Okay. So, Dr. Yeh, I think you've hit all the criteria, but do you have any comments on the need for imaging follow-up?

Dr. Yeh: I think, at least some subgroup, maybe these 500 patients, should have whether it's ultrasound, maybe ultrasound imaging follow-up for the concern about long-term renal artery stenosis. I know the numbers were very low, there was one patient who had a 50 to 70%, I think. Even if it's 0.5% or 1%, that's clinical information that we're going to want to know about if it pops up and I don't think in the sample sizes that we've seen, we know that for sure. So, I would love to see some renal arterial imaging in some number of patients, larger than what has been done.

Dr. Zuckerman: You mentioned specific subgroups, and others have, specifically African Americans, Hispanics, elderly, diabetics, I'm assuming a greater number of women. But are there any other subgroups that you would think are important?

Dr. Yeh: I think many of those are the important ones: patients with coronary cardiovascular disease like heart failure, patients with diabetes, and the extremely elderly. Those are just some off the top of my head looking at it.

Dr. Zuckerman: Thank you.

Dr. Lange: I wrote them all down, but another subgroup is for those with a GFR of less than 60. Dr. Zuckerman: Good.

Dr. Lange: Dr. Starling, Ms. Hesser, Dr. Nachman, Dr. Saville, and then we'll wrap it up.

Dr. Starling: So, I'll give a quick, but complex answer. I would view this as a registry. I would focus on those meeting a definition of uncontrolled hypertension, collect the patients that had renal

nerve denervation, and potentially, collect a population that did not do ambulatory blood pressure monitoring at specified intervals. I would check renal function periodically and use that as a trigger for imaging. I would collect the medication usage and I would consider extending beyond two years and, definitely, collect major adverse cardiovascular events.

Dr. Lange: Okay. Mrs. Hesser.

Mrs. Hesser: On my patient wish list, we've already addressed the expanded demographic subgroups, patient-reported outcomes, let's not lose those, the need for patient education materials, and the inclusion of a defined physician training program.

Dr. Lange: Thank you, Deneen. Okay. Dr. Nachman and Dr. Saville.

Dr. Nachman: I'm assuming that if we're talking about expanding the patient population to those who are either excluded or underrepresented, I'm not sure that I'm very comfortable with the idea of doing this in an uncontrolled setting. The issue of safety is going to be different for these patient populations, and we can't take it for granted that the safety here is going to translate into safety there. That's one comment. For a registry-type follow-up study, I think that there are other measurements that could be useful. I echo Dr. Starling's comment that we need to not just count the number of medications that they're taking, but what kind of medications they are taking. Dr. Bates raised the issue that we use different medications for different indications and some of these medications have benefits that go well beyond just blood pressure reduction. Aldosterone antagonism, and SGLT 2 inhibitors were not mentioned today. So, I think we need to look at those and what effect they might have. If it is an open study, it's an opportunity to look at other outcomes or other measures of benefit, outside of just blood pressure: the kidney, the heart, the cardiac echoes, and LVH. For the kidney, I noticed that there was no change in UPCR, but nobody had proteinuria as the average UPCR was 0.1. So, that's another group that we need to be careful about how we study them, but it should be measured as well. Thanks.

Dr. Lange: Dr. Saville?

Dr. Saville: Thanks. Just a couple of comments. First of all, I agree with Dr. Somberg that I don't think a single-arm study is really going to give us that much more information than we have right now, regarding treatment durability, unless, of course, you have some registry and some other data. I like Dr. Starling's idea of having your own registry if you don't have access to the registry for comparisons. But if you collected both data, those with intervention and those who choose not to, even though it's not randomized, there are analyses you can do. Propensity scores can be done for some of those longer-term comparisons. But I don't think this idea of getting a post-marketing study is going to give the FDA additional data, quickly. I don't think that's going to necessarily solve that. With respect to the sample size, no one's really commented on the sample size. The number 500 seems to be a number that someone threw out and said, “Let's do 500! That seems to be something we could afford. We do. I’ll put my finger in the wind and that seems like a good number.” Usually, the trial sample size is going to depend on your objective so, typically, in a clinical trial, you'll have a powered study. You'll have some assumptions about what treatment effect you're trying to detect, and you come up with a sample size. It's not a perfect science but you have some justification for that sample size. Here, I don't know what is that justification. Perhaps, it's going to be that you think about what your objective of the study is with respect to looking at safety events. Maybe it's the precision of estimates that you get on the mean reduction of blood pressure or maybe some sort of sustaining effect. Perhaps it’s the precision around the number of medications. It could also just be the minimum number of participants in certain subgroups, African Americans or Hispanics, and these underrepresented minorities that you want to make sure you have sufficient data on. Then, you plan the full study to have a certain sample size of all these other subgroups to be well-represented. That's all. Thanks.

Dr. Lange: All right. I'm going to try to summarize what have been some outstanding comments for this post-approval study. There were at least two measurements that I think everybody harped on. One is to have accurate blood pressure measurements that are reliable, and you can trust. And to that end, the ambulatory blood pressure was the blood pressure of choice. The second is a very detailed list of medications, numbers, types, and doses. The objective will be to make sure the blood pressure is better controlled, in which case, we're looking for an absolute reduction, or we're looking whether we've reached the target blood pressure, or whether it's affected medications or not. Without reliable information about those two domains, this single-arm study would not be very helpful. There's been a tremendous amount of interest in looking at the underrepresented patient populations: Blacks, Hispanics, once you mentioned diabetics, congestive heart failure, cardiovascular disease, chronic kidney disease, women, and the elderly. As was mentioned, getting patient-related outcomes, patient education, and a training program, would be important. Dr. Saville summarized it very well. Instead of picking some number out of the air, it is important to decide what we expect the blood pressure change to be, what is the target blood pressure we're looking for, what percentage of people we expect to get there, and how many people we would need to see to make sure that the change in medications is meaningful. Particularly for the subgroups, it is important to make sure there's an adequate number. 500 isn't going to be enough to cover all the groups we've talked about. In good faith, if the sponsor is talking about extending this to groups that haven't even been tested yet, they have to make sure there's an adequate number of those. As Dr. Lewis first said, this will certainly tell us whether it's safe in a real-world setting, by extending this even in a single-arm study. I've tried to summarize the recurring themes. Is this sufficient, Dr. Zuckerman, or is there additional information you would like from the group? Dr. Zuckerman: That was an excellent summary of a very helpful panel discussion. Thank you.

Dr. Lange: Good. And I know that the sponsor is listening. I hope you're still listening. I hope you haven't left, yet. I know it's after five where you're at. But I would take this to heart. Those of us that have been involved with breakthrough devices take this extremely seriously. The fact that we would even consider approving a device with uncertain benefit to the patients, even with a low risk, really is dependent upon us conducting very good post-approval studies that are informational, reliable, and we act upon them. With that, we're ready to close down as that's the last question. Are there any other comments before we go onto the panel vote?

Vote

All right, so we're now ready to vote on the panel's recommendations. I would remind you there are eight voting members of this panel. I only vote if there is a tie. Although we appreciate the insights of the industry, consumer, and patient representative, we'll hear from you a little bit later. You are non-voting members, as well. We're now ready to vote on the panel's recommendations to the FDA for the ReCor Paradise Ultrasound Renal Denervation System. The panel is expected to respond to three questions related to safety, effectiveness, and benefit versus risk. Mr. Collier will now read two definitions to assist in the voting process.

Mr. Collier: The medical device amendments to the Federal Food Drug and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allow the Food and Drug Administration to obtain a recommendation from an expert advisory panel on designated medical device pre-market applications that are filed with the agency. The PMA must stand on its own merits and your recommendation must be supported by safety and effectiveness data in the application, or by applicable publicly available information. The definitions of safety and effectiveness are as follows. Safety, as defined in 21 CFR, section 860.7(d)(1), there is reasonable assurance that a device is safe when it can be determined, based upon valid scientific evidence, that the probable

benefits to health from the use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. Effectiveness, as defined in 21 CFR, section 860.7 (e)(1), there is reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results. The proposed indications for use, submitted by the sponsor, as stated in the PMA are as follows. The ReCor Paradise Ultrasound Renal Denervation System is indicated to reduce blood pressure in adult patients with uncontrolled hypertension, who may be inadequately responsive to, or who are intolerant to, antihypertensive medications, which is intended to be used in renal arteries of diameters ranging from 3.0 to 8.0 millimeters.

Panel members, we will now begin the voting process. I will read each of the three voting questions and send each of the voting members an email to respond to. Voting members, please vote for each question and remember to add your name to the ballot. Once I read all three questions, we will tally the votes and read them into the record.

Reeve-Stoffer: I'm sorry to interrupt but the indication statement that was just read is not the current indication statement. The current indication statement is included in the FDA briefing document.

Dr. Lange: Okay. Can we read that into the record, please? Let's read the correct indication.

Reeve-Stoffer: 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 antihypertensive medications.

Dr. Lange: Okay. Thank you. That's what we'll be voting on. Dr. Bates?

Dr. Bates: I would ask for a point of clarification on how to make my decision since I haven't done this before. The FDA challenged the company to prove safety and benefit, at two months, in an approved protocol they worked on together. I think the FDA and the panel agree that they have done that. Is that all we need to do to make our decision on a breakthrough device approval? When we're talking about longer term follow-up durability subgroups, there seems to be a mixed approval by the committee based on the comments. Does that get included in how we vote on these three questions for a breakthrough device protocol?

Dr. Zuckerman: Okay. Dr. Bates, at this point, you need to individually decide. Mr. Collier will read into the record the definition of safety and the definition of effectiveness. The third point for any panel member is to recommend that this is a breakthrough device. With such a device, if the device is approved, we continue to regulate products throughout the total product lifecycle. As Dr. Lange indicated, there would be a continued need for appropriate data collection. Based on the discussion, you'll need to independently make your determinations.

Dr. Lange: Dr. Wittes?

Dr. Wittes: Yes. When we vote on the question about efficacy, does a vote “yes” mean that we accept all that language? What does a “yes” and “no” mean?

Dr. Zuckerman: When we get to the definition of effectiveness, which is voting question two, it means that you are accepting that language for this particular product. Yes, Dr. Wittes.

Dr. Lange: For those who meet the criteria specified in their proposed indication, that was just read.

Mr. Collier, I'm sorry to interrupt, but with the indication that was provided by the company, please proceed with reading voting question number one.

Voting Question One

Voting question number one: "Is there reasonable assurance that the ReCor Paradise Ultrasound Renal Denervation System is safe for use in patients who meet the criteria specified in the proposed indication?" Please, vote now: "yes", "no," or "abstain."

Voting Question Two

Voting question number two reads as follows: "Is there reasonable assurance that the ReCor Paradise Ultrasound Renal Denervation System is effective for use in the patients who meet the criteria specified in the proposed indication?" Please, vote now: "yes", "no," or "abstain."

Voting Question Three

Voting question number three reads as follows: "Do the benefits of the ReCor Paradise Ultrasound Renal Denervation System outweigh the risk for use in the patients who meet the criteria specified in the proposed indication?" Please, vote now: "yes", "no," or "abstain."

At this time, please give us a moment, as we tally and verify the official votes. Thank you.

Dr. Lange: I appreciate everybody's patience, which allowed the voting panelists to cast their votes. The votes have all been received and Mr. Collier will now read the votes into record. Jarrod.

Vote Results — Question One

Dr. Collier: Thank you, Dr. Lange. On question one, the panel voted 12 "yes", zero, "no", and zero "abstain", that the data shows reasonable assurance that the ReCor Paradise Ultrasound Renal Denervation System, is safe for use in patients who meet the criteria specified in the proposed indication.

Vote Results — Question Two

For question two, the panel voted eight "yes", three, "no", and one "abstain" that there is reasonable assurance that the ReCor Paradise Ultrasound Renal Denervation System is effective for use in the patients who meet the criteria specified in the proposed indication.

Vote Results — Question Three

For question three, the panel voted 10 "yes", two, "no", and zero "abstain" that the benefits of the ReCor Paradise Ultrasound Renal Denervation System outweigh the risk for use in the patients who meet the criteria specified and the proposed indication.

The three voting questions are now complete, and I'll now turn it back over to Dr. Lange. Thank you.

Vote Discussion

Dr. Lange: Thank you, Mr. Collier. I'll now ask the panel members to discuss their votes, and if you answered "no" to any question, please state whether any changes to the labeling, the indications, restrictions on use, or other controls would make a difference in your answer. I'll call you out, so if you want to unmute, you're welcome to do that. At the end, I'll ask our Patient Representative, Consumer Advocate, and Industry Advocate to discuss. And then we'll turn it over to the FDA for some brief comments. So first of all, Keith, your votes?

Dr. Allen: I clearly voted that the device is safe. I voted "no" on efficacy based on concerns about durability, and I voted "no" on risk-benefit despite being a breakthrough device because I have real concerns based on how it's currently listed for its IFU, and how it would be used in the real world.

Dr. Lange: Okay. In that case, some changes to labeling could affect your answer?

Dr. Allen: I don't think it would affect my efficacy vote. It might affect my risk-benefit vote.

Dr. Lange: Okay. Thank you, Dr. Allen. Dr. Blankenship.

Dr. Blankenship: We are going through all three questions at once, right?

Dr. Lange: Yes, sir.

Dr. Blankenship: I voted "yes" for the first one. The major complications attributable to the procedure were the vascular access. It's likely to be largely done radial, which will take those away. For the second question, I voted "yes", I think it is efficacious. One of the points that was not discussed much is that even though there isn't much long-term difference between the Sham and the treatment, in the real world, we're going to compare it to a situation where half of the patients are non-compliant, and I think that will make the benefits compared to Sham clearer. On the third one, I voted "yes", for obvious reasons.

Dr. Lange: Thank you, Dr. Blankenship. Dr. Starling?

Dr. Starling: Yes. For question number one, I voted "yes." Based on the totality of the information, I was very comfortable with that. Question number two, "Is there reasonable assurance that it's effective?" Again, I voted "yes", and that's within the boundaries of the discussion today. As I indicated during the prior discussion, I feel that as far as a post-market registry, longer-term information and continuous monitoring, of course, are important. For question number three, acknowledging the unmet need in this population, I voted "yes", as well. Thank you.

Dr. Lange: Thank you, Dr. Starling. Dr. Yeh.

Dr. Yeh: I voted "yes" for safety. I voted "yes", as well, for efficacy, clearly, effective in the short-term, more uncertainty for the long term, but some strong signals for durable efficacy that I think the post-market studies will be helpful to confirm. And I voted "yes" for risk-benefit.

Dr. Lange: Thank you very much. Dr. Bates.

Dr. Bates: I voted "yes" three times, based on the perception or misperception that the FDA challenged the company to show safety efficacy against Sham control, as a process toward a

breakthrough device requiring further investigation. I have to say, clinically, I'm skeptical that this is an important clinical breakthrough. I'm a little worried about overuse when it's released to the clinical community. My long-term support for this device requires further information on durability, appropriate use, syndication training, and all the other things we talked about.

Dr. Lange: Thank you, Dr. Bates. Dr. Corriere.

Dr. Corriere: I voted "yes" to the first question, nothing to add to the previous discussion. I also voted "yes" to question number two. My only additional comment would be that it was effective within the parameters of the study design, but the effect was quite modest. There are very important contextual factors that require clinical judgment about whether or not to use this device based on the severity of the presentation and what alternatives there are to denervation. I agree wholeheartedly with the durability being my biggest question. That's a really important one. And I voted "yes" on question three. Thank you.

Dr. Lange: Thank you, Dr. Corriere. Dr. Damluji.

Dr. Damluji: Yes, thank you. I also voted "yes" for safety, mainly because the risks related to vascular access and closure are quite low. I also voted "yes" for efficacy, based on the collectiveness of the data from the three trials when looking at them all together. Regarding the third question, I also voted "yes" with the caveat that there will be more studies to define the high responders for this therapy, which I think may be in practice.

Dr. Lange: Great. Thank you, Dr. Damluji. Dr. Hirshfeld.

Dr. Hirshfeld: I voted "yes" on safety. I voted "yes" on efficacy with some misgivings. The misgivings are based on the small effect size and the heterogeneity of the response. But I voted "yes" because I felt that since this is a novel mechanism for treating hypertension, it's important to have it in the toolbox. I think that hopefully once it's in the toolbox, it will be used responsibly

by the clinical community and promoted responsibly by the sponsor. For question three, I voted "yes", as well.

Dr. Lange: Great. Thank you. Dr. Lockhart.

Dr. Lockhart: I voted "yes" for safety as I felt the safety profile was very good. I voted "no" on the efficacy. I think there was an effect at the two months as was the goal of the study. I feel that the duration is still at odds or we're still unclear. With the current indication as written, I think the studies really didn't cover those, referring back to our conversations on the need for improved wording of the indication. But I think there is potential to get a "yes" based on just the wording of the indication. There is a subset that I think could help patients. With efficacy versus risk, since it's so risky and there is that potential for efficacy, I voted "yes."

Dr. Lange: Thank you, Dr. Lockhart. Dr. Saville.

Dr. Saville: I voted "yes" for safety. I thought that safety was quite robust. I voted "no" for both efficacy and the risk safety profile primarily because I didn't feel comfortable voting "yes" based on the precise wording of the indication and given all the feedback that my clinical colleagues in this panel have given about their various issues with that indication and the wording. That was my main concern there. My vote could certainly be "yes" if my clinical colleagues were more comfortable with that wording. In my opinion, there's clearly a benefit. In the study population based on their inclusion/exclusion criteria, the benefit that's been demonstrated is more short-term. At least the benefit we see is clinically meaningful in the short-term, but it's unknown and unclear to me what sort of longer-term benefit we may have. But in the spirit of the breakthrough devices, this could get my vote for "yes", if it had the right wording for the indication.

Dr. Lange: Thank you, Dr. Saville. Dr. Somberg.

Dr. Somberg: I voted "yes", "yes", and "yes." My votes are predicated on the FDA working with the sponsor on the labeling. I think what has been said is very important to make changes and I

also think that the sponsor should listen to the panel in terms of all the doubts about long-term durability. They should negotiate with the FDA on a subsequent study that has a control and will definitively show long-term durability which will be very important for the commercial success of this modality.

Dr. Lange: And the last voting member, Dr. Wittes.

Dr. Wittes: I voted "yes" for safety, I abstained, and I'll tell you why, for efficacy, and then I voted "yes" for the third. My abstention was because I don't really understand the breakthrough device business. I didn't like the current indication so I couldn't vote "yes" there. And I'm worried about the duration and the small effect size. If it hadn't had a breakthrough device, which I don't understand, I would've voted "no." But because I thought the breakthrough device meant that there would be lots of information later, I abstained, and that's why I voted "yes" for the third. The post-marketing study will be very important, and I totally agree with Ben and the issues that he raised. I was a little cavalier about not saying things about the fact that the sample size just seems arbitrary, and you have to really specify what you're trying to ask, in the post-marketing study. I think that will be very important to understand this device and to use it.

Dr. Lange: Thank you. I only vote if there's a tie, so I did not vote. But I would've voted just as Dr. Saville did, "yes", "no", and "no", for the precise reasons stated. But those could become a "yes" with a change in indications or additional information. I'd like to hear from our representatives. Deneen.

Dr. Zuckerman: Dr. Langue, could I interrupt a moment just for the purposes of the record? Dr. Lewis is no longer present due to the weather conditions and did not vote.

Dr. Lewis: I'm not a voting member because I'm a SGE for CDER.

Dr. Zuckerman: Okay.

Dr. Lange: Neither she nor Dr. Nachman, who both participated, were voting members.

Dr. Zuckerman: Thank you.

Dr. Lange: Thank you. Not that we really don't care about you guys. We're glad you're here but you don't get to vote, sorry about that. And Julie, you can invite me to your panel, and you can tell me I can't vote.

Dr. Lewis: It's not my panel anymore, two terms was my duty.

Dr. Lange: All right. I really appreciate both of your expertise, so, thank you very much. Deneen, let me turn it over to you.

Drs. Hesser: Thank you for welcoming the patient perspective into this discussion today. I think that the breakthrough program helps us fail fast where we should and move forward cautiously when there is potential innovation. I'm comfortable with the way that the vote fell out, and I believe that ultimately, it reflects our conversation today. Thank you.

Dr. Lange: Thank you for your input and thank you for participating as well. William Vaughan.

Dr. Vaughan: I strongly agree with Dr. Allen and Dr. Saville, and I hope there will be strong follow-up studies. I think Dr. Somberg hit the nail on the head when he said this will not be a commercial success with the nation's payers unless they can prove durability.

Dr. Lange: Thank you for being our consumer advocate, Mr. Vaughan. Dr. Cetnarowski, as the industry representative.

Dr. Cetnarowski: Yes, thanks. From an industry standpoint, I find it rewarding that, generally, the panel thought that the sponsor demonstrated reasonable assurance of safety and effectiveness and an overall acceptable risk-benefit profile. I think some of the pending questions, whether it's cardiovascular outcomes, durability, ideal target population, or perhaps even medication reduction or elimination, those things are very important, and we can certainly hope for some of those answers in the post-marketing study that comes forward. And so, thank you.

Dr. Lange: Thank you. At this time, the panel will hear summations comments, or clarifications from the FDA, and you have up to 15 minutes.

Mr. Pullin: Hi, this is Brian Pullin. I'm the director for Coronary and Peripheral Interventions at FDA. I don't want to take much time. I'm not going to take 15 minutes since it's been a full day, and we will have another long day tomorrow. But first, I'd just like to thank the sponsor ReCor for their responsiveness to questions today and in addressing FDA's request throughout the review process. I'd also like to thank the FDA team for all their work on this device, from the initial development of the study designs, through the most recent data, in addition to all the preparation that went into a successful meeting today. And finally, we understand the commitment that it requires to serve on the panel and we're grateful to all of you for your participation in the meeting today as panelists. I'd like to thank you for a very informative discussion and a thoughtful discussion, I think your insight has given us much to consider and has been very helpful for the review team. Thank you very much.

Dr. Lange: I want to add again my appreciation and gratitude to the sponsor. The presentations were terrific, your responsiveness to the questions was good, your willingness to work with the FDA on this presentation, and in the studies, as well, is to be commended. And I hope if other industry leaders are listening, they'll understand how important it is to the panelists, to the FDA. and to the public, that we serve. So, take that seriously. I want to thank the FDA. You guys always do a terrific job. Your presentations were excellent. You have a great grasp of the information you presented to us and it's a privilege to serve on the panel. To the panelists, you guys get paid so much for doing this, I really appreciate you guys sticking it out. Obviously, this is a great public service. For the ones who are serving for the first time, I appreciate the fact that everybody feels comfortable giving candid opinions. We're not looking for the same opinion, we're looking for your perspective and this has been an outstanding panel that wrestled with a lot of issues. Lastly,

when I started this, the sun was rising over my shoulders, now setting in the other window right now. So, I think this is an appropriate time to. Stop the meeting, and we'll conclude it. And then I'll see most of you tomorrow morning, bright and early.

Dr. Lewis: Great job as chair!

Dr. Hirshfeld: We can't break up without thanking the chair for an outstanding job.

Dr. Blankenship: Yes, great job. Thank you.

Dr. Lange: Thank you. Dr. Zuckerman, any last comment?

Dr. Zuckerman: No, I just wanted to join with everyone in thanking Dr. Lange for a superb effort. Dr. Lange, please go to your baseball game.

Adjournment

Dr. Lange: All right, see you all in the morning.