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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 23, 2023

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Via Web Conference

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Patient Representative	Deneen Hesser, MSHSA, RN	Research Advocate, National Cancer Institute, Innovative Molecular Analysis Technologies Program	Chicago, IL
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	Raymond R. Townsend, MD	Co-Director of Hypertension Section, University of Pennsylvania School of Medicine	Pennsylvania, PA
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Open Public Hearing Speakers	Bertolet, Barry, MD	Private Practice Cardiologist; Tupelo, MS	
	East, Cara, MD		
	Cash, Danny		
	AbuRahma, Ali, MD	Charleston Area Medical Center; West Virginia University Charleston Division	

	Schlaich, Markus, MD	Dobney Hypertension Centre; Perth, Australia	
	Bradford, Ken		
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	Saucer, Naomi		
	Voora, Raven, MD		
	Copeland, Jessica, MD, MPH	National Center for Health Research	
	Schmieder, Roland, MD	University Hospital Erlangen, Friedrich Alexander University Erlangen/Nürnberg, Germany	
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	Robert Steinbrook, MD	Public Citizen, Health Research Group	

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Call to Order and Panel Introductions

Dr. Lange: It's August 23rd. I would like to call this meeting of the Circulatory System Devices Panel to order. I am Dr. Richard Lange. I'm President of Texas Tech University Health Sciences Center in El Paso. I'm also the Dean of the Paul L. Foster School of Medicine, and I have the privilege of chairing this panel.

I note for the record, 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 pre-market approval or pre-market application, the PMA, for the Medtronic Symplicity Spyral Renal Denervation System by Medtronic PLC, which is composed of the Symplicity Spyral multi-electrode renal denervation catheter, and the Symplicity G3 RF generator. Before we begin, I would like to ask our distinguished committee members and FDA attending virtually to introduce themselves.

Committee members, please turn on your video monitors, if you have not already done so, and unmute your device before you speak and turn off your phones. When I call your name, please state your area of expertise, your position, and your affiliation. We'll start with Dr. Keith Allen.

Dr. Allen: Hi there. This is Keith Allen. I am a cardiac as well as vascular surgeon. I'm the Director of Surgical Research and the Surgical Director of the Structural Heart Program at the MidAmerica Heart Institute in Kansas City, Missouri.

Dr. Lange: Thank you, Keith. Dr. Randall Starling.

Dr. Starling: Hi. Good morning. Randy Starling. I'm a cardiologist. I specialize in heart failure and transplantation. I'm interim Section Head at Cleveland Clinic Heart Failure, and I am a Professor at Cleveland Clinic Lerner College of Medicine. Thank you.

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

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

Dr. Lange: Thanks, Bob. Dr. Eric Bates.

Dr. Bates: Good morning. I'm formerly an interventional cardiologist for almost 40 years, and now a general cardiologist. I'm a Professor of Medicine at the University of Michigan.

Dr. Lange: Thanks, Eric, for joining us. Dr. Matthew Corriere.

Dr. Corriere: Hi. I'm Matthew Corriere. I'm a vascular surgeon and Associate Professor at University of Michigan. I'm also the director of our cardiovascular center operating rooms and a member of the Center for Health Outcomes and Policy and the Institute for Health Policy and Innovation.

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

Dr. Damluji: Yes. Hi. Good morning. My name is Abdulla Damluji. I'm an interventional instructional cardiologist at Inova Heart and Vascular Institute, and I'm the Director of the Inova Center of Outcomes Research Associate Professor at Hopkins.

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

Dr. Hirshfeld: John Hirshfeld. I practice interventional cardiology at the University of Pennsylvania for 44 years and now on Emerital status.

Dr. Lange: All right. Four years on you, Eric. Did you hear that? All right. Dr. Benjamin Saville.

Dr. Saville: Good morning. My name is Ben Saville. I'm a biostatistician by trade. I'm the Director of Consulting and Trial Design and a Senior Statistical Scientist at Berry Consultants. And my expertise is in Bayesian and adaptive clinical trial design.

Dr. Lange: Great. And, Ben, you're the only other Texan on this panel, is that right? Besides me?

Dr. Saville: I think so. Yes.

Dr. Lange: All right. Good.

Dr. Saville: We even got a little bit of rain yesterday, the first time in three months, so it was a good omen.

Dr. Lange: Dr. John Somberg.

Dr. Somberg: Good morning. I'm John Somberg. I am Professor Emeritus of Medicine, Cardiology, and Pharmacology at Rush University. I'm a cardiovascular pharmacologist and a cardiac electrophysiologist.

Dr. Lange: Thank you, John. Dr. Janet Wittes.

Dr. Wittes: Hi. I'm Janet Wittes. I'm a biostatistician. I've been involved in clinical trials for over 50 years, so that's five decades. And I'm now simply consulting on my own.

Dr. Lange: All right. Sounds like you have bragging rights now.

Dr. Wittes: The advantage of being old, right?

Dr. Lange: Dr. Julia Lewis.

Dr. Lewis: Hi. I am a nephrologist at Vanderbilt University, a Professor of Medicine and former two-term chair of FDA Cardiorenal Advisory Committee.

Dr. Lange: Dr. Patrick Nachman.

Dr. Nachman: Yeah. Good morning. I'm Professor of Medicine. I'm a nephrologist and Division Chief of Nephrology and Hypertension at the University of Minnesota in Minneapolis.

Dr. Lange: Great. It's the first time I have had the opportunity to serve with two nephrologists. So thank you guys, Julia and Pat. Thank you very much. We have our patient advocate Deneen Hesser.

Ms. Hesser: Good morning. I am Deneen Hesser, the patient representative for this meeting. I'm a hypertension patient and a nurse whose career has been in research advocacy.

Dr. Lange: Great. Thank you, Deneen, for joining us. Our consumer advocate is William Vaughan.

Mr. Vaughan: Hi. Thank you. I'm mostly retired. I do some volunteer Medicare counseling in Virginia, but a long background in consumer issues.

Dr. Lange: Thank you, William. And our industry advocate or representative is Dr. Wes Cetnarowski.

Dr. Cetnarowski: Good morning. I'm Wes Cetnarowski. I'm a primary care physician, presently the Chief Medical Officer for B. Braun Medical, Inc., and the industry representative on the panel.

Dr. Lange: Great. Thank you, Wes. Dr. Bram Zuckerman.

Dr. Zuckerman: Good morning. My name is Bram Zuckerman. I'm the Director FDA Office of Cardiovascular Devices and a cardiologist by training.

Dr. Lange: Terrific. And lastly Jarrod Collier.

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

Dr. Lange: Great. And, as such, Jarrod will now provide the conflict of interest statement, as well as the appointment to temporary voting status memo for today's meeting. Mr. Collier, it's yours.

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 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 Medtronic Symplicity Spyral Renal Denervation system by Medtronic.

The proposed indication for use statement is as follows. The Symplicity Spyral, multi-electrode renal denervation catheter and the Symplicity G3 RF generator are indicated for the

reduction of blood pressure in patients with uncontrolled hypertension, despite the use of anti-hypertensive medications, or in patients in whom blood pressure lowering therapy is poorly tolerated. 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 related contract with a competing firm to 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. Lewis's employer was awarded funding between $501,000 and $700,000 by the competing firm.

Dr. Nachman's waiver addresses his involvement in a leadership position as Councilor at Large for a professional organization that received contributions from a PMA sponsor and the parent of the competing firm. The professional organization received between $100,000 and $200,000 from the PMA sponsor, and between $1 million and $1,500,000 from the parent of the competing firm. Dr. Nachman does not receive any personal remuneration from the funds, and he is not compensated for his services at the professional organization. Dr. Starling's waiver and Dr. Yeh's waiver addressed their employer's related contract with a competing firm to the PMA sponsor. Dr. Starling's employer was awarded between $50,001 and $70,000, and Dr. Yeh's employer was awarded between $201 and $300,000 from the competing firm. Both Dr. Starling and Dr. Yeh reported that they are not involved in this 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 waiver are described in the waiver documents, which are posted on FDA's website. Copies of the waivers may also be obtained by submitting a written request to the agency's Division of Freedom of Information, 5630 Fishers 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 by B. Braun Medical Incorporated. We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an 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 the 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 23rd, 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 of the Center for Devices and Radiological Health on July 26th, 2023. Thank you.

For the duration of the Circulatory System Devices panel meeting on August 23rd, 2023, Dr. Julia Lewis and Dr. Patrick Nachman have been appointed to serve as temporary voting members. For the record, Dr. Lewis and Dr. Nachman serve as consultants to the Cardiovascular

and Renal Drugs Advisory Committee at the Center for Drug Evaluation and Research. These individuals are special government employees who have undergone the customary conflict of interests review and have reviewed the materials to be considered at this meeting. The appointments were authorized by Russell Forney, Director Advisory Committee Oversight Management staff on July 25th, 2023. Thank you.

Dr. Lange: Thank you, Mr. Collier. You just identified two special individuals, Julia Lewis and Patrick Nachman, who will be voting. And there's another special person that I forgot to introduce, and I want to apologize to Dr. Mark Lockhart.

Mark, will you please introduce yourself to the public.

Dr. Lockhart: Yes. Good morning. My name is Mark Lockhart. I'm an abdominal imager and Professor of Radiology at the University of Alabama at Birmingham. Thank you.

Dr. Lange: And my sincere apologies, Mark. I couldn't read down the list accurately. So glad you're joining us. Thank you so much. We'll now proceed to the Medtronic presentation. I would like to invite the Medtronic representative to begin shortly. I will remind the public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except as a specific request of the panel chair, and that would be me. The sponsor representative will have 75 minutes to present.

Medtronic, you may now begin your presentation. Thank you.

Sponsor Presentation — Medtronic

Dr. Mauri: Good morning. Thank you to the Chair, members of the advisory Committee, and FDA for giving me the opportunity to introduce the Symplicity Spyral System for Renal Denervation. My name is Laura Mauri, and I'm the Chief Scientific Medical and Regulatory Officer at Medtronic. I'm also an interventional cardiologist, and I practiced at the Brigham and Women's Hospital for 15 years. We're pleased to be here today to share the data supporting the

positive benefit risk profile of renal denervation with the Symplicity Spyral System to treat patients with uncontrolled hypertension.

Hypertension is a global health crisis. It remains the leading modifiable cause of death worldwide. Hypertension is a silent killer, and morbidity and mortality results from irreversible target organ damage, including heart attack, stroke, and renal failure. Underserved communities are particularly impacted, contributing to health disparities within the United States. As we'll explain today, currently available treatment options have not adequately addressed uncontrolled hypertension. The prevalence of hypertension in the US is high. Latest epidemiologic data from the CDC indicate that nearly 120 million Americans, or about 48% of the US adult population, have hypertension. Despite the very high prevalence, about 77% of US hypertensive adults have uncontrolled blood pressure according to current American Heart Association, American College of Cardiology Guideline targets.

These poor control rates lead directly to increased morbidity and mortality. In 2021, hypertension was a primary or contributing cause of nearly 700,000 deaths in the United States. Thus, uncontrolled hypertension defines a profound unmet need for patients who would benefit from new therapy options in addition to drugs and lifestyle changes. Lowering blood pressure towards target goals reduces cardiovascular risk. The beneficial effect of blood pressure lowering therapies on morbidity and mortality has been examined in multiple randomized trials, establishing blood pressure as a valid surrogate of cardiovascular outcome.

This figure shows results of a large meta-regression of 55 randomized placebo-controlled trials, including more than 265,000 patients. Each trial is shown as a circle with a size corresponding to the number of patients. The X axis represents blood pressure reductions, and the Y axis is a relative risk reduction in major cardiovascular events. The regression line is shown in red. We see a continuous treatment effect where reductions in blood pressure are

associated with reductions in cardiovascular events. Each five millimeter reduction in systolic blood pressure corresponds to a 10% reduction in cardiovascular risk. Thus, it's critical to promote blood pressure lowering in all hypertensive patients. Unfortunately, non-adherence to existing therapy options has severely limited their impact on patient outcomes, and a clear clinical need exists for alternative therapies.

So now let me briefly describe the mechanism of action behind renal denervation for hypertension. The renal nerves play a critical role in the regulation of blood pressure. Renal innervation facilitates two-way communication between the brain and kidney. Sympathetic efferent nerve signaling from the brain has a direct effect on the renin angiotensin aldosterone system. Efferent nerve signaling results in an increase in renin release, increased tubular absorption of salt and water, as well as renal vasoconstriction, which leads to decreased renal blood flow. This sympathetic activation contributes to increased blood pressure. Renal afferent nerve signaling to the brain also participates in the regulation of blood pressure. Renal sensory afferent nerve activation potentiates central sympathetic activation, resulting in arterial vasoconstriction and increased blood pressure.

The Symplicity Spyral system is a minimally invasive catheter-based procedure, which modulates renal efferent and afferent nerve activity to reduce hypertension. This effect on renal nerve activity is present throughout the daytime and nighttime. The main components of the system include the catheter with a self-expanding four electrode array and the G3 generator. This design builds on the first generation Symplicity Flex, which was a single electrode device previously approved outside the United States.

Next, I'll show a video of how these components work as part of the renal denervation procedure. The system was designed to facilitate consistent deployment, and the catheter is compatible with many commonly applied devices. The generator employs a responsive algorithm

based on real-time temperature and impedance feedback to precisely and independently control the radio frequency energy delivered to each of the four catheter electrodes to optimize procedural outcomes. Once connected to the generator, the six French compatible catheter is inserted percutaneously, and then guided to the renal artery via the abdominal aorta. Once the catheter is positioned at a desired treatment location within the renal artery, the guide wire is retracted to deploy the catheter, which naturally conforms to the patient's anatomy.

The helical shape of the deployed catheter, along with its Spyral electrode pattern, allows for four quadrant ablation, which separates ablation zones longitudinally. The natural coil of the Spyral provides consistent apposition to the arterial wall so that each of the four electrodes can efficiently deliver RF energy. A non-occlusive catheter design also allows for blood flow to naturally irrigate and cool the arterial wall, avoiding excessive heating and potential damage to the vessel wall. The Symplicity Spyral catheter is designed to treat arteries between three and eight millimeters in diameter. The proceduralist is able to select or deselect each electrode independently to precisely localize treatment. The main renal artery and extra parenchymal branches greater than three millimeters are treated. Next, the catheter is repositioned in the contralateral renal artery. Similar to other cardiac catheter procedures, the procedure is performed under conscious sedation.

Next, let me provide an overview of the clinical program we'll share with you today. The Spyral HTN Clinical Trial Program was designed to assess the safety and blood pressure lowering effect of renal denervation, while incorporating learnings from the previous Symplicity HTN-3 trial related to the earlier single electrode version of the device and the procedure and trial conduct. The current Spyral clinical program we're presenting today includes monitoring of anti-hypertensive drug use post-randomization. The OFF-MED study enrolled patients who were on anti-hypertensive medications and discontinued them prior to randomization or who were not

on medications at the time of screening. It's important to note that the OFF-MED design is the gold standard for clinical trials and hypertension when evaluating a therapy such as renal denervation, so that one can truly isolate the effect of therapy. This is why we conducted our pivotal study off of medications, to demonstrate blood pressure reduction achieved with RDN. This approach is consistent with placebo-controlled trials done for anti-hypertensive drugs.

It was also important to confirm the impact of RDN in the presence of medications. The protocol intended to keep the medications unchanged, but there is a challenge in setting patients on medications and that patients participating in a clinical trial naturally have heightened awareness of their own blood pressure and the associated risks. They may monitor their own blood pressure at home and possibly adjust their anti-hypertensive medications. This is why it was important to monitor changes in medication use post-randomization. With these considerations in mind, it's essential to look at the totality of data across studies. The OFF-MED studies enrolled patients with hypertension in the absence of antihypertensive medication at the time of randomization. The vast majority of these patients were previously treated with medications and either agreed to drug washout prior to randomization, or were off treatment at the time of screening. The pilot study enrolled 80 patients and was followed by an expansion cohort, which yielded the pivotal study.

The randomized sham-controlled ON-MED studies were designed to support the results of OFF-MED trials. The ON-MED trials enrolled patients with uncontrolled hypertension despite the use of antihypertensive medications. The Patient Preference Study provides insight into patient attitudes regarding the risks and benefits of procedural treatment for hypertension compared with medications, and the ongoing Global Symplicity Registry captures long-term safety and efficacy among a larger, broader, unselected patient population in a real world setting. The proposed indication for this Symplicity Spyral system is supported by data collected from

patients enrolled in our clinical development program. It's not intended to be the first course of treatment for patients with hypertension. Rather, it's meant to complement lifestyle modifications and the use of anti-hypertensive medication treatment from a care provider when medication can't be tolerated.

Therefore, our proposed indication is the Symplicity Spyral Catheter and G3 RF generator are indicated for the reduction of blood pressure in patients with uncontrolled hypertension despite the use of antihypertensive medications or in patients in whom blood pressure lowering therapy is poorly tolerated. Our goal for today is to share with you the positive benefit risk profile of the Symplicity Spyral system. As I noted before, hypertension is a leading modifiable risk factor for cardiovascular events and death, and yet blood pressure remains uncontrolled for many patients despite the awareness for decades of lifestyle and pharmacologic interventions. Given this, there remains a large unmet need for additional complimentary treatment approaches to lower blood pressure.

We'll demonstrate today that the Symplicity Spyral System provides clinically meaningful and sustained blood pressure reduction, both in the presence and absence of treatment with medication. Blood pressure reductions were achieved continuously throughout the 24-hour circadian period. Both short and long-term safety are excellent, and this includes procedural safety and maintenance of both renal artery and kidney function. Radiofrequency renal denervation compliments the established treatment options for the management of hypertension and provides patients with a non-drug intervention option.

Here's the agenda for today's presentation. Dr. Raymond Townsend will describe the current landscape and the unmet need that exists for patients with uncontrolled hypertension. Dr. David Kandzari will then present the efficacy data from the clinical program, followed by

Dr. Felix Mahfoud with the safety and durability data. Dr. Townsend will then return to conclude with a clinical perspective on renal denervation with the Symplicity Spyral system. And then Vanessa DeBruin from Medtronic will moderate the question and answer period. We also have additional experts with us to help address your questions. All outside experts have been compensated for their time and expenses.

Thank you. I'll now turn the presentation over to Dr. Townsend.

Dr. Townsend: Thank you. My name is Raymond Townsend, and I'm part of the hypertension section at the University of Pennsylvania in the Perelman School of Medicine. I've spent my career studying and managing hypertension, both in research and clinical practice, funded by industry and NIH. In addition, I've served on both the US and the Canadian Hypertension Guideline Committees. I've been working in the area of denervation since 2011. When it comes to treating patients with hypertension, lifestyle modifications and antihypertensive medications are first-line therapy. Lifestyle modifications include a healthy diet, maintaining a healthy weight, physical activity, limiting alcohol, and ensuring sufficient sleep. Many proven classes of antihypertensive medications are available. And to manage high blood pressure, many people need to take medications from multiple classes as there can be complimentary benefit from treatments that have different mechanisms of action.

Adherence is one of the limitations of antihypertensives. Adherence may be dynamic and changing over time and can be due to poor persistence, or often it's related to drug side effects. ACE inhibitors have been known to cause cough; beta blockers, fatigue; diuretic sympotents, calcium channel blockers, swelling; and on it goes. When there are disruptive side effects, we try making changes to the class or the regimen itself. However, it's difficult to predict who will respond to which medications, especially in patients on multiple agents. So there are some limitations to the changes we can make when seeking tolerable and effective medications.

Additionally, poor response can impact adherence. When we increase dosage or introduce an additional class, this is sometimes met with resistance on the part of patients. Multiple investigators have quantified antihypertensive drug adherence among patients who've been prescribed medications by measuring blood and urine concentrations of the drugs. This graph shows medication adherence rates across these reports. Partial non-adherence is shown in the hatched blue and total non-adherence, meaning no detectable anti-hypertensive drugs, is shown in solid blue. Among treated, but uncontrolled hypertensive patients, 44% were not taking all of the prescribed anti-hypertensive medications, and 17% were not taking any.

Because these data represent patients seen in clinical hypertension practices, they likely underestimate non-adherence that could be present in a more general setting. These numbers are concerning and are a big part of the reason why we're here today. Addressing the gap in adherence is important to improve hypertension related morbidity and mortality. Getting patients to adhere is a major problem and likely tied to the fact that overall hypertension control rates in the US are worsening. From 2013, there has been a steady decline in blood pressure control rates, despite the longstanding availability of effective drugs. This decrease is primarily due to worsening control rates in women and Black Americans. For this reason, treating clinicians and hypertensive patients consistently search for newer options to integrate with medication and lifestyle. Ultimately, in order to improve outcomes, patient preference is an important consideration in the shared decision-making process around how to treat patients with hypertension.

To gain insight into this, Medtronic conducted a patient preference study to calculate the level of treatment related benefits and risks that patients will accept. The purpose of this study was to quantify patient's preferences after reviewing the benefits and risks of an interventional treatment, like the Symplicity Spyral system, with or without pharmaceutical treatment, and to

compare it with pharmaceutical treatment alone for the management of uncontrolled high blood pressure. The study was designed based on FDA guidance with input from the agency. Pretest interviews were conducted to ensure patient understanding around the hypertension treatment options, the efficacy of each, including reduction in office systolic blood pressure and duration of effects, and also to ensure understanding around adverse events associated with each. Where needed, the questionnaire was refined to enhance patient understanding.

As part of this study, patients evaluated treatments with different attributes. These are shown along the Y axis here. Results of the analysis include estimates of how much weight each individual attribute had in their decision-making process. Blood pressure reduction reflected in the top bar was the most important attribute. With even modest reductions, less than five mmHg, being important to patients. Potential risks, such as vascular injury, drug side effects and temporary pain, carried less weight. Determining the relative importance of these different attributes was a key aspect in the patient preference study.

Based on these findings, a model was developed to predict the percent of patients likely to select one treatment over another. Patients also assessed different scenarios, including scenarios with blood pressure reductions and risks, similar to both the OFF- and ON-MED studies. The model indicated that while patients generally indicated a preference for medication over an interventional treatment, a subset, up to 31% of patients, would choose an interventional treatment with the characteristics of renal denervation in terms of blood pressure reduction and likely risks.

In summary, there remains a large unmet need for additional treatment approaches to lower blood pressure and a patient interest in complimentary solutions to medication and lifestyle changes. We know the current options are not adequate, as we have a plethora of medications today, over a hundred different drugs, and yet many patients with hypertension

remain uncontrolled. Importantly, some patients are willing to undergo an interventional procedure to achieve blood pressure reductions. So thank you. And with that, I will turn the presentation over to Dr. Kandzari to cover the clinical efficacy results.

Dr. Kandzari: Good morning. And thank you, Dr. Townsend. My name is David Kandzari, and I am the Chief of the Piedmont Heart Institute and Cardiovascular Services line and Director of Interventional Cardiology for the Piedmont Heart Institute and the Chief Scientific Officer of Piedmont Healthcare in Atlanta, Georgia. I specialize in interventional cardiology, peripheral arterial disease, and cardiovascular medicine with a clinical focus on catheter-based revascularization of complex coronary and peripheral arterial disease, cardiovascular disease prevention, and clinical trial design. I have served as the primary author and coordinator of the Hypertension Academic Research Consortium statement, in addition to lead or contributing author roles to multiple international expert consensus documents related to renal denervation therapy.

I'm very much pleased to be here today to present the efficacy data for the Symplicity Spyral System, importantly, the reductions in blood pressure that remain continuous over a 24-hour period and with sustainability through late-term follow up. Following the outcomes of the Symplicity HTN-3 study, additional work was performed to incorporate learnings and improve the study design for the Spyral program. Symplicity Spyral Clinical program all review builds on the safety of the first generation of the device technology. The Symplicity Spyral system was first approved in October, 2013 with CE mark approval in Europe. The Global Symplicity Registry or GSR began enrolling patients utilizing the Spyral catheter shortly thereafter in 2013. The OFF and ON-MED pilot feasibility studies then began enrolling patients in mid-2015 and were expanded as pre-specified following the review of results from the successful pilot study.

In December, 2018, a general issues panel meeting was convened by FDA to determine appropriate study designs, as well as to seek alignment on imaging protocols to support safety. And in 2020, FDA granted Medtronic breakthrough designation for the Symplicity Spyral System, and in November, 2022, Medtronic submitted their PMA for US approval. The Symplicity Spyral System is also already approved and in use in 70 countries worldwide. I'll begin this morning with an overview of our pivotal OFF-MED study, which consists of both the pilot and expansion cohorts. The OFF-MED study was designed to isolate the effects of renal denervation therapy and to limit potential confounding related to anti-hypertensive medications, specifically their variability and efficacy, medication changes, as well as patient adherence. Screening took place over two visits. Patients were either not taking antihypertensive medications or had to discontinue their antihypertensives before randomization, and there was at least a three to four-week week washout period prior to randomization.

In addition to recording reported medication use, patients also provided urine and blood samples for further confirmation of abstinence from antihypertensive medications and with the patient's awareness of the purpose of such testing. All patients had renal angiography and then were randomized, one-to-one, to renal denervation or the sham-control, the latter of which was defined as the performance of renal angiography alone. Unless patients met pre-specified criteria for escape, they were to remain medication free through the three month visit for analysis of the primary efficacy endpoint. Patients with an office systolic blood pressure at or above 140 mmHg were then to resume their medications after ascertainment of the primary endpoint at three-month follow-up. And at the end of the six-month visit, patients were unblinded and the sham-control group could elect to crossover and receive renal denervation therapy.

Treatment patients and sham patients are being followed through 36 months and crossover patients through 24 months after the renal denervation procedure. Key inclusion

criteria required that patients were either not taking or willing to discontinue anti-hypertensive medications at least three to four weeks prior to randomization. Patients also had to have a baseline office systolic blood pressure between 150 and 180 mmHg, a diastolic blood pressure of at least 90 mmHg, and an average systolic blood pressure between 140 and 170 mmHg, as measured by the 24 hour systolic blood pressure. Key exclusion criteria included ineligible renal artery anatomy, an eGFR below 45, type II diabetes mellitus with an A1C greater than 8%, or type I diabetes, and other criteria represented in this figure. The primary efficacy endpoint is the change in systolic blood pressure from baseline to three months, as measured by the 24-hour ambulatory blood pressure monitoring assessment, or (lost audio/video).

Dr. Lange: We lost your video.

Dr. Kandzari: -- as measured at multiple time intervals and medication abstinence evaluated using drug testing. 80 patients were randomized for the pilot study, and an additional 286 prospective patients were randomized in the expansion phase, for a total of 366 patients. Overall, 182 patients then were randomized to the renal denervation group, and 184 patients were randomized to the sham-control group. Nearly all patients completed the three-month follow-up visit, and thus had data available for both office blood pressure and 24-hour systolic blood pressure measurements. Of those patients without blood pressure data, the majority were escape patients who resumed medications ahead of the three-month primary follow-up visit.

After six months, patients were unblinded and sham-control patients were given the option to cross over to receive renal denervation therapy. 125 patients, or 68%, did exactly just that. Average age of patients was approximately 53 years with a fair representation across racial groups. OFF-MED was an international study conducted in the United States, Japan, Canada, Australia and European countries where CE mark applies. And, as such, outside the United States, many sites were not allowed to ask participants their race due to local laws or regulations.

Importantly, approximately 50% of the study participants were from the United States. Most patients had hypertension for more than five years. Rates of comorbidities such as diabetes and obstructive sleep apnea were evenly balanced between the two groups. Coronary artery disease was the only characteristic that significantly differed between the two treatment groups with none in the renal denervation group and 4% in the sham control group.

The OFF-MED pivotal study met both its primary and secondary efficacy endpoints. Represented in this figure is the distribution of the treatment effect with 24-hour systolic blood pressure. Almost all of the posterior distribution is to the left of the red line, demonstrating that with greater than 99.9% probability, renal denervation therapy is superior for 24-hour systolic blood pressure, compared with the sham-control. The right-hand panel are shown the results for the powered secondary endpoint off the systolic blood pressure and has demonstrated the results also show superiority for renal denervation therapy compared with sham-control. So we would expect with this level of treatment effect, using the frequentist ANCOVA analyses, we observe consistent, statistically significant reductions in 24-hour and office systolic blood pressure from baseline to the three-month follow up with the renal denervation group.

Beginning with the pilot study, the reductions in blood pressure in the renal denervation group were significantly greater at three months, compared with those in the sham-control group. Now focusing specifically on the expansion cohort, the reductions observed with renal denervation were very consistent with that of the pilot portion of the study. Furthermore, the full cohort had a statistically significant absolute reduction of 4.5 mmHg for 24-hour systolic blood pressure and a reduction of 9.4 mmHg for office systolic blood pressure with renal denervation. These levels are also notably well within the range of what is established as a clinically meaningful reduction, and though not shown here, a very similar pattern of reductions was also observed with diastolic blood pressure, favoring renal denervation therapy.

As might be expected based on the observed treatment effect of renal denervation in the OFF-MED study, significantly fewer patients treated with renal denervation met the escape criteria. Escape criteria were met if a patient's office systolic blood pressure reached 180 mmHg or higher, or if there was a safety concern related to hypertension from randomization to the three-month follow-up visit. If the patient had an office systolic blood pressure at or above 180 mmHg, the patient was again assessed within 72 hours, and if the blood pressure remained at or above 180 mmHg, the patient was then placed back on medication and considered to be an escape patient. As evident in this figure, fewer patients treated with renal denervation met escape criteria at one month, and this effect was carried out through the three-month follow-up time point.

To illustrate further the physiologic benefit to a patient, it's insightful to examine blood pressure over the course of an entire 24-hour period. The OFF-MED pivotal study is the best opportunity to demonstrate this benefit since it does not include the compounding effects of medication. In this figure, systolic blood pressure is represented on the Y axis and hours of the day on the X axis. At baseline, systolic blood pressure was similar between the renal denervation group on the left and the sham-control group on the right. However, at three-month follow-up, the renal denervation group experienced significant constant reductions in blood pressure throughout the entire period, whereas blood pressure in the sham group was largely unchanged. Of particular importance, the renal denervation group experienced the benefit of blood pressure reduction overnight. This included the nighttime and early morning hours of finding, especially relevant to individuals with nocturnal and early morning hypertension that conveys a higher risk for cardiovascular events that includes stroke and mortality.

Though not shown here, diastolic blood pressure results also demonstrated precisely the same trends favoring renal denervation. This figure illustrates systolic blood pressure reductions

for the 24-hour period, as well as for daytime defined as 7:00 AM to 10:00 PM and then nighttime defined as 10:00 PM to 7:00 AM. Again, consistently significant reductions were observed with renal denervation compared with sham control, representing what has been termed an always-on effect of this therapy. Now, considering subgroups in this study, the interaction P-values were not statistically significant, indicating that the treatment differences observed with renal denervation were consistent for 24-hour systolic blood pressure in the OFF-MED pivotal study. This was also the case for treatment differences observed among subgroups for office systolic blood pressure.

Focusing for a moment on subgroup analyses of change in office systolic blood pressure, and according to baseline blood pressure tertiles, there is notably a consistent effect across tertiles with renal denervation therapy with a trend of a greater effect in patients with the highest baseline blood pressure. Importantly, this trend was not seen in the sham-control group, a finding that would argue against potential for regression toward the mean. In summary, the OFF-MED study demonstrated that catheter-based renal denervation lowers blood pressure in the absence of medications. Importantly, these reductions were statistically significant and clinically meaningful for 24-hour and office blood pressure compared with sham-control at three months post-procedure. In addition, renal denervation therapy provided persistent sustained reductions in blood pressure over a 24-hour period throughout the daytime and nighttime period specifically.

Complementing the pivotal OFF-MED study, the ON-MED study was performed to better understand the impact of renal denervation in the context of anti-hypertensive medications used in medical practice. As such, the study design was similar to OFF-MED except for the highlighted elements represented in this figure. The trial was conducted in the presence of medications, and thus patients were required to be on a stable course of one, two, or three commonly prescribed standard anti-hypertensive medication classes with no changes permitted

through the primary efficacy assessment, unless escape criteria were met and changes were performed for patient safety. Patients were randomized in a two to one fashion to renal denervation therapy or sham-control, and the primary efficacy assessment was performed at six months follow-up, compared with three months in the OFF-MED study.

Drug testing was also performed in this study, but in this case to confirm adherence to the prescribed medication regimen and, importantly, with the patient's awareness of the purpose of such testing. Important to note as well that these results were not shared with the study centers to ensure that the patient physician relationship was maintained. At the end of the six-month visit, patients were unblinded and those in the sham-control group had the option to crossover and receive renal denervation. All patients will have 36 months of post-procedural follow-up. Inclusion and exclusion criteria were the same as that for the OFF-MED study, again, except that patients were on anti-hypertensive medication.

Now to review the efficacy endpoints of the study. The primary efficacy endpoint was the change in 24-hour systolic blood pressure at six months. The secondary endpoints were similar to OFF-MED. In addition, medication adherence analyses were performed using results from urine and blood tests to assess the potential impact of medication changes on observed blood pressure outcomes. In the ON-MED study, there were, again, 80 patients in the pilot study, and then an additional 257 patients in the expansion phase, for a total of 337 patients randomized in a two to one fashion. That is 206 patients randomly assigned to renal denervation, and 131 patients to the sham-control group. Of note, 80% of patients in the expansion cohort were enrolled during the COVID-19 pandemic. Primary endpoint completion was higher in the renal degeneration group at 93%, compared with 89% in the sham-control group. This was partly due to a higher rate of escape patients in the sham arm, who did not have an evaluable 24-hour blood pressure measurement prior to medication changes, and, therefore, also not before the primary endpoint.

After six months, patients were unblinded, and 74% of the sham patients opted to receive renal denervation therapy.

This high rate of crossover patients in both studies reflects patient interest in an alternative treatment option, aside from their anti-hypertensive medication. The average age of patients in this study was approximately 55 years with a fair representation across racial groups. ON-MED also was an international study conducted in the United States, Canada, Japan, Australia, and European countries where CE Mark applies. As with the OFF-MED study, outside of the United States, many sites were not permitted to ask patients their race. Approximately 50% of the study participants were from the United States. Most patients had hypertension for more than 10 years. The number of medications and the rates of comorbidities such as diabetes, coronary artery disease, and obstructive sleep apnea were evenly balanced between the two groups.

Similar to the OFF-MED trial, the primary efficacy endpoint analysis used a Bayesian design incorporating the pilot data as an informative prior but to the extent that the data were consistent with the expansion cohort. In ON-MED, however, the differences in 24-hour systolic blood pressure at six months were not consistent between the pilot and the expansion groups. Indeed, only approximately 20% of the pilot denervation group data and none of the pilot sham data could be used for the primary efficacy endpoint analysis. It was our first clue that something was very different in the ON-MED study. As a result, the analysis relied heavily, almost exclusively, on the expansion data, and the primary efficacy endpoint in the ON-MED study was not met.

Let us now review the frequentist ANCOVA analysis for both studies that included all the data from the pilot and the expansion groups. First, we review the data from the pilot portion of the study. The renal denervation group experienced a mean 9.3 mmHg decline in 24-hour

systolic blood pressure and a mean 9.2 mmHg decline in office systolic blood pressure, yielding significant differences that favored renal denervation for both 24-hour systolic blood pressure and office systolic blood pressure. Now focusing on reductions for the expansion cohort, we observe a lower absolute reduction in 24-hour systolic blood pressure with renal denervation compared with what was seen in the pilot study, but a similar absolute reduction in office systolic blood pressure. What's also notable is that for both 24-hour and office systolic blood pressure, the absolute reductions observed in the sham-control group were more than twofold higher than that observed in the pilot study, despite best efforts, again, to keep patients on stable medications.

Now, considering the full cohort, which includes combined data from the pilot and the expansion groups, we observed the impact of changes that occurred during the expansion phase are carried over to the full cohort. Important to recognize that the level of reductions observed with renal denervation throughout the ON-MED study are within the range of what has been established as a clinically meaningful reduction. Though not shown here, a very similar pattern of reductions was also observed with diastolic blood pressure.

Given the differences observed between the pilot and the expansion study, it's important to direct our attention to changes in patient behavior, and specifically medication use from one phase of study to the next. Medication burden was based on number, dose, and class of anti-hypertensive medications as determined by urine and blood analysis and, again, with the patient's knowledge of the purpose of this testing. This figure represents the percent of patients in each group who increased or decreased their medication burden prior to the primary endpoint ascertainment at six months for both the original pilot study group and for the expansion group. Recall that both the pilot group and the expansion group together constituted the full study population.

Prior to primary endpoint ascertainment, it's clear that compared with renal denervation patients, there was a greater proportion of sham-control patients in the expansion phase who increased their anti-hypertensive medications, and, conversely, a greater proportion of renal denervation patients who decreased their medications. Both of these changes could have potentially impacted their respective blood pressure results for each group at six months, which we've displayed in the right-hand panel on this slide. Also important to note, that a greater number of patients in the sham group were missing their 24-hour systolic blood pressure data, due to more patients meeting the escape criteria and not having the recommended ambulatory blood pressure obtained prior to these medication increases.

Post hoc analysis of office blood pressure data in this subset of patients with missing 24-hour data shows statistically significant blood pressure reductions that favor renal denervation compared with sham control. These differential changes in anti-hypertensive medications post-randomization may be expected to attenuate the treatment effect in the expansion phase compared with the significant treatment difference that favored renal denervation therapy, as was observed in the pilot study. It's also important to note that per protocol, the office blood pressure was initially assessed at the beginning of the study visit prior to witness pill intake, representing a trough in medication dosing at that time. Therefore, the 24-hour blood pressure assessment not only included this witness pill intake, but the next day pill intake as prescribed. And, importantly, any escalation in medication burden would be expected to influence ambulatory blood pressure measurement disproportionately more than office systolic blood pressure.

Importantly, reductions in nighttime ambulatory systolic blood pressure too were significantly greater among renal denervation patients compared with sham-control patients. Nighttime systolic blood pressure is an important indicator of renal denervation efficacy, as it is the most significant prognostic marker of cardiovascular morbidity and mortality, and it is

independently associated with an increased risk of cardiovascular events, including myocardial infarction and stroke. Treatment differences by pre-specified subgroups in the ON-MED trial, were mostly consistent. However, statistically significant differences were observed in the subgroup analysis comparing non-US versus US sites for 24-hour systolic blood pressure.

Comparison when considering the differences in office systolic blood pressure, no significant difference between US and non-US sites was identified. Because the US and non-US did not differ though by any patient procedure or blood pressure characteristic that would explain this difference, we also explored medication use and whether it differed here. We identified that blood pressure differences between the US and non-US populations were largely driven by differential changes in medications and again confirmed by medication testing. The US population had larger increases in medications in the sham-control group, merger decreases in medications in the renal denervation group confirmed by medication testing. While the non-US population did experience medication changes, these changes were more evenly balanced between the renal denervation and the sham-control groups.

As with the comparison of pilot and expansion groups, these disparities may be expected to attenuate the treatment effect in the US patient group compared with a significant treatment difference that favored renal denervation in the non-US patient group of this study. Given the challenges of interpreting the efficacy results from the ON-MED study, it's important to consider the totality of efficacy across the trials. In the OFF-MED study where we were able to isolate the effects of renal denervation therapy, we very clearly see a treatment effect. Consistent, statistically significant reductions in 24-hour systolic blood pressure from baseline to the three-month follow-up were achieved with renal denervation compared to sham. In the ON-MED study where the Bayesian primary endpoint analysis was not met, we still do observe reductions

in 24-hour systolic blood pressure with renal denervation therapy in the range of six to nine mmHg.

However, what stands out are the blood pressure reductions observed in the sham-control group, approximately an order of magnitude higher than what was observed in the OFF-MED study, and, again, despite efforts to keep patients on stable medication. Not only were all the reductions identified in the ON-MED sham group higher compared with the OFF-MED study, but the reductions observed in the sham group in the ON-MED expansion and full cohort are notably more than twofold greater than those observed in the ON-MED pilot study for the sham group. With office systolic blood pressure overall, we witnessed a similar pattern.

Again, for the OFF-MED study, we observed consistent, statistically significant reductions in office systolic blood pressure of more than nine mmHg with renal denervation therapy from baseline to three-month follow-up. In the ON-MED study, the reductions achieved with renal denervation were consistent with that of the OFF-MED study between nine and 10 mmHg. Yet, again, what stands out are the blood pressure reductions observed in the sham-control group in the ON-MED expansion and full cohort group. The sham-control group achieved reductions of at least twofold higher than that observed in the sham control for the OFF-MED study and the ON-MED pilot study, again, despite best efforts to keep medications stable for these patients prior to ascertainment of the primary outcome.

Despite the inconsistencies observed with the sham-control group in the ON-MED study, the level of reductions observed with renal denervation for 24 hour and office systolic blood pressure across both studies are clinically meaningful reductions for our patients. Though not showing, a very similar pattern of reductions were also observed with diastolic blood pressure that favor renal denervation. The totality of data demonstrate that the Symplicity Spyral system

provides clinically meaningful blood pressure reductions, both in the presence and absence of medication.

In the OFF-MED pivotal trial, the primary endpoint was met. Reductions were both statistically significant and clinically relevant for 24-hour and office blood pressure compared with the sham at three months. For ON-MED, there were significant reductions in 24-hour and office systolic blood pressure at six months compared to the sham group in the pilot cohort favoring renal denervation. While the ON-MED trial did not meet the primary endpoint, there were differential medication changes between the renal denervation and sham control arms that attenuated the treatment effect and reduced the ability to demonstrate differences between the two treatment arms. There were significant reductions in office and at nighttime systolic blood pressure for renal denervation compared with sham. Importantly, we saw consistent reductions from baseline in the renal denervation treated patients across all of the studies. Thank you very much.

This concludes the efficacy presentation, and I'll now transition to Dr. Mahfoud for presentation of the safety and durability data.

Dr. Mahfoud: Thank you. And good morning. My name is Felix Mahfoud, and I'm a Professor of Medicine and Deputy Director of Cardiology at the Saarland University Hospital in Homburg in Germany. I performed my first renal denervation procedure back in 2009, and since then I've seen more than 400 patients who underwent renal denervation. I've also served as a writing committee member of the latest European guidelines on hypertension management.

I'm very pleased to be here today to review the safety and durability data, which demonstrate that renal denervation performed with the Symplicity Spyral system is minimally invasive, provides durable reductions in blood pressure, and has an excellent short and long-term safety profile. I represent the pre-specified primary safety endpoint, which includes data from the

first 253 patients treated with renal denervation in the off and ON-MED studies, including crossover patients.

It is important to note that both the OFF-MED and ON-MED study utilized the Clinical Events Committee or CEC to adjudicate all protocol defined reportable safety events. The CEC was comprised of multiple clinicians with pertinent expertise who were not participating in any of these studies and had no potential conflicts of interest. An independent data safety monitoring board also reviewed these events.

Let's now review the pooled primary safety outcomes. The pooled primary safety endpoint was the major adverse event type and rate at one-month post procedure, except for renal artery stenosis, which was evaluated at six-month follow-up. The performance score was based on expected events and event rates from other renal intervention procedures. The performance score was pre-specified and agreed with the FDA to be 7.1%. The pool data set met the endpoint with a major adverse event rate of 0.4% at an upper 95% confidence bound of 1.9%, significantly less than the pre-specified performance goal. Importantly, there were no death reported in either study in patients treated with renal denervation.

Looking at the major adverse event rate by study, one can see in the OFF-MED pivoted study at three months, the major adverse event rate was 0.6% in the denervation group, at 0.5% in the sham group. In the denervation group, one patient was hospitalized for hypertensive emergency. In the sham group, one patient experienced two events shown here. In the ON-MED study, the incidence of major adverse events from enrollment to six months was 1.0 and 0.8% in the denervation and sham groups respectively. These events were pseudo-aneurysms, and each resolved without sequalae.

Let me now review the vascular safety results. Renal artery imaging was done at 12 months or later post-procedure to assess for any potential renal artery stenosis, which was

defined as greater than 70%. There were 474 patients with long-term imaging at 12 months or later. There was one patient with renal artery stenosis in an accessory renal artery, which was identified more than three years post-procedure. There was no deterioration of renal function observed, and the patient exited the trial prior to invasive follow-up imaging. These data provide a possible rate of greater than 70% stenosis of 0.2% in patients treated with renal denervation. Literature reports a yearly incidence rate of renal artery stenosis between 0.5. and 5% in hypertensive patients. Furthermore, no other cases of accelerated progression of disease have been identified when comparing baseline evaluations to follow-up imaging.

I will turn now to renal function. To assess for functional kidney changes, we utilized estimated glomerular filtration rates or eGFR measured through the modification of diet and renal disease or MDRD equation. Shown here are the findings from the pool safety analysis for the OFF-MED studies, displayed on the left, and the ON-MED studies, which are displayed on the right. Accounting for risk factors at baseline, including hypertension, age, diabetes, obesity, and chronic kidney disease, the reductions in eGFR following renal denervation were within the range of eGFR over time in hypertensive individuals. Importantly, the changes in eGFR seen in patients treated with renal denervation were consistent with the decline observed in the sham group. In summary, the OFF-MED pivoted study and the ON-MED supportive study both demonstrate the positive safety profile of renal denervation using the Symplicity Spyral system.

The pooled primary safety endpoint was met with a low rate of major adverse events. There were no device related safety events observed, a low rate of procedure related events, and no increased risk of renal denervation associated renal artery stenosis. Additionally, we saw sustained renal function over time following renal denervation.

Now I'd like to present the results on durability and long-term safety. Long-term data on durability come from the ON-MED study from the patients enrolled in the pilot cohort and

include data available up to 24 months. Shown here are the different measurements. Systolic blood pressure change from baseline to 24 months. The ambulatory and office blood pressure reduction seen on the order of 15 to 20 mmHg are both durable and clinically meaningful. As for long-term safety in these studies, the incidence of reported adverse events was low with similar rates between study arms. As with earlier data, reductions in eGFR were consistent with that expected for patients with hypertension. Similarly, the rate of suspected renal artery stenosis was within the range reported in the literature for hypertensive patients. In all, the totality of safety results continues to support the use of the Symplicity Spyral system and raise no new safety concerns.

Let me now share the long-term results from Medtronic's Global Symplicity Registry, also called GSR. The GSR was designed to capture and assess long-term safety and efficacy data in a real world setting out to three years. This prospective open-label registry includes a broad range of patients with various comorbidities and is conducted at 245 sites across the world. It began enrolling patients back in 2012 in countries where the system was approved and commercially available. As of July, 2023, more than 3,400 patients were enrolled, but represents more than 7,000 patient years of follow-up. This experience includes approximately 800 patients treated with the Symplicity Spyral system, as well as those treated with the previous device design, the flex catheter.

Shown here are the high-level blood pressure data available to date for the Symplicity Spyral system. The same catheter, which was also used in the Spyral off and ON-MED studies. These data demonstrate significant and sustained offers in 24-hour systolic blood pressure reductions following renal denervation, persisting out to three years. These results are also consistent with those obtained for the Flex catheter in a larger population and in high-risk subpopulations with common comorbidities, such as CKD and diabetes, treated with either the

Spyral or Flex catheter. Importantly, these reductions translated into more patients reaching systolic blood pressure values below 140 mmHg through follow up. As shown on the bars on the left-hand side, the percentage of patients systolic blood pressure below 140 mmHg significantly increased from 13% at baseline to 35% at three years, a nearly threefold increase.

This improvement cannot be credited to medication changes, as there was no significant change in the average number of medications over the same time period. We also looked at time and target range to further examine the clinical benefit of lowering blood pressure with renal denervation. This measure estimates the percent of time a patient spends at or below an office systolic blood pressure of 140 mmHg, or at or below a 24-hour systolic blood pressure of 130 mmHg through six months. This percentage was then correlated with long-term MACE rates between six and 36 months using a hazards regression model. Shown here are the Kaplan Meyer estimates for MACE rates between six and 36 months by the percent of time in target range. Blue corresponds to having no time and range, red is anywhere from one to 52% of the time, and green is more than 52% of the time in range. As you can see, the greater the time spent in target range, the lower the MACE rate. These decreases are extremely clinically meaningful in terms of lowering patient's risk for cardiovascular events.

We are also collecting long-term safety data with the Global Symplicity Registry, including information on renal function. This plot shows the change in eGFR over time. Tools across patients treated with the Symplicity Spyral system and the GSR, the original proof of concept study, which included 50 patients, and the off and ON-MED studies. When we look at renal function over time, we see the same trend as seen in the clinical studies with a small decrease in eGFR consistent with those expected in patients with hypertension as they age. In patients with pre-existing chronic kidney disease, defined as an eGFR below 60 mls per minute, we see a small decrease in eGFR, which is again consistent with a natural progression of the

disease. The safety data from GSR demonstrate consistent procedural safety. There were no events of stenosis dissections or renal artery reinterventions, which further supports and substantiates the safety results from the off and ON-MED studies.

To summarize, the long-term data, which includes the efficacy data from the clinical trials, as well as the Real World Global Symplicity Registry, demonstrate the durability of the blood pressure reductions through three years of follow up. The GSR real world data come from a broader population than the sham-control trials, and include patients with older age diabetes and other high risk comorbidities. Nonetheless, we see consistent and significant reductions in both office and 24-hour blood pressure following renal denervation. In turn, more patients reach target blood pressure and increase their time and target range while medication remains stable. Importantly, the blood pressure reduction seen in the GSR were associated with an increase in time in target range and reduced risk for major cardiovascular events.

With safety assessed through three years, no long-term risks have been identified, further substantiating that renal denervation is a safe, minimally invasive procedure that can help patients manage their hypertension over time. In addition to the data we've shared today, Medtronic has also initiated a new study to follow patients treated with the Symplicity Spyral System, the AFFIRM study. The AFFIRM study is an ongoing, international, multicenter, prospective, interventional single-arm study designed to evaluate the safety, efficacy, and durability of renal denervation in a real world population with varying levels of hypertension and associated comorbidities. The study includes a continuation cohort with eligible patients from both the off and ON-MED studies. Target enrollment is up to 1200 patients. The primary endpoint will be assessed at six-month post procedure. To ensure consistency, patients will remain on the same medication from six weeks prior to baseline through the six month follow-up, unless changes allowed for safety reasons. For long-term safety and efficacy, patients will be

assessed at 48 and 60 months. Data from this study will add to the comprehensive data sets already collected to supplement our understanding of the real-world long-term outcomes with renal denervation therapy. Thank you very much for your attention. I will now turn the presentation back to Dr. Townsend.

Dr. Townsend: I'd like to conclude by bringing things back to the patient. When meeting with hypertensive patients, treating caregivers initiate conversations in which we introduce or reinforce lifestyle modifications. However, the response to this is often disappointing. Some patients will make every effort, while others, often most, make minimal progress here. This is in part related to hypertension, as an often-asymptomatic disease, where patients don't feel the benefits of lifestyle changes and, at the same time, don't directly feel the risks of hypertension on their target organs. We also discuss antihypertensive medications. Although these do work and have documented benefits, some patients are challenged with taking medications as directed or, commonly at our center, patients have already been on many of them in the past. This fosters some skepticism and contributes to the low adherence to medications, which you've seen is striking.

Adherence can be challenging for patients for a number of reasons. It can also make deciding what to prescribe next a challenge in some cases, when multiple agents have not worked or have not been tolerated. Although many factors contribute to non-adherence, there are few of these that I, as a physician, can impact in order to improve adherence, aside from a caring and flexible attitude. This is why, despite having well over 100 separate anti-hypertensive medications available, we still struggle to control blood pressure with the majority of hypertensive patients failing to achieve controlled blood pressure.

The SPRINT trial with which many of you are familiar, enrolled high-risk hypertensive patients and demonstrated blood pressure and clinical outcome benefits in the randomized group

treated with more intensive drug therapy. However, in a large subset of patients followed for 10 years, using electronic health records, the blood pressure benefit of intensive therapy started to decline immediately after completion of the active trial phase, and the mortality outcome benefit was no longer detectable by year six. So even in the confines of a well-funded clinical trial, the therapeutic effect of differentiating the two groups was attenuated over time, providing evidence that in the absence of a research study coordinator, blood pressure control with drugs alone worsened over time.

And these data demonstrate that there are clear health benefits of blood pressure reduction. We know that each millimeter of mercury in office systolic blood pressure reduction translates into clinically significant reductions in mace risk. Shown here are the results from two meta-analyses demonstrating a relative risk reduction that is proportional to the five to 10 millimeter reductions in office systolic blood pressures achieved. A five millimeter reduction in systolic blood pressure shown in yellow, resulted in clinically significant reductions in cardiovascular risk, and there was proportional benefit with higher blood pressure reductions. Although there was an outlier in the sham results for the expansion phase of the ON-MED study, we have consistently seen about 10 millimeter reductions in office systolic blood pressure following renal denervation therapy across the multiple studies that measured the impact of the Symplicity system.

Taken as a whole, the Spyral hypertension program, including the sham-controlled Spyral hypertension trials, and the Real World Global Symplicity Registry, demonstrated very consistent, durable, and clinically relevant blood pressure reductions. So the question on the table today is whether RDN therapy with the Symplicity Spyral System, a non-drug intervention, should be an option available for patients who remain uncontrolled despite trying any hypertensive medications or for patients that simply cannot tolerate blood pressure lowering

therapies. RDN represents a complimentary option that we could provide patients that have tried anti-hypertensive lifestyle changes in medications and yet remain uncontrolled with a reasonable clinical option for blood pressure improvement. The trials presented along with the patient preference study indicate hypertensive patients are willing to consider denervation. And from a clinical perspective, this is supported by many thousands of people worldwide already treated with RDN, and more than 10 years of clinical data.

This is also supported by what we saw in the OFF- and ON-MED studies where about three quarters of the sham control patients opted to crossover to treatment with renal denervation. RDN can lower a patient's blood pressure continuously over a 24-hour period without having to be repeated daily, which virtually eliminates the adherence issue. And as Professor Mahfoud has shown you, the blood pressure reductions are durable for at least three years. Although RDN can be a compliment to current drugs, unlike medications, RDN doesn't produce a lot of off-target side effects. As you have heard, the Symplicity Spyral System demonstrates a positive benefit risk for patients. In addition, we have shown that there is an unmet need that Symplicity Spyral has the potential to help address. The safety profile reflects a low rate of adverse events and sustained renal function. And, finally, we see that the efficacy demonstrated in the OFF and ON-MED studies are also aligned with the clinically meaningful reduction in blood pressure that is equal to or greater than that seen in control.

The data you've heard today add to the body of evidence that supports renal denervation to treat patients with uncontrolled hypertension. The number of patients in the US who fail to control their blood pressure is growing. To improve the current situation, we must empower patients to be part of the decision-making process, and we need complimentary therapeutic options. With renal denervation, we can reduce blood pressure continuously over 24 hours. The magnitude of reductions observed are clinically meaningful and blood pressure is a recognized,

validated surrogate for cardiovascular event reduction. By adding the Symplicity Spyral system to our available treatment options, we could reduce the number of uncontrolled patients at significant risk for heart attack, stroke, heart failure, and kidney failure progression.

Thank you. I'll now turn it back to the sponsor.

Ms. DeBruin: Thank you, Dr. Townsend. My name is Vanessa DeBruin, and I'm the Senior Director of Clinical Research at Medtronic. I'd be happy to take any questions the panel might have.

Questions to Medtronic

Dr. Lange: I'd like to thank the sponsor's representative for their presentation and apologize for the technical issues that put us on pause for a couple minutes. But now is the opportunity for the panel members to ask brief clarifying questions of the sponsor. And so, I see a number of individuals have their hand up first. So, Deneen, let get to you first.

Dr. Hesser: Thank you. Deneen Hesser, I'm the patient representative. Given that you have some long-term data, do you have any quality of life or patient-reported outcome data to share with us?

Ms. DeBruin: We do have some outcome data from the Global Symplicity Registry. That's probably our largest data set with data from the EQ-5D questionnaire.

Dr. Lange: Great. So, I'll ask the sponsor if you'll provide that data after the break.

Dr. Hesser: Thank you.

Dr. Lange: Thank you. Dr. Somberg.

Dr. Somberg: Thank you, Dr. Lange. I have four questions, which may be after the break. The sponsor can reply to one. Could they discuss a little bit on the ON- and OFF-trials, that was presented today? How did they deal with the variability in anatomy, specifically, were auxiliary renal arteries ablated as well? And give the number of ablations that were performed. Was it just

once in each artery, bilateral, or was it multiple? And was there a correlation with the outcome? That's one question.

The second question is, was there a training effect? Was the pilot study in the on medications? It's a small study. And when there was an expansion, was there a training effect seen with this device?

My third question was for the ON-MED radiance group, could they give the ABPM for per-protocol and as-treated groups as well?

And my fourth question is, could we see the magnitude of the effect for each individual patient? I think that's a waterfall plot for the radiance ON-MED and radiance OFF-MED studies. Those are my four questions. Thank you.

Dr. Lange: Okay. So, to the sponsor, do I need to repeat those?

Ms. DeBruin: No, I'm happy to attempt to answer these questions right now. So, I'll start with the variability in anatomy. The direction to the sites was to treat any vessel in the treatable diameter range of three to eight millimeters. That includes the main renal arteries, accessories, and the branches. Of course, we told the sites to stay outside the kidney parenchyma, and otherwise all eligible arteries were to be treated.

Dr. Lange: Thank you. Did you see a training effect?

Ms. DeBruin: We did not see a training effect. For your third question regarding ON-MED and the per-protocol and as-treated analysis, I'd like to invite Dr. Kandzari to speak to this further.

Dr. Lange: David?

Dr. Kandzari: Yes, sir.

Dr. Lange: Can you present that after lunch? I want to get everybody's questions in.

Dr. Kandzari: Yes. With your permission, I'll present that, and I'll also address in the second session Dr. Sandberg's question with regard to the magnitude of blood pressure reductions.

Dr. Lange: Perfect. Thank you, David. Thank you very much. And then, I'll also ask, that we provide a waterfall plot OFF-MED and ON-MED, if that's possible after lunch. So, thank you. Dr. Yeh.

Dr. Yeh: Thank you. I was going to ask for, one, the distribution of changes. If there's a histogram option too, that would be great, in addition to the waterfall. Can we go to slide 55 quickly? I was wondering here if you could provide rates of the escape rates in the US versus non-US for the ON-MED, and if that was potential explanation, also contributor, for slide 69. I noticed that this is very specific to ON-MED pilot and I'm wondering if these data are available for the other studies as well.

And then finally for slide 74, the Global Symplicity Registry. I'm just noting that the denominators for baseline and three years, and the slide previous to this, these are very different denominators and I'm wondering, obviously there's a lot lost to follow up between baseline and three years. And, even in the slide before this, on 73, it just looks like there's a fair amount of attrition. I'm wondering how these patients at the 36-months equals 200 versus 517. How are these patients selected for follow-up? Are they self-selecting? And what are the characteristics, potentially, of the patients who are staying in, and do we have data that would have patients who were the same patients across the time periods, which might be a more appropriate comparator? Thank you.

Ms. DeBruin: So I'll start with the histogram. Specifically, if you look at the Bayesian histogram, I think that's probably the best example. If you can pull that up from the core deck, please? What we found from both ON- and OFF-MED is that they did have normal distributions. We did not find any challenges with that. Here's the OFF-MED study, and here you see the distribution. And then, similarly, I'll give everybody a minute for the ON-MED study.

Dr. Yeh: I'm sorry to interrupt you. Interpreting correctly, this is the histogram of the potential average difference between the groups as opposed to the observed. I think what we're asking for is that the varied, observed--

Ms. DeBruin: We can provide that after the break, I'm sorry.

Dr. Lange: And, if you'll provide, after the break, the escape rates for the US and non-US, that'd be great. Slide 69, run back to that if you would for a second, because Dr. Yeh was asking for something very specific. And you wanted the, Robert?

Dr. Yeh: Yep.

Dr. Lange: This is the ON-MED pilot, you wanted it for the ON-MED expansion?

Dr. Yeh: Well, for any of the studies, I mean, I think that there's expansion and then there's OFF-MED as well. And I just wondered if there's long-term data, notwithstanding all the limitations of interpreting those. I just see that there's presentation of one set of data here, but not all.

Dr. Lange: Great. Okay. Super. And then we'll let the sponsor talk about the denominators after lunch as well.

Ms. DeBruin: If I just may, Dr. Yeh, I think you had one other request regarding the Global Symplicity Registry as well, correct?

Dr. Yeh: That's right.

Ms. DeBruin: We'll provide that.

Dr. Yeh: It was related to just understanding the denominators and how patients were selected to continue on for follow up, and whether or not there are differences between those patients who are seen at six months versus 30, 36, et cetera.

Ms. DeBruin: We'll be happy to provide that. Thank you.

Dr. Lange: Perfect. Dr. Lewis.

Dr. Lewis: Yes, I have several questions. One, it's similar to Dr. Yeh's, but expands on it. In the ON-MED study one of your explanations for the expansion group was that there was an increase in medication used in the sham group. Could you please let us know what proportion of that was related to protocol violations, which speaks to the validity of the conduct of the study, and what proportion of the medication changes in the sham group, and I guess you should show us it for the renal degeneration group as well, were due to escape and not protocol violations? Also, could you please show us the data in the ON-MED study for the three-month values for the primary outcome? And, did you document intolerance, in any way, when you enrolled patients? Those are my three questions. Thank you.

Ms. DeBruin: Dr. Lange, would you like me to start addressing these now?

Dr. Lange: Not right now.

Ms. DeBruin: Okay.

Dr. Lange: I mean, if we have time before the break, we'll do that. But otherwise, we'll wait until after the lunch break. Okay?

Ms. DeBruin: Okay.

Dr. Lange: There's a lot of interest. I want to make sure everybody has the opportunity to ask you all questions, and to give you plenty of time to get the data. So those three things again, the medication changes, were they protocol violations or in response to escape, the ON-MED three-month primary outcome, and did you document intolerance? Great. Dr. Lewis, did I get it all?

Dr. Lewis: Yes, sir.

Dr. Lange: Thank you. Dr. Allen.

Dr. Allen: Thank you. That's a very nice presentation. Keith Allen. I've got three questions. Maybe I'm doing the math wrong, but it looks like in your ON-MED, it's a one-to-one

randomization, but there were 206 in the RDN group and 131 in the sham. How did that add up to not being one-to-one?

The second question is a little bit of a follow up to Dr. Lewis's question a minute ago with regard to the RDN patients in the ON-MED, having a reduction in meds and in the sham group having an increase in med, since they were all supposed to be on the same meds and not adding until the endpoint, it would imply that patients perhaps were aware of which arm they were in and they were no longer blinded. That would be an a very plausible explanation for what's going on. So, can you discuss the efficacy of your blinding and assuage my concerns that particularly the sham group didn't figure out that they were in the sham arm?

And then, finally, I love Dr. Lewis's questions, but I'm going to be a little more blunt in that your IFU is requesting that this device be used in patients with uncontrolled hypertension despite medications or those that can't take medications. Nowhere do I see that patients are optimized prior to enrollment in the study. I would use the predicate of, for example, the COAPT trial where GDMT therapy was initiated. And what we found was if you got on GDMT therapy, a lot of patients, MR got better. I don't see that you've done that in the hypertension group to warrant that IFU request. And if you could expand on that a little bit.

Dr. Lange: First of all, I'll address the reason why. In the ON-MED, the pilot was one-to-one and then the expansion was two-to-one. That's why they're different in the numbers. But we'll ask the sponsor to address the other two. Were patients aware of blinding, particularly in the sham group, and then, ask the sponsor to expand after the break on the IFU and whether the study represents their IFU. So, thank you very much. Dr Corriere.

Dr. Corriere: Thank you. Sort of related to the previous question, I was curious about the ON-MED study. There was a range of one to three medications for six weeks and I'm curious because of the rationale for a patient with stable blood pressure on one medication and also why there

would be a cap at three and not include patients on four or five medications, which seem more consistent with the labeling.

I also would be interested in just some elaboration on the lack of race and other demographic information. What percentage of the cohort was that? And you know, that certainly would be a big problem for publishing in most of our peer-reviewed journals in this day and age. And especially for a question where there's so much relevance of race and ethnicity to the clinical problem.

And then my third and final question would be, I noticed your patient preference study relied on interviews to verify understanding. That's a little bit unusual in that there's usually some kind of more objective understanding assessment that's built into the instrument. And I'd just be curious a little more about how exactly that worked. Thank you.

Dr. Lange: Okay. Have that? So, the question again is to explain the number of medications, why only one, why stop at three, a percentage of, individuals in whom we don't identify the race, and then finally, patient-preference interviews and curious about the instrument. Dr. Saville.

Dr. Saville: Yeah, thank you. I have several questions. I'll try to be brief so we can get quickly through these. If we go to slide 50, what I would really like to see, this has been mentioned before by other panel members in terms of looking at the distributions, and Dr. Wittes and I mentioned this in yesterday's meeting, that we really want to see box plots here. So, these bars could all be replaced by box plots by treatment group. Also, with data points superimposed over those where they're jittered across the x axis. So, you get a sense for how much variability there are in the data, a sense of outliers, that would be really helpful in terms of interpreting the data and that may compliment those other histograms. Those histograms that were shown earlier, by the sponsor, those were Bayesian posterior distributions. Those are not distributions of the raw

data. So, I just want to be clear there. So, if that could be presented after the break, that would be great. A question for the sponsor: was the primary analysis a complete case analysis?

Ms. DeBruin: Can you please clarify? Was the primary analysis a complete case analysis? Is that what you asked?

Dr. Saville: Yeah. Dealing with missing data, were the missing data points just excluded and the analysis conducted just on observations that were observed?

Ms. DeBruin: Yes, that's correct. We use last observation carried forward for any 24-hour ABPM. If there was not a 24-hour ABPM prior to escape, then we did not include that in the population.

Dr. Saville: Okay. So that's not a complete case analysis that's imputation. So you are actually imputing values for those who have missing data. First of all, did you do a complete case analysis? And then number two, did you have other imputation strategies that you explored or have analyses looking at other strategies of imputation?

Ms. DeBruin: Yes, we did. And, we can expand on that now or after the break, whichever you prefer.

Dr. Saville: I think after the break.

Dr. Lange: Let's hit that after.

Dr. Saville: Next question, I want to understand more about the timing of the analysis plan. So, this idea of Bayesian borrowing, borrowing from the pilot studies, was this plan put in place after you'd seen the results of the pilot studies, after those data were finalized?

Ms. DeBruin: Yes, that is correct.

Dr. Saville: Okay. That's helpful. So, I just want to say state that I love the idea of Bayesian borrowing. I consider myself a Bayesian biostatistician, and I do a lot of trials with Bayesian borrowing. So, I do love the idea conceptually. I don't particularly love the way it was

implemented here. And the reason why, if you look at slides 34 and 35, 35 in particular, if you look at, for example, let's look at the office systolic blood pressure. You have point estimates of -7.1 for the pilot, and -6.6 for the expansion. When you pull everyone together, you get a -7.1, but yet when you do the Bayesian borrowing, you end up with -6.5. The intuitive Bayesian says, we have a prior, we think its 7.1 benefit, we're going to collect some data, we're going to update that belief, and we'll come up with what's called a posterior.

And, typically, that posterior is somewhere that's in between the prior and what you get for your updated data and the 6.5 doesn't even fall within the window there. And it's kind of odd because I believe this was closer to full borrowing, so both those discount parameters were equal to one, which indicates it should be full borrowing, so I would've expected your treatment effect with the Bayesian borrowing to be closer to a -7.1 here. So, I'm surprised that it's a -6.5. So, this is good for the sponsor, because I think you've introduced some bias in this analysis and the treatment effect is probably a little bit larger than what we're seeing here in the slides.

The reason why I think that bias comes in is because you have potentially differential borrowing on the two treatment arms. So, you borrow on the control arm and then you also borrow on the treatment arm, and you have an alpha-discount parameter that you're estimating for each one of those. In this case, actually, it's supposed to be equal to one for both. So, it's not even that differential, but certainly in the OFF-MEDs there's differential borrowing there. And, typically, when we do Bayesian borrowing, we want to borrow on the treatment effect. So, we might sometimes do two-dimensional borrowing, we're borrowing on the control arm and the treatment effect. But I haven't seen one like this where we're borrowing on the control and the treatment arm, but not on the treatment effect itself. So, we're interested more in the delta, and the assumption that comes with that is exchangeability of the treatment effect between the studies.

So, I don't think this affects, on a high level the conclusions of the studies. Like I said, I think what this means is you get some bias introduced in your analyses. I can kind of sort through and figure out which direction I think that bias is. For example, here, I think your treatment effect in the office

Dr. Zuckerman: Dr. Saville can I pause you a moment? Very interesting observations, but what is the question for the sponsor versus your panel deliberations with other panel members in the afternoon? Would you like the sponsor in the afternoon to talk in a bit more detail about the methodology and why the methodology does not, according to the sponsor, produce a biased result?

Dr. Saville: Yes, absolutely, and thanks for bringing up the question, I was trying to get there. I was getting there too slowly. And also, the question, have they done additional analyses with borrowing on the treatment effect or have they done analyses in the context of the way they did it where they had essentially equal borrowing on a two arm? So, instead of this differential borrowing, did they do analyses where they did both? So, I'd be interested in seeing both of those if they have them, as well as details maybe talking more about why they came up with this plan. Two things that weren't shown were the 12-month data. There's no mention of adaptive sample size. If those aren't talked about by the FDA, I'd love to hear the sponsor address those as well as why are there no comparisons in this global registry between those who have the intervention and those who don't. I think there's interesting analyses that could be done there. That's all. Thank you.

Dr. Lange: Alright, great. Dr. Bates. We have a limited amount of time; I want to get the questions to the sponsors so they can work on them. So, we'll leave our comments to deliberations and leave the questions to the sponsor. So, Eric?

Dr. Bates: So the good news is, I'm not a statistician, so I have simple questions. I believe you had a presentation of the ON-MED study at the American Heart Association meeting last November. Is that correct?

Ms. DeBruin: That is correct.

Dr. Bates: And, did that include the pilot and expansion studies as the pivotal trial report?

Ms. DeBruin: Yes, it did.

Dr. Bates: Has that primary manuscript been published? I couldn't find it on a literature search.

Ms. DeBruin: Yes. It's currently in review.

Dr. Bates: So, the hard question is why was it not a simultaneous publication, and why, nine months later, have we not seen the data published? The problem of course, being that if we took the three studies from yesterday and your two studies and put them into a meta-analysis, which I hope the FDA has done, the test of the technology reducing blood pressure might produce a result of three to four millimeters reduction with this technology below the five-to-ten-millimeter reduction goal that the FDA set for the technology.

Dr. Zuckerman: Okay, Dr. Bates, let me pause you here.

Dr. Bates: Yeah, go ahead.

Dr. Zuckerman: Explain the FDA perspective. We're dealing with a Medtronic PMA today. The data that Medtronic has collected must stand on its own. You have a full data set. The company can provide other data, but we should not be asking questions about a competing device today or about whether or not a publication has gone to press. Thank you.

Dr. Bates: Okay. Fair enough. But my concern is, had the report been published, as is convention, the spin on the technology of the last six months in preparation for this meeting might've been muted compared to what I'm reading in the lay and in the medical press.

Dr. Zuckerman: Sure. But that's why we have an open advisory panel today.

Dr. Bates: Just making a comment. Thank you.

Dr. Lange: Sure. William Vaughan?

Mr. Vaughan: Yes, please. If the device is approved there might be some labeling questions. You are operating in a bunch of countries overseas. Could we get for like two, three countries, restrictions on use? Like it should only be used in a specialized center, shouldn't be used on 90-year-olds, that kind of thing, say for Germany, England, and Canada after the lunch break.

Ms. DeBruin: Yes. Happy to provide that.

Mr. Vaughan: Thank you.

Dr. Lange: Thank you. Dr. Wittes.

Dr. Wittes: Yes. So not surprisingly, Dr. Saville, addressed some of the questions I had, but I want to go a little farther than he did, or a little differently, because I'm really having a lot of trouble understanding your analyses. When you come back and explain what analysis you did to handle the missing data, please tell us for the primary analysis, what you did, how you handled analytically those who escaped, and, also in both the ON- and OFF-studies, when you moved to the frequentist analyses, did you stratify by the pilot and the expansion studies and the analysis? It looks like they were just mushed together.

And, also, in slide 74 and 78 and 77, all of those where you show the values over time with very different denominators and no standard errors, that's true. In 77 and 78, can you give us some more information about, so we can understand what happened to cohorts of patients? Not just what happened to the 792 in the beginning and 210 later on and so forth and over time. So that's my first question. Just help us understand how you dealt with all this missing data and explain to us why you have more office measurements than you have ABPM measurements in, in several of the measures.

Second question: You pointed out that it's hard to predict who will benefit from drugs. Have you done any analyses that would let us predict who will benefit from the device? And finally, you said the OFF-MED is primary. Does that mean that the P-value was less than 0.05, which it certainly was, but does that mean that it met the five-millimeter difference, which I don't think it did. So those are my three questions.

Dr. Lange: I'm sorry, the last one again, I missed it.

Dr. Wittes: Yes. What does it mean that you meant that the OFF-study met its primary? Because I thought the primary was that you had to have a difference of at least five millimeters and be statistically significant. What I see is statistical significance, but not five millimeters.

Dr. Lange: Okay. Thank you very much. We're going to move quickly. Dr. Lockhart.

Dr. Lockhart: So, my questions are all related to the imaging for the renal artery stenosis and the safety profile. You said you identified the anatomy. It doesn't say how, if you found multiple renal arteries, were they notified so that in the follow-up with the ultrasounds, they knew they had renal arteries. And this is an easy one. Did the ablations ever cross the renal artery origin? That's all going to be needed later to discuss the ultrasound. And then, you described ultrasound training, but I didn't give a whole lot of detail of how much training or how they were trained. And there's no mention of your training for CTA / MRA, which is important based on the results we're seeing on those parameters. And then I need to know slice thickness and timing of the CTA / MRA if we've got such bad quality results on the CTA / MRA. Slice thickness, timing, CTA / MRA, ultrasound training, and the renal arteries.

Dr. Lange: Great.

Ms. DeBruin: Thank you.

Dr. Lange: And so we're going to talk a lot about that after the break. So, thank you very much, Dr. Lockhart. Dr. Zuckerman?

Dr. Zuckerman: Yes. I'd like to extend Dr. Corriere's request regarding the diversity analysis. The effect of renal denervation in the African American population is an important one to consider. After lunch, can you please come back with your results from both HTN-OFF and HTN-ON in this important subgroup and explain that place.

Dr. Lange: Great. So, hypertension off, hypertension on results in the black population. Great. I've got three more, Dr. Cetnarowski.

Dr. Cetnarowski: Thank you. So, with regards to ON-MED expansion, are there any patient diary data to corroborate the findings in increase in medication use? That's the first point. And then, are there any medication increase or decrease data for the long term, meaning beyond that six to 12 month, from that six to 12, out to 20, 24 months? Are there any medication data for increase or decrease in that population? Thank you.

Dr. Lange: Great. All right, Dr. Corriere?

Dr. Corriere: Real quick, sorry if I missed it earlier. I was just curious if these were all transfemoral access, if there was any transradial cases, and if there was specific training or access-specific considerations related to the protocol. Thank you.

Dr. Lange: Okay. And then Dr. Starling, and then Dr. Damluji. And that will wrap us up.

Dr. Starling: My questions relate to the escape criteria and, what was the blood pressure measurement that was used? What was the adjudication? Was it investigator discretion, et cetera? And secondly, were these patients censored? That's the impression I got. And/or is there follow-up data on the patients that met escape criteria?

Dr. Lange: Thank you. And then Dr. Damluji.

Dr. Damluji: Yes, sir. Thank you. So, my comment and question is on the ON-MED study about 74%, 97 patients, crossed over after six months from the sham control to the RDN. Is there any efficacy data for those who crossed over in the unmet study?

Dr. Lange: Okay, great. Alright, we're going to take a 10-minute break.

FDA Presentation

Dr. Lange: Great. We will now proceed to the FDA presentation. I would like to invite the FDA representative Mr. Hiren Mistry. To begin, the FDA representative will have 75 minutes to present and the presentation can begin now.

Mr. Mistry Good morning. Today, FDA will be discussing the pre-market approval application, or PMA, for the Symplicity Spyral Renal Denervation system. We appreciate the panel's time today and the opportunity to discuss this novel device.

My name is Hiren Mistry. I'm a biomedical engineer in the FDA's Office of Cardiovascular Devices and the lead reviewer for this PMA. A few members from the team are presenting today. However, we would like to acknowledge the expertise and feedback provided by the entire clinical and statistical review team listed on this slide.

This is an outline of the topics on which we will present today. I will begin by discussing background information on hypertension, the PMA device, the proposed indications for use, and an overview of the clinical studies. Dr. Adrijo Chakraborty will then discuss the clinical studies from a statistical perspective. Dr. Meir Shinnar will then discuss clinical study results and Dr. David Gebben will discuss the patient preference study. I will then discuss the post-approval study design and summarize today's conclusions.

The proposed device aims to treat patients with hypertension, a condition that remains a major public health issue. 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 of Black Americans at 57%, than either Caucasian or Hispanic Americans, both at about 44%. Additionally, the link between hypertension and an increased risk of serious conditions including stroke, heart disease, heart failure, vascular disease, renal disease,

et cetera, is well established. To date, anti-hypertensive medications have been the mainstay of treatment, but patient adherence to blood pressure medications is only about 60%, and less than 50% of patients achieved their target blood pressure goal.

2017 guidelines published by the American College of Cardiology, American Heart Association, and other organizations, set thresholds for the 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 above 140 mmHg, or a diastolic pressure above 90 mmHg.

A patient is considered to have uncontrolled hypertension if their blood pressure remains above goal, either because of non-adherence treatment or despite adherence to treatment. Treatment-resistant hypertension is present if a patient has an above-goal blood pressure, despite the use of three anti-hypertensive medications with complimentary mechanisms of action, one of which is a diuretic. These definitions are important when considering the specific patient populations evaluated in the clinical studies and for the population for which 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 by the figure on the right, the renal vasculature is mainly innervated by efferent sympathetic nerves. Stimulation of these efferent nerves leads to increased sodium and water reabsorption, increased vasoconstriction, which reduces renal blood flow and the renal filtration rate, and increased renin angiotensin aldosterone system activity, all of which increase blood pressure. Thus, renal nerves are a therapeutic target for modulating sympathetic activity, in an effort to reduce blood pressure. The subject device delivers radiofrequency energy bilaterally in the main renal artery, accessory renal arteries, and distal branch arteries, just proximal to the renal parenchyma.

Renal Denervation is an approach to reduce sympathetic activity by ablating the nerve surrounding the renal artery. This can be achieved by percutaneously 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 renal denervation technologies were promising, showing large decreases in blood pressure. However, subsequent sham-controlled studies did not show the same degree of blood pressure reduction and there is no significant difference found between renal denervation treatment and sham-controlled groups. Further, several animal studies have shown evidence of re-innervation following the denervation treatment, which has implications for the durability of the treatment effect in humans.

Because of the uncertainty surrounding renal denervation technologies, FDA convened an advisory committee meeting in 2018 to discuss clinical trial design and sound ways to evaluate safety and effectiveness in hypertension devices. Some of the panel's key recommendations included: the use of a sham control study arm to help identify renal degeneration effects; the use of two trial designs, one in which patients are taken off their blood pressure medications in order to demonstrate proof of concept and one where blood pressure medications are standardized for study patients in order to minimize the confounding effect of blood pressure medication regimen changes; the use of ambulatory blood pressure as a primary measure of effectiveness due to limitations of measurement methods such as office blood pressure. The definition between group difference in blood pressure reduction of at least five mmHg is being clinically significant, although it was not specified if there should be 24-hour, daytime, or nighttime ambulatory systolic blood pressure. And finally, the value of patient preference information and weighing benefits versus risks.

The PMA device is the Spyral Radiofrequency Renal Denervation System, which consists of a percutaneous catheter used to deliver radiant frequency energy to ablate nerves surrounding

the main, branch, and accessory renal arteries. The electrodes are positioned in a helical pattern at the distal tip to deliver circumferential ablation and allow blood flow. The catheter is paired with a radio frequency generator, which provides the energy source and a user interface to control and monitor the treatment. The proposed indication for the Symplicity Spyral system is for the reduction of blood pressure in patients with uncontrolled hypertension, despite the use of anti-hypertensive medications or in patients in whom blood-pressure-lowering therapy is poorly tolerated.

The Symplicity Spyral system was granted breakthrough device status in March of 2020 based on its potential to provide benefit to patients with 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 a potential for significant impact by expediting their development, assessment, and review.

The Breakthrough Devices Program offers benefits listed here, intended to help bring these devices to market more quickly. However, it is important to note that a breakthrough device designation does not alter or reduce the statutory requirements for device approval. FDA still requires that a breakthrough device demonstrate a reasonable assurance of safety and effectiveness.

For breakthrough devices, FDA may be willing to accept greater uncertainty for pre-market submission, along with timely post-market data collection. If the uncertainty and the benefit risk profile can be balanced by other factors, including 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.

The Symplicity Spyral System was evaluated by multiple nonclinical and pre-clinical tests as detailed on this slide. FDA has determined that there are no outstanding nonclinical concerns.

I will now provide a brief overview of the clinical studies evaluating the Symplicity Spyral system.

Medtronic conducted HTN-off and HTN-ON as pilot studies, and then studied the device in expansion studies. For all studies, potential subjects were first screened by measuring office blood pressure. HTN-off subjects underwent a blood pressure medication washup period, while HTN-ON subjects remained on a stable blood pressure medication regimen. Then, subjects from the HTN-off and HTN-ON studies had to meet criteria for office and ambulatory pressures to be randomized in to the study. The pilot and expansion studies followed the same process. However, 26 subjects from the HTN-ON expansion were randomized at a one-to-one ratio, while the remainder were randomized at two-to-one, renal denervation to sham control. Some key study features include that: after three months, subjects in the HTN-ON studies were able to add medications per investigator discretion to reach a target blood pressure of less than 140 mmHg; and the subjects in pilot studies were unblinded and allowed to crossover at 12 months while the unblinding and crossover occurred at six months in the expansion studies.

Some of the key enrollment criteria for the HTN-off and HTN-ON studies include an age between 20 and 80 years old, having an office systolic blood pressure between 150 and 180, Office diastolic blood pressure over 90, and 24-hour ambulatory blood pressures between 140- and 170-mmHg. Additionally, blood pressure enrollment criteria would need to be met after blood pressure medication washout in HTN-OFF, or a blood pressure medication stability period in HTN-ON. In HTN-off, subjects discontinued blood pressure medications and underwent a

three-to-four-week washout period. In HTN-ON, subjects remained on a stable blood pressure medication regimen consisting of one to three meds for six weeks.

Subject follow-up activities include: measuring office blood pressures and ambulatory blood pressures through 36 months; renal duplex ultrasound studies, at six months for the pilot studies, and at both six and 12 months for the expansion studies; and if subjects have suspected renal artery stenosis, they may receive additional CTA or MRA imaging at six and 12 months.

I will now pass the presentation to Dr. Adrijo Chakraborty, who will discuss the statistical analysis plans for the HTN-OFF and HTN-ON studies.

Dr. Chakraborty: Thank you, Dr. Mistry. My name is Adrijo Chakraborty, I'm a statistician in CDRH's Office of Clinical Evidence and Analysis. I will discuss the statistical methods used for evaluation of the primary and secondary endpoints.

This table presents the number of subjects enrolled under each cohort in the pilot and expansion phases of the HTN-OFF and HTN-ON studies. For HTN-ON 257, subjects were enrolled after 80 pilot study patients were evaluated. For HTN-OFF 251 expansion cohort patients were enrolled after the pilot data were evaluated. For the primary effectiveness endpoint assessment, a Bayesian approach was implemented. The method allows for pooling the pilot information partially or entirely in conjunction with the expansion data to compute the treatment effect. The primary Bayesian cohort consists of all expansion subjects but may include partial pilot cohort information. Following the positive result of the HTN-OFF study, as interpreted by the sponsor, 35 additional subjects were enrolled.

The primary safety endpoint was defined as the occurrence of at least one of the major adverse events listed in the slide. The components of the MAEs had two parts. The first part consists of seven different types of major adverse events through 30 days. The second part is

defined as new renal artery stenosis defined as a greater than 70% diameter stenosis within six months of randomization, confirmed by renal angiography.

The pre-specified analysis set for the primary safety endpoint was the first 253 evaluable RDN-treated subjects from the HTN-OFF and the HTN-ON studies. However, additional analyses were performed based on all RDN-treated subjects. The safety event rate performance goal, or PG, was set at 7.1%. The PG was derived from the literature review. The null and alternative hypotheses for the primary safety endpoint are presented in the slide. Here, pi is the proportion of subjects who had experienced at least one major adverse event. Success of the primary safety was based on the p-value obtained using a binomial exact test.

The primary effectiveness endpoint was defined as change in SBP from baseline to three-month post-procedure measured by 24-hour ABPM for HTN-OFF and change in SBP from baseline to six-month post-procedure measured by 24-hour ABPM for HTN-ON. Note that primary effectiveness endpoint was evaluated for each trial individually. The intent to treat population was used for the effectiveness assessment. Baseline BP was used as a covariate in the statistical model to derive the treatment effect estimate.

A Bayesian approach was used for analyzing the primary effectiveness endpoint. This approach allows for incorporating prior information in the current context, information from pilot data with the pivotal or expansion data to derive estimate of the parameters of interest. The prior distributions of the parameters of interest, such as BP changes in the treatment and control groups were obtained using a Power Prior approach. The amount of information used from the pilot was based on the similarity between the outcomes of the pilot and expansion cohorts. This method allows for mitigating the influence of the prior information depending on the similarity of the pilot cohort outcomes to the expansion cohort outcomes. Greater similarity would indicate larger amount of pilot information will be incorporated. If the pilot and expansion cohort

outcomes are somewhat similar, pilot cohort information will be incorporated only partially. The diagram presented here is taken from the article cited on the slide. The diagram shows three different scenarios:

The top panel shows that prior outcome data and the current outcome data are very similar. Therefore, in this case, a large amount of prior information will be used in the posterior, which is derived using both current data and pilot information, and is impacted by both current and pilot data results. The middle panel shows that the prior and current data are somewhat similar, but not as similar as the first panel. In this case, the amount of information to be used from the pilot data is less than the scenario described in the first panel. In this case, the impact of pilot data in the posterior will be less than the scenario described in the first panel. The third panel presents a scenario when outcome of the prior and current data are very different. In this case, very little or no pilot cohort information will be used. Therefore, the posterior will be minimally impacted by the pilot data. It will primarily depend on the current data.

This slide presents the primary effectiveness hypothesis used for HTN-OFF and HTN-ON studies. The statistical hypotheses were formulated as a superiority test to compare the performances of the treatment and control devices. Pre-specified Bayesian-adaptive designs were implemented to each study separately. Pre-specified statistical success criteria were established for each study. The Power Prior approach described in previous slides was implemented to evaluate the primary effectiveness endpoint for the two studies. For each HTN-OFF and HTN-ON expansion studies, interim analyses were planned. For HTN-OFF, interim analyses were planned when 210 and 240 evaluable subjects were available. Enrollment was stopped after the first interim analysis. For HTN-ON, interim analyses were planned when 110 and 149 evaluable subjects were available to determine if enrollment could be stopped.

For this study, the enrollment continued to full enrollment.

Note that, for the proposed approach, the amount of information to be used from the pilot study is determined separately for treatment and control arms. The Power Prior approach uses outcome data to determine similarity of the pilot and expansion data. The amounts of pilot data leveraged may vary at each interim analysis or the final analysis. Sensitivity analyses were conducted to study the robustness of the result. As a secondary analysis of the powered primary effectiveness endpoints, an analysis of covariance method was used to determine the baseline-adjusted treatment effect estimate.

Several secondary effectiveness endpoints were proposed to compare the performances of the treatment and the control devices. In addition, medication burden was analyzed by the number of anti-hypertensive medication and medication index. In the following presentation, Dr. Meir Shinnar will discuss the definition of medication index and the medication burden analysis in detail. The Bayesian approach discussed for the primary endpoint assessment was also used for analyzing the change in office BP endpoint for the HTN-OFF and HTN-ON studies. For the rest of the endpoints for both HTN-ON and HTN-OFF studies, this Bayesian method was not used. Note that the results of the secondary endpoint assessment may not be interpretable if the primary endpoint was not met. Several secondary endpoints were analyzed with no pre-specified plan for multiplicity adjustment to control for the overall type 1 error rate. Therefore, the p-values associated with most of these endpoints should be interpreted with caution.

Pre-specified subgroups were analyzed to study the consistency of the results across subgroups. Note that, for the primary endpoint assessment, the Bayesian method allowed for incorporating partial pilot cohort information. This approach wasn't used for subgroup analysis. Unlike the primary effectiveness endpoint assessment, the full cohort, that is pooled pilot and expansion datasets was used for subgroup analysis. Now I would like to turn our presentation over to Dr. Meir Shinnar, our primary clinical reviewer. Thank you.

Dr. Shinnar: Thank you, Dr. Chakraborty. I'm Meir Shinnar, a heart failure transplant cardiologist, and a Senior medical officer at the Office of Cardiovascular Devices. I'll be discussing the clinical study results.

This is a summary of the clinical trial design. There were two sets of trials, HTN-OFF and HTN-ON targeting somewhat different populations. HTN-OFF enrolled patients with blood pressure medications, could be held for four months. HTN-ON had patients on one to three antihypertensive medications whose medications could not be held. Each set of trials had a pilot and an expansion cohort. A recurring issue will be whether and how to combine the results of the pilot and expansion cohorts.

This is HTN-OFF subject accountability that includes both the pilot and expansion cohorts. There were eight patient withdrawals through 12 months, three in the RDN group and five in the sham group, and one death in the sham group. 81 patients crossed over from Sham to RDN.

This is the subject accountability of HTN-ON that includes both the pilot and expansion cohorts. There were four patient withdrawals in 12 months, one in the RDN group and three in the sham group. 60 patients crossed over from Sham to RDN.

The HTN-OFF blinding assessment showed that subject blinding was effective and was comparable between off RDN and sham subjects.

Similarly in HTN-ON subject blinding was effective and was comparable between rfRDN and Sham subjects.

In HTN-OFF, pilot and expansion cohorts in both treatment groups were similar on most demographic or clinical characteristics. Mean age in the fifties, predominantly male at 63%, roughly equal US and OUS, except in pilot trial, which was 65% OUS. Note that about half of

subjects did not specify race, which can be challenging data to obtain in OUS subjects leading to small sample sizes for the race/ethnicity subgroups.

The mean baseline office systolic blood pressure and 24-hour ASBP in HTN-OFF was similar across the pilot and expansion cohorts in both RDN and sham groups, averaging in the low to mid 160 mmHg for office blood pressure and to the low 150s mmHg for 24 hours ASBP.

In HTN-ON, pilot and expansion cohorts in both treatment groups were similar in most demographic and clinical characteristics, except that the pilot cohort had more OUS subjects than the expansion cohort. Compared to HTN-OFF, there was a higher proportion of OUS subjects and a male preponderance, 78-87%, was more pronounced. The mean age was in the fifties. Similar to HTN-OFF, about half of the subjects did not specify race, leading once again to small sample sizes for the race/ethnicity subgroups.

The mean baseline office systolic blood pressure and 24-hour ASBP was similar across the pilot and expansion cohorts in both RDN and Sham groups, averaging in the low to mid 160 mmHg for office blood pressure and the high 140 to low 150s milliliters mercury for 24-hour ASBP.

Here, the often-procedural results. Procedural success was high in both HTN-OFF and HTN-ON, with only one procedural failure in HTN-ON.

I'll now review the HTN-OFF data for effectiveness.

Although the pre-specified analysis was Bayesian, we are presenting the frequentist data on the pilot expansion in full cohorts first, to show the similarity between the pilot and expansion cohorts. The figures show generally concordant results between the pilot and expansion cohorts for both 24-hour ASBP and Office systolic blood pressure, which will be reflected in pilot and expansion cohort data pooling in the patient analysis on the next slide. In this and all subsequent slides, the full cohort includes pool data from the pilot and expansion subjects without any

discounting. For 24-hour ASBP, the figure on the left, there was a 3.9 mmHg relative blood pressure reduction observed in the full cohort analysis in favor of RDN versus sham. For office blood pressure, the figure on the right, the systolic blood pressure, a difference was 7.1 mmHg in favor of RDN. P-values were not adjusted for multiplicity.

The primary effective endpoint in HTN-OFF was a Bayesian analysis of the reduction of 24-hour ASBP at three months. Because of similarity of pilot and expansion cohort results, the Bayesian analysis included most of the pilot cohort data, 30 of 35 rfRDN subjects and 34 of 35 sham subjects. The 24-hour ASBP reduction effect size was 3.9 mmHg in favor of rfRDN, with a posterior probability of 0.9996, which met the study success criterion. Of note, the 3.9 mmHg treatment difference is less than the five mmHg difference between treatment groups discussed at the 2018 advisory panel as being clinically meaningful for ASBP reduction. For the secondary effectiveness endpoint, the office BP reduction of the difference was 6.5 mmHg in favor of RDN and the posterior probability also met the study success criteria.

This slide shows a full cohort 24-hour ASBP results at three months. With 24-hour ASBP in the left plot, nighttime ASBP in the middle plot, and daytime ASBP in the right plot. For nighttime ASPB, RDN was associated with a slightly larger numerical effect size versus sham compared with daytime. A reduction in nighttime ASBP is considered an important endpoint, but without consensus yet on what is a significant reduction.

This slide shows, for the full cohort, the proportion of HTN-OFF subjects with an office systolic blood pressure reduction between five and greater than or equal to 20 mmHg at three and six months. Recall that patients remain blinded and received protocol-driven blood pressure medication escalation as needed between three and six months to reach a goal of less than 140 mmHg. At three months, the left figure, a higher proportion of RDN subjects had office blood

pressure reduction in all blood pressure treatment tiers, but at six months, the middle figure, the OSBP difference between RDN and the sham subjects, was no longer present.

The figure on the right shows the proportion of full cohort subjects that achieve the target ASBP goal of 140 mmHg. At three months, when the subject were OFF-MEDs, more audience subjects were below the 140 mmHg versus sham, but, that said, the proportion of audience subjects at target was only 16%. At six months, after blood pressure meds could be restarted, there was a 4.8 difference in the proportion of subjects with an office blood pressure less than 140 mmHg in favor of the RDN group. Also of note, were around 50% of subjects in both treatment groups that had not achieved target ASBP at six months.

The primary effectiveness endpoint was assessed at three months. However, a durable blood pressure reduction is important to clinicians and patients when considering benefits and risks of an invasive vascular procedure. In HTN-OFF, there were data through 24 months. Looking first at the RDN group alone, the blue bars in the figure, the 24 ASBP reduction versus baseline increased from 4.5 millimeters at three months, to 15.3 mmHg at six months, and the blood pressure reduction was sustained through 24 months. But, it's important to consider blood pressure changes over time in RDN subjects versus sham subjects, the gray bars in the figure. Recall that at three months, there was a 3.9-millimeter greater reduction in 24-hour ambulatory systolic blood pressure in favor of the RDN groups versus the sham group. 24-hour ASBP declined in both treatment groups after three months and by six months, the ASBP reduction compared to baseline was now greater in the sham group versus the RDN, the 1.7 mmHg. At 12 and 24 months, the ASBP reduction compared to baseline continued to be greater in the sham group by 3.9 and 3.1 mmHg, respectively. There are factors to consider in interpreting the longer-term blood pressure data. BP meds could be added to improve blood pressure control. The expansion cohort was unblinded to treatment assignment after six months, and the pilot cohort

was unblinded after 12 months. The impact of unblinding is uncertain, but could have introduced bias, and the number of patients in the sham group declined due to crossover with an unclear impact on the treatment difference. P-values were not adjusted for multiplicity.

Medication burden is important in assessing changes in anti-hypertensive therapy. We focus on Medication Index 1, also known as anti-hypertensive load index, as a measure of medication burden, which is defined as the sum of all anti-hypertensive medications of the dose the patient is taking over the maximum standard dose for that medication. It has the following properties: For individual patients, MI1 translates to the number of maximum standard medication doses they are taking. That is, for a patient taking one med at full dose, a second med at one half max dose, and a third medication at one quarter of maximum dose, the medication index one equals 1.75. For a population, MI1 has a straightforward clinical interpretation, which is why we prefer it rather than Medication Index 2. The average MI1 for the population is the average number of maximum standard doses a patient group is taking. In the medication burden analysis, we look at the average change in MI1s from baseline to a given follow-up time point for both the RDN and the sham populations. The relative change over time is a difference of the average change between the two populations. Thus, a relative change of -1.5 at three months compared to baseline, means that at three months, the sham population on average increased the MI1 over baseline by 1.5 full medication doses more than the RDN population increased its MI1 over baseline.

On this slide, we show the changes in 24-hour ASBP with RDN versus Sham to 12 months, along with the relative change in Medication Burden Index 1 or MI1. At three months, the 3.9-millimeter greater reduction in favor of RDN was associated with a 0.1 MI1 greater increase of a baseline in the RDN group versus sham. At six months, the sham group had a 1.7-millimeter greater blood pressure reduction versus RDN that was associated with a 0.2 MI1

greater increase over baseline in the sham group versus RDN. For perspective, a 0.2 MI1 difference corresponds to an increase of one fifth of a full dose pill. At 12 months, the sham group had a 3.9-millimeter greater BP reduction versus RDN that was associated with a 0.19 MI1 increase over baseline in the sham group versus RDN. The factors to consider in interpreting the longer-term data that we discussed previously should also be considered here.

This is a subgroup analysis at three months. Overall, the reduction 24-hour ASBP in favor of RDN at three months was generally consistent across subgroups. We do know plasma ran activity, which had a 0.09 p-value for interaction.

Patients with a low plasma renin activity had four mmHg, less blood pressure reduction than patients with a high plasma renin activity. This is consistent with sympathetic activity physiology. This suggests that patient with low PRA may have a reduced response to RDN. Further research is needed here.

Next, I'll turn to the clinical effective results of the HTN-ON study.

As with HTN-OFF and HTN-ON, the pre-specified analysis was Bayesian. We are presenting the frequentist data on the pilot expansion and full cohorts, first, to show the dissimilarity between the pilot and expansion cohorts, in both RDN and sham arms. The discordant results between the pilot and expansion cohorts will be reflected in the limited pooling of pilot cohort data and expansion cohort data in the patient analysis on the next slide. ASBP results are shown in the left figure. In the pilot cohort, the plot of the farthest left, there was a 7.3-millimeter difference in ASBP reduction in favor of the RDN group. In contrast, in the expansion cohort, the center plot in the left figure, there was a negligible less than 0.1-millimeter mercury ASBP reduction difference between RDN and sham groups. Compared to the pilot cohort, in the expansion cohort, the RDN underperformed and the sham group overperformed. In the full cohort that pooled pilot and expansion cohorts, there was a 1.9-millimeter ASBP

reduction difference in favor of the RDN Group. For office blood pressure, the right figure, the RDN results in the pilot and expansion cohorts were generally similar, although the expansion group arm showed a greater blood pressure reduction than in the pilot sham arm. The office BP reduction treatment difference observed in the full cohort, the plot on the right, was 4.9 millimeters in favor of the RDN group. P-values were not adjusted for multiplicity.

The HTN-ON primary effectiveness endpoint was the Bayesian analysis of the reduction of 24-hours systolic ABPM at six months. Because of the discordance between the pilot and expansion cohort results, the Bayesian analysis included very little of the pilot data, only seven of the 36 RDN subjects and practically no sham subjects. The patient estimate of the treatment effect was a negligible 0.03 mmHg with a posterior probability of 0.508, which failed to meet the study's success criterion. For the office blood pressure secondary effectiveness endpoint, the similarity between the pilot and expansion cohort results allowed using the data from all 38 RDN subjects in the patient analysis, but outcome dissimilarity in the sham group only allowed use of six of 40 sham subjects. The Bayesian estimate of the office systolic blood pressure reduction treatment difference was 4.1 mmHg in favor of RDN, and the posterior probability met the study success criterion. The discordant 24-hour ASBP results between the pilot and expansion cohorts should be considered in interpreting analysis of the HTN-ON full cohort, which pools pilot and expansion data in their entirety.

This slide shows 24-hour full cohort ASBP results at six months in the left plot, stratified by nighttime ASBP in the middle plot, and daytime ASBP in the right plot. For nighttime ASBP, RDN was associated with a larger numerical effect size versus sham compared with daytime ASBP. P-values were not adjusted for multiplicity.

This slide shows the discordant results in pilot and expansion results for nighttime, here defined as midnight to 6:00 AM ambulatory systolic blood pressure. The treatment difference in the pilot cohort was 8.4 mmHg in favor of RDN versus only 0.7 mmHg in the expansion cohort.

This slide shows through the full cohort viewed as one trial, the proportion of HTN-ON subjects when office systolic blood pressure reduction between five and greater than or equal to 20 mmHg at three and six months. Recall that patients remain blinded throughout six months with medication adjustment allowed only for breakthrough or safety concerns. At both three and six months, a numerically higher proportion of audience subjects had office blood pressure reductions at all BP treatment tiers. The figure on the far right shows the proportion of HTN-ON subjects that were below the target SBP goal of less than 140 mmHg. At three and six months, more RDN subjects were below the 140 mmHg goal versus sham. But even in the RDN group, less than 20% of the subjects were at goal systolic blood pressure. Again, p-value is not adjusted to multiplicity.

In view of the absence of a 24-hour ASBP reduction in the RDN group versus a sham group, the sponsor evaluated possible confounders that may have affected the results. These include blood pressure medication changes, the sham group increased medications more than the RDN group, and missing ABPM data in the sham and RDN group may have impacted the effectiveness results.

Looking at the changes in BP medications from baseline to six months, the relative change in medication index 1 at six months was 0.2, corresponding roughly to an increase of slightly less than an eighth of one additional full dose pill in the sham group versus the RDN group.

For missing ABPM data, there were 29 unevaluable ABPMs in the full cohort, 14 in the RDN and 15 in the sham group. It's uncertain to what extent, if any, the differences in missing

24-hour SBP measurements between RDN and sham groups in the expansion cohort may have impacted the lack of treatment effect difference associated with RDN in the expansion cohort.

When considering the durability of blood pressure reduction HTN-ON beyond six months associated with RDN, only the HTN-ON pilot cohort data available, recall that HTN-ON expansion cohort, there was no difference in ASBP reduction in the RDN group versus the sham group. In this hypertension analysis, limited to the pilot cohort, 24-hour ASBP reduction versus baseline BP group increased over time. After six months, BP medications could be added to improve blood pressure control, and at six months, the ASBP reduction difference was 7.3 mmHg in favor of the RDN group versus the sham group. But at 12 months, the ASBP reduction treatment difference narrowed to 1.7 mmHg. Not shown on this slide is that the medication index 1 in sham subjects increased by 0.4 more than the RDN group. Patients were unblinded at 12 months and at 24 months, ASBP reduction treatment differences increased to 11.2 mmHg associated with a further drop in RDN ASBP and unexpected smaller ASBP reduction in the sham group. The overall sample size for this entire analysis is very small. These caveats present challenges to interpreting the relative long-term treatment effect of RDN versus sham.

For hypertension on subgroup analysis 24-hour systolic blood pressure at six months, the results were generally consistent across subgroups, but two subgroups, US versus OUS subjects, and black Americans versus non-black Americans, deserve further study. FDA considered interaction p-value of less 0.15 as meaningful and the interaction p-value to the US versus OUS is 0.01. For black Americans versus non-black Americans, interaction value is 0.21, close to the 0.15 level.

Considering US versus OUS subjects in HTN-ON at six months, the figure on the left shows that US sham subjects had a numerically greater 1.5 mmHg, 24-hour ASBP reduction versus RDN subjects. But the treatment effects were reversed in OUS patients with a greater

reduction, 4.8 mmHg in 24-hour ASBP in the RDN group. Office SBP favored RDN in both US and OUS subjects with a larger effect size in OUS subjects. In HTN-OFF there was an ASBP difference of 2.7 and 4.7 millimeters respectively in US and OUS patients, both in favor of RDN with a non-significant p-value for interaction.

More US sham subject increased BP meds and fewer reduced BP meds and US RDN subjects. The increase in BP meds in US sham subjects was 0.24 meds more than RDN subjects. BP med changes were similar in OUS RDN and sham groups.

In Black Americans, the sham groups had a 5.4 millimeter greater 24 SBP reduction versus RDN. However, for the office SBP the treatment difference was reversed, favoring RDN by 3.4 millimeters. Discordant SBP trends were not observed in non-black Americans or in non-US subjects. Black Americans in the sham group increased BP meds versus baseline by 0.3 meds versus Black Americans in the RDN group. Results in the Black American subgroup should be interpreted with caution due to very small sample sizes. Plasma renin activity was not evaluated in HTN-ON trial. On average, black patients have a lower plasma renin activity versus Caucasians evaluating the potential impact of plasma renin activity on BP changes post RDN maybe a target for future research.

They will now review the safety results of HTN-OFF and -ON. The primary safety endpoint with a composite of 30-day major adverse events and hemodynamically significant renal artery stenosis at six months.

The primary safety endpoint: In the first 253 evaluable subjects event rate was 0.4%. The upper bound 95% confidence interval was 1.9%. It was far below the performance goal. For pooled HTN-OFF and -on subjects there were only two safety events. Both were femoral pseudo aneurysms.

We were concerned about potential long-term sequela of renal denervation treatment. A less than 70% renal artery may not be detected by duplex ultrasound, but could have long-term clinical consequences if stenosis progressed. We therefore request a sub-study of protocol-driven CTA or MRA of at least 150 patients at 12 months. There were 206 patients with qualifying CTAs and MRAs, over which six had 50-99% lesions, and another two with CTA / MRA with a 76 to 99% lesion at 12 months, who had a green angiogram that was read by the site as negative, but interpreted by the core lab is indeterminate. Therefore, 12 months, the incidents of 50 to 99% stenosis by CTA or MRA could be as high as 2.9% to 3.9%.

Renal function was assessed by estimated glomerular filtration rate, eGFR, which is calculated from serum creatinine for two years for the hypertension of full cohort HTN-ON pilot study since long-term data is not available for the expansion cohort. eGFR was similar between the RDN and sham groups through two years. There were only 23 patients with baseline eGFR less than 60. That is not adequate data to assess safety in that population.

I'll next briefly discuss some supplementary clinical data. The GSR, Global SYMPLICITY Registry, is a prospect of multi-center, single-arm, open label registry. The registry aims to include a patient population resembling real world clinical practice. Enrollment began in 2012 in countries where Medtronic Renal Denervation system is approved.

Here are 24-hour BP results supported by the sponsor and patients treated with a current PMA device. This showed a persistent reduction of about 8-10 mmHg in the first two years with further drop of another five to six millimeters by 36 months. These effects are somewhat larger than seen in the sham-controlled trials. There are some limitations in interpreting the clinical significance of RDN registered data. The GSR is unblinded in single arm. Other factors beside the RDN procedure itself can impact BP responses, including placebo and Hawthorne effects. Regarding the importance of blinding and sham controls, the Symplicity HTN-2 of the earlier

generation Flex catheter, which was a randomized unblinded study, showed a 32 millimeter of mercury office blood pressure reduction in audience subjects versus control. The sham control Symplicity HTN-3 trial only showed a two-millimeter blood pressure reduction difference.

The sponsor provided data on, blood pressure in time and target range from the GSR registry. The data are interesting and there is data suggesting that the BP control assessed by TTR is associated with improved clinical outcomes. The following caveats applied to the GSR TTR data. Placebo or Hawthorne effects can affect BP reduction that can be independent of the effects of renal denervation. TTR does not resolve this issue. It gives a measure of blood pressure control. TTR is not yet fully validated for clinical outcomes. BP measurements were infrequent with measurements done six or 12 months apart, and they were missing data requiring imputation. The clinical impact of data amputation is uncertain. The TTR literature often use BP measurements spaced one or three months apart. I'll now turn the presentation over to Dr. David Gebben, who will discuss the patient preference study.

Dr. Gebben: I am David Gebben. I'm 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's 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 would not result in a substitution of clinical data, but instead assesses the relative value the patient’s place on a treatment profile or

its alternatives. Patient preferences can help evaluate how patients view trade-offs between 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 assessments 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 the patient's willingness and unwillingness to accept the benefits and risks of the subject device of a PMA relative to its alternatives.

To be included in 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 valid 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 of minimal cognitive bias, features or attributes relevant to the treatment options.

The sponsor conducted a patient preference survey through a discrete choice experiment on 400 US patients to view how attitudes towards rfRDN intervention treatment versus pills only to treat hypertension. The study was conducted in alignment with CDRH PPI guidance recommendations and published literature, and followed good ethical research practices like getting IRB approval and informed consent. The sponsor incorporated FDA feedback on the design of the study and the attributes, characteristics, and levels of the treatment options presented to respondents in the PPI survey, which were based on the clinical protocol, literature, and discussions with the FDA. In the actual survey, respondents saw educational material on each of the attributes shown on the left side of the figure, along with the levels associated with

the attribute in the columns labeled treatment A and treatment B. The educational material defined the attributes and levels that the respondent saw in the survey. The respondent then faced a series of choices similar to the one shown here with variations in the characteristics and levels presented for each option. 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 weights.

These preference weight results are shown in the figure on the right. The results of the study were generally what would be expected. Levels that we would expect to be preferred were given greater importance. For example, in general, for their duration of effect, regardless of the treatment option, a duration of 10 years was preferred over a duration of three years, which was preferred over a duration of one year. The longer the distance or length of each line representing an attribute labeled at the bottom of the figure, the greater importance that respondents on average gave to that attribute. The reduction in office systolic BP has the largest vertical distance. Therefore, it was the attribute given the most weight on average by respondents. In comparison, the shorter vertical distance of the risks associated with treatments indicate that for either surgical treatment or pills, respondents gave less weight to the risks when choosing between treatment options.

In general, the study showed that respondents were willing to accept greater levels of risk from in the interventional treatment or pills with greater levels of blood pressure reduction. The sponsor created various clinical scenarios to estimate what percentage of patients would choose a specific treatment profile. The estimate suggests that between 15.1% to 30.9% would choose sponsor’s interventional treatment. I'll now turn it back to Mr. Mistry.

Mr. Mistry Hello, this is Hiren Mistry again. I will now go into details regarding the proposed post-approval study and then summarize conclusions from the day.

Medtronic has proposed the AFFIRM study to serve as a continued access study, which can then transition into a post-market study. Medtronic plans to continue follow up of up to 200 treated subjects from the HTN-off and HTN-ON trials for an additional 24 months. These subjects would therefore have a total of 16 months of follow up after renal denervation treatment. Additionally, the AFFIRM study plans to enroll subjects with varying severities of uncontrolled hypertension and associated cardiovascular risk factors and comorbidities, including patients with chronic kidney disease, isolated systolic hypertension, and type-2 diabetes. These subjects will be followed for 36 months.

To evaluate safety, the study will capture major adverse events throughout the trial. To evaluate effectiveness, the study will assess the change in office systolic blood pressure, home blood pressure, and 24-hour ambulatory systolic blood pressure. Other endpoints include procedural characteristics, blood pressure medication version, the proportion of subjects requiring repeat renal denervation, and Time in Target range. Additionally, powered analyses are planned for specific patient subgroups evaluating the change in office systolic blood pressure from baseline to six months.

Panel input is requested for the following post-approval study considerations: training to help facilitate procedural success with new clinical users; evaluation of important patient subgroups such as pre-specified enrollment targets, who were female subjects, black Americans, and others; the need for long-term renal imaging; and assessment of blood pressure reduction durability.

I'll now summarize the overall conclusions from the presentation today to prepare for our discussion.

To summarize today's conclusions, HTN-off and HTN-ON, were designed to demonstrate the safety and effectiveness of the Symplicity Spyral System, prior to sham control subjects in

patients with under controlled hypertension. Regarding safety, there were no major safety issues identified. The primary safety endpoint was met, and the overall safety event rate, pooling all subjects from the HTN-OFF, and HTN-ON studies, was 0.4%. There are no cases of clinically significant renal arteries stenosis detected. A Bayesian power-prior method was used to analyze the primary effectiveness endpoints for HTN-OFF and HTN-ON. The HTN-OFF study met the primary effectiveness endpoint, demonstrating a between group difference in mean ambulatory systolic blood pressure reduction of 3.9 mmHg at three months in favor of renal denervation. The HTN-ON study did not meet the primary effectiveness endpoint at six months, and multiple hypotheses were proposed to help explain the potential reasons for the negative results.

Strengths of the clinical investigational plan include a powered, randomized, sham-controlled, blinded study design. Limitations of a clinical investigational plan include limited, long-term, randomized controlled trial data, and challenges interpreting the durability of blood pressure reduction because of confounding factors, such as medication changes, unblinding of study patients, and sham subject crossover to radio frequency renal denervation that reduced control group sample size. Lastly, the Patient Preference Study found that some patients may prefer the renal denervation procedure to taking an additional blood pressure pill. Thank you all for your time and attention. We look forward to hearing your discussion and recommendations.

Questions to FDA

Dr. Lange: I want to thank the FDA for their thorough and thoughtful analysis, and we'll now open it to the panel to ask any clarifying questions to the FDA or if we need to pose anything to the sponsor. So, Dr. Lewis, I'll let you start it off.

Dr. Lewis: I have two questions. The mean baseline blood pressures in the ON-MED study were similar between the sham and the denervation group. I wonder if you have analyzed though, a distribution of those blood pressures because I'm still trying to sort out why there was a

difference in medication use because your James Blinding index suggested blinding was effective. So, if you have a distribution or a histogram, did the average not really reflect the distribution?

Dr. Lange: Okay. So, Dr. Lewis, I'm going to put that to the sponsor. That's the sponsor's data. And so, let's ask them to produce a distribution of blood pressures for the online.

Dr. Lewis: Okay. That's fine. Whoever can answer it. I didn't know if the FDA may have done that analysis. My next question I think is definitely for the FDA, which is that the 2018 meeting and the briefing document from the FDA suggests that a clinically significant change in blood pressure, the lower limit of which would be five mmHg, and do they consider the 3.9 to be clinically relevant? Also, since, arguably, this is a single study proposal, do they consider the 0.02 p-value to be compelling?

Dr. Zuckerman: Okay, so let me give you a brief answer. Number one, the FDA doesn't want to bias the panel regarding clinically significant. The 2018 panel meeting was a general advisory panel to give more instructions to FDA and the industry as to what our realistic trial designs are. Five millimeters was suggested. We would really benefit from a thorough discussion this afternoon, given that blood pressure is a continuous variable, and when we look at any drug or device, it's always benefit versus risks, given potential benefits of treating blood pressure to reduce stroke, heart attacks, and other hard endpoints, Dr. Lewis. The second thing is that, again, the Center for Devices utilizes a different paradigm from the Center for Drugs, and we just need to accept that, by virtue of Congressional regulations, one trial with a p-value less than 0.05 is often very acceptable. In fact, the Center for Devices is most interested this afternoon in the clinical interpretation of the data. There's statistical significance and clinical significance, and I think all the panel members are aware of certain circumstances where the p-value might be 0.07, but there's convincing clinical evidence of a favorable benefit risk profile versus some studies

where the p-value might be 0.001. But there are potential problems with bias or design, which really render a finding of clinical significance non-evident.

Dr. Lewis: Thank you. Thank you.

Dr. Lange: Thank you. So, Julie, that that'll be one of the discussions we have this afternoon. There's a p-value and then there's a clinical value, so we'll talk about that. Thanks for bringing that up. Dr. Hirshfeld.

Dr. Hirshfeld: Yeah. I have two questions related to the relationship between the sham group and the RDN group, in terms of how we interpret the smaller differences of effect. And the first has to do with the medication issue that when the sponsor made their presentation, they indicated that there was a greater frequency of medication adjustment post-randomization in the sham group, and they implied that that crowded for some of the smaller differences than they might have wished for. Dr. Shinnar's presentation right now suggests that the magnitude of those changes was very small, and I'd like to try to get a better sense for just what sort of an impact that medication adjustment had. The second has to do with the cross.

Dr. Lange: So, John, I'm sorry. Obviously, we can talk about that. Is there something you want the FDA or the sponsor to answer?

Dr. Hirshfeld: I think it would be a question primarily of the sponsor. FDA's presentation suggests that the medication adjustment was very modest.

Dr. Lange: Okay.

Dr. Hirshfeld: And, so the sponsor should have an opportunity to rebut that. The second has to do with the impact of crossovers. For example, one might hypothesize that the people in the sham group who crossed over were the patients who had the poorest outcomes, and that therefore, the crossing over would've diluted the sham group of patients with poorer outcomes. And I haven't yet seen any data that showed the comparison between what the results were in this

crossover patients and the non-crossover patients and whether or not that might have affected the composition of the residual sham group following the crossovers. So, I think the sponsor could maybe clarify that for us as well.

Dr. Lange: Alright. So Vanessa, you have both of those things? Great.

Ms. DeBruin: As part of the answers we'll provide after the break.

Dr. Lange: Thank you so much. Thank you. Uh, Dr. Wittes?

Dr. Wittes: Yes. So, I have a few questions. The additional 35 patients, were they randomized one-to-one, and why did you include them in the frequentist analysis, but not in the Bayesian? Who were these people?

Dr. Lange: Okay, we'll ask the sponsor to address that. Great question. And next one?

Dr. Wittes: And then, again, I don't know whether this is FDA or sponsor, but on slides 47 and 48, how did you deal with the missing data in the middle and the last panels? And in 48, these cohorts aren't the same. I don't know how to interpret data when I'm looking at cohorts. They're not the same. And then, on slide 54, and there's a lot of discussion about how the sham in the pilot study and the expansion study, how they behave differently, and also how the active behave differently. Has there been a careful analysis to see, I mean the pilot is a tiny little study, so we don't see much variability. How do we know that what looks like a difference is actually a statistically significant or meaningful difference? Is this just the result of noise or is this a real difference?

Dr. Zuckerman: Okay. Could we pause here a moment? Vanessa, do you have copies of FDA slides 47 and 48? Misti Malone will send them to you during the break, because I think all of Dr. Wittes' questions could be answered by the sponsor when she's in possession of those two slides.

Ms. DeBruin: Okay, great, thank you.

Dr. Lange: So Vanessa, I'm sorry I inadvertently cut you off. She asked first about how the 35 patients, were they randomized and you were prepared to answer and also they were handled differently in the frequentist and Bayesian, if you'd like to address that now, I'll let you do so.

Ms. DeBruin: Great, thank you. So, in the OFF-MED pivotal study the DSMB met and considered that we could stop at the first interim analysis with the 331 patients. After that time point, we had patients that still remained in screening that were close to the time where they would've been receiving the randomization and the procedure. So, we let them finish going through that process, which is why we have the remaining patients, the 35 that you see as part of the full frequentist analysis. Since the Bayesian analysis was conducted on the 331 because that was what the DSMB used to determine whether or not the study would stop, we included the additional patients in the frequentist for completeness.

Dr. Wittes: Okay. Thank you. That's very helpful.

Dr. Lange: Great. And then we'll send slide 47 to slide 48 over to you, Vanessa. Thank you.

Ms. DeBruin: Thank you.

Dr. Lange: Dr. Yeh?

Dr. Yeh: My question is also on slide 48, can we put that FDA slide 48 up? Is that possible to do?

Dr. Lange: Certainly

Dr. Yeh: Is this FDA data or is this sponsored data that we're looking at on slide 48?

Dr. Lange: This is the data from the FDA.

Dr. Yeh: From the FDA.

Dr. Lange: I assume let's make sure that we're talking about, this is a HTN-OFF durability of blood pressure reduction slide.

Dr. Yeh: That's right.

Dr. Lange: Okay. That's the FDA generated slide. Go ahead Dr. Yeh.

Dr. Yeh: Well, I'm just noticing the same thing that Dr. Wittes and Dr. Hirshfeld were alluding to, which is that the data at 12 months and beyond, the denominators are so wildly different between the two groups, and I'm just trying to understand what this comparison is. It's clearly not a randomized ITT comparison that we're seeing at 12 months. Just, N drops from 159 at six months to 92 and then to 45. And does this reflect the crossover patients? How are the crossover patients being grouped here? Just trying to understand what we're seeing here. They don't look to be like randomized data that we're seeing at 12 months and 24, and I'm wondering if that partially explains what we're seeing. And my second data ask is that with these relatively small medication changes, I am thinking about it, it seems like we talked about this yesterday, that medication change is sort of an outcome in the same way that blood pressure's an outcome of the study. And I'm just wondering if the mean differences alone don't capture the full extent of potential differences between groups. And similarly, might it be beneficial to look at distributions of medication changes to understand if there are some patients who maybe had more, maybe on average the number is low, but maybe there's some variability there. It might be useful to look at.

Dr. Malone: Hi, this is Misti Malone. I'm the director of the Peripheral Interventional Devices team at FDA. This slide was actually one that was provided in Medtronic summary, so if they want to describe that patient population after the break, that would be helpful. And was there another question you wanted us to address regarding that or else I'll let them address it?

Dr. Yeh: No, that's it.

Dr. Lange: And Vanessa, are you able to provide the distribution of medication changes?

Ms. DeBruin: Yes.

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

Dr. Bates: I may have the same question as the previous three commenters. Could I ask slide 54 to be projected?

Dr. Lange: Yes, sir.

Dr. Bates: I also am impressed by the argument that the better-than-expected reduction in the sham group is a potential reason for obscuring a better treatment effect. So, I wonder if this slide could be reproduced at three months to see how the creep happened between early and six months. And if there could be even a simple histogram by month how many medications each group was on. Because the explanation would be that the sham patients were getting more anti-hypertensive medicines then we wanted them to get to show the treatment effect. Does that make sense?

Dr. Lange: It does. So, Vanessa, if we could provide this information at three months?

Ms. DeBruin: Yes.

Dr. Bates: Number of medications each group was on at the time point.

Dr. Lange: Yes. Great. Either a number of medications or med index, whatever you have.

Dr. Bates: Yeah. So, we see how the medications accelerated over the six-month treatment period, even though they weren't supposed to cross over.

Dr. Lange: Okay. Terrific. Thank you. Dr. Saville?

Dr. Saville: Yeah, just few questions here. I had the same question about the crossover, how that affects things. And the slide I was actually interested in was slide 50. My question is, were crossovers excluded from that analysis when we look at 12 months? That's one question, if you want to answer that now or if this is going to be answered after the break and maybe it will be.

Dr. Lange: Yeah. So, FDA are crossovers included in this slide or not?

Dr. Malone: This is Misti, I'll let Dr. Shinnar address that one.

Dr. Lange: Thanks.

Dr. Shinnar Hi. So, the data to six months has no crossovers and at 12 months is the data on all the patients we had, which excludes all the crossovers. This is similar to all of the durability slides that you have had on all the others where the crossover patients are excluded or imputed. So this data has to be interpreted, as we said, with caution for 12 months because all the crossover patients are excluded. There is also, many of the patients are unblinded between six and 12 months. The expansion cohort patients are all unblinded. And so, the multiple issues that affect the interpretation of the 12-month data, the six months data is relatively clean.

Dr. Saville: Okay. Thank you that, that answers my question. Stay on the same slide for just a minute. I was confused also with the delta, the medication index. Comparing this slide to slide 60, so for example, the numbers don't match up and I don't know if that's the same change of medication index or are we talking about something different because those numbers didn't align between those two sites.

Dr. Shinnar: So the, the change in the medication indexes, I look at the medication index in the sham group at baseline and that is 1.17. At six months, it's 1.34. So, they increase by 0.17 from baseline.

Dr. Saville: My question is typically on the delta between the treatment groups.

Dr. Shinnar: Right, so 0.17 and the RDN increased by 0.5. So, the delta is 0.12. Between 0.17 and 0.05. The delta is: RDN increased by 0.12 more than the RDN group.

Dr. Saville: I understand that, but what I don't understand is why the 0.07 difference doesn't line with slide 60 at three months. That says 0.1 difference. I'm confused why those two numbers don't match up.

Ms. DeBruin: Given the amount of time, can we address this after the break?

Dr. Lange: Yes.

Dr. Saville: Okay. One more question here. On 63, the FDA was shown the treatment effects by those various subgroups and one of those subgroups was specifically focused on the black Americans and non-black Americans. And that's the only subgroup in this whole table that isn't study-wide. So, I'm curious, is there a certain reason why we're looking at the treatment effect by race within a subset of US patients as opposed to race within the overall study population?

Dr. Malone: I can take this. If the subjects in the OUS may not have been captured, the race, I believe this was a question that was mentioned earlier regarding the distribution and the sponsor maybe you'll address more.

Dr. Lange: I mean outside the US, we don't have any race data.

Dr. Saville: Okay. That's helpful. Very last question, this will be quick, on slide 73, the GSR, I just want to make sure my understanding is correct. That registry database, that only includes persons who have undergone this renal denervation procedure or does it also include participants who don't have this intervention?

Dr. Shinnar: To my understanding, it's only patients who have undergone the procedure. Some of them have gone with a Symplicity and some have gone with the older Flex catheter. And so, they have separate data for both, but they've all undergone the procedure.

Dr. Saville: Okay. Thank you.

Dr. Lange: Dr. Nachman.

Dr. Nachman: Yes. Thank you, Dr. Lange. I have a question that's really maybe a request for more information from the sponsor. I was intrigued by the fact that, on the HTN-ON study, it seems to have been a particularly greater effect in the RDN-treated group compared to the sham with respect to nocturnal decrease in blood pressure. So, my understanding is that this is actually a clinically potentially very significant finding, and B. Not very common in studies of blood pressure treatment. So, it raised in my mind the question as to whether so-called non-dippers

because of the always on effect of renal denervation. Do non-dippers have a particularly good response to renal denervation and did the sponsor analyze age did you have non-dipper? And if you did, did you analyze those patients in particular as a subgroup compared to the others? I do have another question that maybe I will be asking in the afternoon, but this is not particularly to the sponsor, but maybe to my both statistical colleagues and cardiology colleagues.

This is, for example slide 58 and the HTN-ON study, it seems to me that the between group difference and blood pressure reduction was greater for higher degrees of blood pressure reduction. So, the between group difference was statistically, significantly different for those who dropped their blood pressure by 15 to 20 millimeters as opposed to only five millimeters, or 10 millimeters. And the way I'm interpreting this is that there seems to be quite a heterogeneity in response.

Dr. Lange: So Dr. Nachman, if there's a question to the sponsor or FDA, we'll entertain that. If not, I want you to hold that thought because that is important.

Dr. Nachman: Will do.

Dr. Zuckerman: Okay. Dr. Lang, could we ask the sponsor to better describe what they're showing here and whether they can see a heterogeneity in response if they pull these data out in a different manner? Dr. Nachman, you want to know if, for patients who had a better response of 15 or 20 millimeters, there seems to be a bigger delta between renal denervation and control? If the sponsor can better explain this heterogeneity, where the deltas at certain points seem to increase as the millimeter Hg difference increases. Is that your question?

Dr. Nachman: Yes. It seems to me that there is a subgroup of patients that seem to be particularly responsive to the treatment, and I'm very curious to know if that's the case, number one. And number two, has there been an effort to identify who these particular subgroups are?

Dr. Lange: That's a great question. Thanks Dr. Nachman. I don't see any other hands up right now. So, we're going to take a break. The sponsor won't be taking your break and the FDA will have a little break, but I appreciate the responsiveness, both of the FDA and to the sponsor. We're going to conclude this portion of the meeting. We will break for lunch.

Open Public Hearing

Dr. Lange: Welcome back. It's now 1:30 PM. I'd like to call this panel 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. And 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, 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 day published in the Federal Register, the FDA received 12 requests to speak, and each of the speakers will provide prerecorded presentations. They have three to five minutes allotted for their comments, and the first speaker is Dr. Barry Bertolet, who is a practice and private practice cardiologist in Tupelo, Mississippi. Dr. Bertolet, please proceed.

Dr. Bertolet: Hi there. I'm Dr. Barry Bertolet. I'm an interventional cardiologist from Tupelo, Mississippi, and thank you so much for allowing me to testify today regarding the Medtronic Spiral ablation catheter. In full disclosure, I was a US investigator in the spiral studies, but my following comments are my own, and I'm not being compensated by Medtronic or its subsidiaries for this testament.

As you all are aware, hypertension is one of those base diseases that leads to substantial end organ damage, like stroke and heart attack. But a greater concern to me is the adverse effects of hypertension that are felt unequally across the United States, affecting African Americans with a greater prevalence. Representing a state whose demographic is 39% African American in a state where nearly one out of two deaths are related to cardiovascular illnesses, hypertension control is of paramount importance to me and my practice and my patients. Nationally, the awareness of hypertension may be high, but the control with our present therapy is quite poor, less than 50%. And then beyond this, if we look at adherence to those chosen therapies at one year, it's also around 50%.

Now, we know that the impact of any given medical therapy for hypertension is about a 10-point reduction in blood pressure, as compared to placebo. Now in the SPYRAL OFF-MED study, we saw that similar 10-point drop in blood pressure in the treatment arm as compared to the sham arm. The big difference that I see in these spiral studies is that the suppression of blood pressure both day and night was independent of medical adherence and medication use. Many

have referred to this therapy as always on, so it's generally accepted that a five-millimeter blood pressure reduction, with medical therapy, we'll reduce stroke by 14%, coronary heart disease by 9%, and total mortality by 7%. So, I may assume that we will see a similar, if not greater reduction of these endpoints with RDN.

Finally, I will reassure you as an interventional cardiologist with oh-one-4our wire skills and a knowledge of renal anatomy. This procedure fits well within our skillset. The access and closure for this procedure is quite similar to a left heart cath, and the procedure's done using conscious sedation and it can be done in less than an hour. Since our nation's track record for control of hypertension is poor at best with our present technologies, and the consequences for failure of blood pressure controllers are so high, I would encourage the FDA to follow the lead of our European counterparts and approve this novel technology for the treatment and management of hypertension. Thank you again.

Dr. East: I'm Doctor Cara East. I'm a board-certified cardiologist and a clinical investigator of over 150 trials over the past 30 years. I have been involved in the Spyral Symplicity hypertension studies from their onset about eight years ago and have been involved in all the trials done to date. I am not being compensated for my testimony today, but I feel that this procedure gives us an opportunity to treat some patients for whom we do not have other therapeutic options. Patients with resistant hypertension may be on all three to four classes of blood pressure medications that have been shown to have cardiovascular endpoint reduction, and yet they still have high blood pressure that's not under control. Some patients have contraindications to some blood pressure medication classes. Others are intolerant to some of the blood pressure medication classes, and we need opportunities to treat these patients down into an optimal range.

Our renal artery nerve ablation can do that. In my experience, most of the endpoints for the trials were at three and six months, but when we followed these patients out to three years, just by adding medications and adding the procedure, we saw their blood pressures continue to go down and down and down, so that a large number by the end of three years are within the optimal range. I think this is important, that we have this as an as available therapeutic choice when we can't get patient blood pressure control any other way. It thus meets an unmet need today. So, I thank you for your time and appreciate all the work that you do.

Mr. Cash: Hello, my name is Daniel Cash. I am 59 years of age, a white male non-smoker and occasional drinker. I am a patient that has high blood pressure along with a family history of high blood pressures. I have not, nor will I receive any type of financial compensation for my testimony. I had the Medtronic renal denervation procedure in February of 2021. Prior to the procedure, I had been placed on a couple of different meds, including hydrochlorothiazide, which dehydrated me, causing cramps and headaches. Also, beta blockers were the next option, which I preferred to avoid due to known side effects. I experienced a few other side effects that reduced my quality of life, so we tried changing doses, then meds. My pressure got as high as 165 over 110 a few times, causing headaches and anxiety. This along with side effects caused stress in my life.

My cardiologist recommended I have this procedure. Post-op, my pressures have been very manageable with minimal medication. I am now taking the lowest dose of amlodipine available, five milligrams twice a day. At my recent six-month checkup, my blood pressure was upper one twenties over upper seventies. I rarely experience any blood pressure spikes anywhere near the pre-op levels. I would recommend this procedure to anyone struggling to control their blood pressure with meds and dealing with side effects. Before and after this procedure, I have been exercising very regularly, along with participating in many outdoor activities. This

procedure empowered me to continue to be very active in the outdoors. I also have tried to avoid sodium in order to manage my body fluid level. I discovered that when I sweated due to physical activity, my blood pressure would decrease substantially. So the management of fluids by avoiding foods that cause water retention, along with physical activity, help me stay within a healthy blood pressure range.

I feel as though this procedure has given me a much better option to control my blood pressure with minimal medication. I think the procedure, along with the healing period, was well worth the small amount of time required. Thank you very much for allowing me to speak to you and giving you my experience.

Dr. Schlaich: Hello. I am Dr. Marcus Schlaich, professor of medicine, nephrologist, and a European Society of Hypertension accredited hypertension specialist. I'm the Dobney chair in clinical research at the University of Western Australia and the Royal Perth Hospital here in Perth, Australia. I very much appreciate the opportunity to briefly speak on this important occasion. I have been an advisor to Medtronic and I received financial support and speaker fees, but not for this meeting. I have no other financial interests. I've been privileged to be involved as an investigator with renal innovation since its very beginnings. In fact, we have performed the very first renal innovation procedure in the world here in Australia at St. Vincent's Hospital in Melbourne in 2007. I feel privileged to have witnessed the progress and the advances we've seen over time. By now, you would've had the opportunity to review the substantial evidence that is now available on catheter-based renal innovation.

So, I would like to focus in these three minutes on two aspects, which in my view, are critical in order to assess the clinical utility of renal renovation as a means of lowering blood pressure and thereby reducing the risk for cardiovascular events. Number one is the safety of the procedure, which has uniformly been demonstrated in every single study that has been

conducted. Number two is the durability of the blood pressure lowering effect with renal innovation. In my view, hypertension management is a marathon, it's not a sprint. And long-term blood pressure improvement and control is critical to ensure maximum clinical benefit. And I would like to share two lines of evidence that speak to the mid and long-term efficacy of renal innovation in a clinical context.

First, here you see the slide data from the Global Symplicity Registry, which included patients with various risk profiles and demonstrated consistent and sustained 24-hour blood pressure lowering until three years, at a level that is associated with substantial risk reduction for cardiovascular events. Second, data from our own group looking at patients who on average had the renal innovation procedure some nine years ago, and who experienced minus 12 over minus nine-millimeter mercury 24-hour blood pressure reduction, and this was on one less medication than they had at baseline. I feel that the long-term efficacy is of very high clinical value for these high-risk patients. I thank you again for the opportunity to speak. Thank you.

Mr. Bradford: Hello, my name's Ken Bradford. I'm a 65-year-old male who has had in the past uncontrollable blood pressure. And I want to thank you guys for letting me at least have my voice heard about what's happened to me since then. About, and I can't remember the date, but about five years ago, I was lucky enough to be recommended by my cardiologist to be part of a study. And that study happened to be all about the rental denervation and the ablation. And again, I had, I was the guy that had 210 over 120 without medications, that couldn't be controlled with medications for very long because they had to change me, because it would just go, it would go crazy after a year or two, and then I'd have to readjust my medications, do different medications. They couldn't control my, my blood pressure.

I'll say that after the ablation, there was a period of time where I had to, during the study, go unmedicated, and during that time my high blood pressure was like 180 over 90. So the

ablation did not cure my blood pressure issues, though it tremendously helped them. It knocked at least 30 points off my blood pressure. That is just one part of it. The other part of it is, since the ablation, I have yet to have my medications altered from the very beginning when they got me down to where I needed to be. That being said, I'm on probably 50% of the medication that I was on prior to the ablation, as well as I've not had to go to the cardiologist with raging blood pressure back, even if it were the 180 over 90. I've never had that issue. Once I got on a medication, I've stayed on that same level of medication since the procedure.

Again, I want everyone to know that I have no part of the company. I have no interest in the company, be honest. I don't even, no I do know it, it's Medtronic. I was going to say, I don't even know the name of the company, but I do know the name of the company. I'm just a lucky patient that got to be a part of this, and I, again, I don't think it fixed me. I think it helped me tremendously and I'm thankful for the procedure and all those that were involved.

Dr. Randolph: Hello, and thank you very much for the opportunity to speak with you today. My name is Dr. Tiffany Randolph. I am a board-certified cardiologist, and I'm also the founder and the director of the Advanced Hypertension Clinic in my community-based hospital. As you likely know, cardiovascular disease is still the number one killer of Americans, and you may know that hypertension is the leading contributor to developing cardiovascular disease. Unfortunately, almost half of our adult population has hypertension. And less than half of those people have their blood pressures actually treated to target.

When I was a fellow in cardiovascular medicine, I really became passionate about ways to help not only treat people who had cardiovascular disease, but to help them prevent, help prevent them from developing it in the first place. And so, I really honed in on hypertension, number one, because again, it affects such a large percentage of our population, but it also disproportionately affects people of African descent. This is something that I've seen in my own

family, not only how hypertension is prevalent, but how it leads to other downstream issues such as strokes, heart attacks, end stage kidney disease, and so on. And so, part of my life's mission has been to help eradicate this disease.

One challenge, though, is that so far the things that we've had in our armamentarium have been diet and exercise, which of course are critically important. And when those are not enough, we add medications. Unfortunately, in my advanced hypertension clinic, I see patients every week who have what we call resistant hypertension, meaning that despite being on three medicines or more, their blood pressures are still uncontrolled. The renal denervation procedures are very exciting because not only have the data shown that overall they're very safe procedures, but they're also effective at helping to lower patients' blood pressures, not only in the short term, but equally as important, if not more importantly, over the long run. We know that despite the fact that we all aim to be perfect patients, sometimes people forget to take their medications. They may not have the money or the means to consistently see their doctors over time or to take all of the different prescriptions that we prescribe. Having an alternative or an additional therapy that not only works every time someone actually remembers or has the ability to take their medicines on a daily basis, but it's still working in the background, can be critically important to helping to control this disease process in the long run. We know that this will never take the place of diet and exercise, and it will never take the place of medications either, but it is another tool in our tool basket that we as doctors will be able to safely implement to patients who are appropriate for the therapy.

I do hope that you consider this therapy and that you approve it because I know that so many of my patients are desperately awaiting additional options to help better manage their hypertension, knowing that it is such a critical risk factor for developing cardiovascular disease. I thank you very much for your time today. I thank you for your consideration knowing that not

only will this help to better the health of people across our country, but that other countries also look to the decisions that our FDA makes, and hopefully this will open up this therapy, not only here in the United States, but that people across the globe where hypertension is globally a huge issue as well, can benefit. Thank you very much.

Mrs. Saucer: Hi, my name's Naomi Saucer and I am a patient in the RDN trial. So, full disclosure, want to let you know that I'm a former Medtronic employee and a current Medidata employee. So, Medidata being the clinical trial software company that supports the Medtronic RDN clinical research. So that said, my involvement in this trial is completely separate from either employer, and I actually learned about this trial through a friend about two years ago, after I left Medtronic. So, just want to let everyone know that I'm speaking on my own behalf and I'm not being compensated in any way for this testimony. So, that said, RDN, this procedure has had a huge impact on my life.

First off, just getting out there and learning about it was exciting, but everything's gone very quickly since the beginning of June. I went through the process and as I wore the wearables as a part of the clinical trial process, I was able to have so many meaningful conversations with people just at random, at the coffee shop, in Target, and understanding how many people are directly affected by high blood pressure or have loved ones, friends and family that are affected. It was great being able to share with them what I was going through and also being able to tell them that, hey, there is an interventional option, that very few of us, I had no idea about it, but fortunately had a friend that was. So, I've shared that, I've shared it with my primary care physician, and just let as many people as I know become aware of this new option.

So, it's also great, since June 19th when I've had the procedure, I've had a number of things that have changed for me. So, I was identified with hypertension in my twenties, and that's been one of those things where you, and for me personally, I always have an extra pill on me in

my pocket or in my purse or in my car, in addition to my actual, you know, containers of medication, because I don't want to run into a problem. In the past year, I caught my blood pressure well over 200, at least 16 times. That's how many times I counted within my notes. So, I can't really imagine where this would've gone as my blood pressure has continued to inch up over the past year. I just know that I am really excited to have made the decision to be part of this and be admitted to this trial. And it's also made advocacy a very important part of my life at this point as I realize the importance of sharing my experience with others within my community. So, to date, my blood pressure has fallen and it's on average about 12 to 18 points lower than it would be. And with that it's just great to see that now, and I can only imagine what that'll look like in three months, six months, and beyond.

And another little observation that I've made, I'm actually a beekeeper, so, when I'm out there, if you can imagine 90 plus degrees, it's been well over a hundred degrees this summer, but being out there in 90 degrees with a suit on, I've noticed that I manage heat better. I can definitely say that Dallas, Texas is not any cooler than it's ever been, quite the opposite, but it was an observation that I made when I put on my suit, maybe the second or third time, and realized it's just as hot as it has always been in the summer, but now I'm a little less miserable. So, that's kind of been something tangible for me, but another very exciting marker of what my life might look like in a couple of months and the other changes that could come along with this. So, I'm extremely excited to see how things are moving forward and really happy that I was selected to be a part of this program and that I chose to move forward with the RDN procedure. So, there's plenty more, but thank you for your time.

Dr. Voora: Before I begin, I just want to thank you for your time today. My name is Raven Voora. I am a nephrologist on faculty at the University of North Carolina in Chapel Hill. I specialize in hypertension, and I see patients with routine and difficult-to-manage hypertension at

the UNC hypertension clinic. I do need to disclose that I am a paid consultant for Medtronic, but I am not receiving any financial compensation related to the outcome of today's meeting. Moreover, I do not have any financial interest in the outcome of today's meeting, nor with Medtronic, any of Medtronic's competitors.

Today I would like to share with you my independent perspective on renal denervation, as a clinician who sees patients with hypertension. From my review of the data, renal denervation is safe, peri-procedurally, and in the long term. I am impressed by the low number and types of complications. In addition, in several studies now, renal denervation has proven to be rather effective in decreasing office and ambulatory blood pressure in both the long and short term. It's really exciting for me, as a clinician, to have potentially another tool in my armamentarium to treat hypertension safely.

That being said, renal denervation is not something that I would recommend for every one of my patients with hypertension. Certainly, patient perspectives and preferences need to be respected and taken into account in a shared decision-making process. For me, priority for renal denervation would be given to patients with true resistant hypertension, meaning those patients who are adherent to an optimal multi-drug regimen, as well as lifestyle modification. These are the patients who are at increased risk of excessive mortality and morbidity related to their hypertension. I would like to offer them something non-pharmacologic to lower their blood pressure and not add to their medication burden. Again, underscoring still the importance of lifestyle modification.

Another group who would potentially benefit from renal denervation that I see are those patients whose blood pressure is out of target range, but yet they cannot tolerate some of the more commonly used medications for dose titrations. This represents another vulnerable

population. Lastly, I suspect that there is a group of patients who would just prefer a procedure to treat hypertension and bypass pharmacologic therapy.

For me, renal denervation is not the holy grail of hypertension, but really an additional tool that could be offered to certain patients. It does not replace lifestyle modifications, and in most cases, pharmacologic therapy, but rather expands therapeutic options. Thank you for your time.

Dr. Schmieder: Dear advisors of the FDA and FDA staff, allow me to introduce myself. My name is Professor Dr. Roland Schmieder. I'm a nephrologist and hypertension expert working at the University Hospital in Erlangen, Germany. I'm working as a clinical scientist, but also as a physician, treating patients over several decades.

I want to share with you my independent perspective as a clinician and a scientist. I declare hereby I have no financial interest related to Medtronic or its competitors. I have no shares of these companies. My only bias is intellectual. I was a member of the guideline committee of the European guidelines on the Management of Hypertension in 2013, 2018, and 2023, latter just released in June this year. The guidelines have been also endorsed by the European Renal Association and the International Society of Hypertension.

In the 2023 guidelines, there was a paradigm shift with respect to the recommendation on renal denervation. This was necessary in face of the high-quality studies performed over the last years. In five sham-controlled, randomized, prospective blinded studies, it was clearly documented that renal denervation reduces blood pressure substantially, and this leads to the new recommendations of the European guidelines. Let me share my screen with you. In these guidelines stated that renal denervation can be considered as a treatment option in patients with an eGFR above 40 who have uncontrolled blood pressure despite the use of anti-hypertensive drug combination therapy, or if drug treatment elicits serious side effects and poor quality of life.

The key message is uncontrolled blood pressure, but also it is stated in the next box in particular, that renal renovation can be considered as an additional treatment option in patients with resistant hypertension if eGFR is above 40. Now, this is the first time that, in addition to lifestyle changes and pharmacotherapy, a device-based therapy has the status of to be considered in uncontrolled hypertension. Thus, renal denervation may emerge as a third pillar of hypertension therapy. These recommendations are in accordance with the European Society of Cardiology, were written by the Council on Hypertension and European Association of Cardiovascular Intervention published in February this year as well.

Having said that, the question arises, which are the patients that have the greatest blood pressure reduction? To date, no guidance exists. Genetic markers failed, clinical parameters failed, and also any kind of testing maneuvers failed to predict the blood pressure response, but intensive research is going on there. So far, I have discussed renal innovation as a new therapeutic option from a physician's perspective. However, clearly the patient's perspective and thoughts and preference on how to treat her or his blood pressure is also of importance in face of the fact that hypertension is a chronic disease, modifiable risk factor that requires lifelong therapy.

In Germany, five years ago, I conducted a survey including more than 1000 patients with hypertension, and approximately one third of them were prone to undergo renal renovation as an additive or alternative therapy instead of taking an additional medication for the rest of their lives. Similar percentages were reported from Japan and the United States as well. Thus, patient's perspective and preference need to be incorporated in a shared decision-making process to individualize treatment. I think with respect to renal innovation, we are in a transition phase from science to clinical practice, and this process needs to be carefully structured. The ESH guidelines underscore that renal innovation should be performed only in experienced specialized centers,

having an interdisciplinary team with an experienced hypertension specialist and treated a well-trained interventionist.

Finally, let me thank you for the opportunity to share with you the European perspective and my personal view on renal innovation. Thank you for listening.

Dr. Shapiro: Hello, my name is Dr. Michael Shapiro. I am the Fred M. Parrish Professor of cardiology and molecular medicine, and the director of the Center for Prevention of Cardiovascular Disease at Atrium Health Wake Forest Baptist. I also serve as the President-elect of the American Society for Preventive Cardiology, a professional medical society whose mission is to promote the prevention of cardiovascular disease and advocate for the preservation of cardiovascular health. I want to state for the record that I have no personal conflict of interest with Medtronic. The American Society for Preventive Cardiology does receive unrestricted corporate support from many pharmaceutical and device companies, including Medtronic.

I want to first thank the FDA for the opportunity to provide comments on the chronic management of hypertension. I've spent my career as a physician, researcher, and patient advocate working to both understand and prevent cardiovascular disease. Of the many cardiovascular risk factors, it is widely accepted that hypertension is the most prevalent. When uncontrolled, can lead to heart attack, stroke, and many other cardiovascular complications. While it is easily identifiable and treatments exist, its chronic management continues to be a major challenge. This is of great concern considering that nearly half of American adults are currently living with hypertension.

The burden of hypertension is immense. Each year, hypertension costs over 130 billion dollars in direct healthcare costs, is responsible for over one million emergency room visits and leads to over 500,000 deaths. Importantly, communities of color are disproportionately impacted, with higher rates of hypertension and related complications. Compared to their white peers,

black Americans are 20% more likely to have hypertension and experience significantly higher rates of cardiovascular disease-related death. Hispanic Americans are more likely to go undiagnosed and to experience kidney complications as a result of their hypertension. And Asian Americans face greater difficulty getting high blood pressure under control and experience more severe stroke.

Rates of hypertension control have been on the decline for years. In fact, they have eroded to a point where today, less than half of hypertensive adults have their blood pressure controlled in the recommended range. Without improved strategies, this situation will worsen. With 25 million more adults expected to develop hypertension by 2035, the burden on our healthcare system will be untenable. It is of utmost importance to not only find ways to support patients with better management tools, but also to address the challenge of non-adherence.

Non-adherence is a major factor in poor blood pressure control and increased cardiovascular risk. One in three hypertensive Americans is non-adherent, and despite a wide array of pharmacologic treatments, adherence remains suboptimal. Asymptomatic chronic conditions such as hypertension pose distinct adherence challenges. Taking daily medications for a condition that largely presents no immediate symptoms continues to be a significant hurdle. We need solutions to promote long-term adherence. Addressing this issue in a meaningful way is likely to be associated with major gains in cardiovascular health.

I believe renal denervation is a tool that can help in achieving these goals. Renal denervation is a minimally invasive procedure that aims to lower blood pressure by reducing the activity of the sympathetic nerves around the artery supplying blood to the kidneys. This technique has been shown to help reduce blood pressure in the presence or absence of background, anti-hypertensive therapy. Importantly, it is a tool to potentially improve adherence. Making this breakthrough treatment available to patients will help to combat the epidemic of

hypertension and its complications. With cardiovascular disease on the rise in the United States, a multifaceted response is needed. This response must address control of hypertension. Business as usual will not suffice. We need every possible tool and that includes renal denervation. Thank you for your attention.

Mr. D'Ingianni: Hi, my name is Vincente D'Ingianni, and I'd like to give my testimony about the renal ablation procedure that I had recently in the study that I participated in. I'm giving this freely of my own accord and I hope this helps out for others who are looking for the same thing that I had. I had been diagnosed with high blood pressure, hypertension in my early twenties. My grandfather was a doctor and he watched both my father and myself and realized at a very young age that I was following exactly in my father's footsteps. And over the years I had watched my blood pressure slowly creep up to the point where I was taking more and more medication for hypertension. And it seemed like it was kind of on that never-ending rollercoaster of medication, constantly having to deal with the side effects from lots of medication. And, over the years I've been looking for some other opportunities besides just diet and exercise to try to slow the progression down. And when I found out about the study for the renal ablation procedure, I had volunteered for it. And fortunately I was chosen. And I had the procedure and had subsequently been going on and having checkups from this. And, I view it as a very big success because my blood pressure, the level of my blood pressure had come down quite drastically. I'm still on medication, but I'm not on that constantly increasing, steep slope of medication. And I view this as a real positive for me because I'm now the age my father was where my father had his first heart attack. He's had quite a few now, four that he's officially counted, and I'm fortunately not following in those footsteps so closely. So that's a very good thing. And again, overall, my blood pressure has been a lot lower. I haven't been needing to increase medication dosages. I haven't been having the side effects from constant high blood

pressure as well as the medication itself. Overall, again, I think this is a real positive. I hope other people can benefit from it, and I thank you very much for letting me have the opportunity to share my experience with this. Thank you.

Dr. Aburahma: Hi, I'm Dr. Ali Aburahma, professor and chief of vascular surgery at West Virginia University, Charleston Area Medical Center, Charleston, West Virginia. I'm here to give a comment regarding the article "Medtronic Denervation Study Misses Primary Endpoint" and relying on duplex ultrasound in detecting renal artery stenosis, as noted even in my landmark study, "Critical Analysis of Renal Duplex Ultrasound Parameters in Detecting Significant Renal Artery Stenosis", which was referred to it by the article titled "Imaging Strategies for Safety Surveillance After Renal Artery Denervation". This study, which they refer to, which is our study, is the largest study in the English literature analyzing the renal duplex ultrasound velocities in detecting renal artery stenosis, compromising of over 300 patients, in which over 600 renal arteries were examined and analyzed to pick the optimal velocities in detecting above 60% renal artery stenosis.

In summary, as noted in that article, the sensitivity and positivity, I'm sorry, specificity in detecting above 60% was in the range of 70 to 80%. This is, in our accredited vascular laboratory, in criteria which were validated comparing to angiography. And looking into other literature, most criteria of renal duplex ultrasound doesn't really detect more than roughly 70 to 80% in regard to sensitivity and specificity. And what does this mean? I really believe other imaging modality, specifically more definitive imaging, whether CTA or anything else, should be more definitive in detecting the incidence of renal artery stenosis after any type of intervention. Therefore, relying only on renal duplex criteria might not be the most appropriate method before verifying clinical outcome of any intervention or therapy we propose. And I hope that clarify the issue.

Mr. Snyder: My name is Scott Snyder. I'm representing Geneticure Inc. in our testimony that renal denervation has not demonstrated to adequately lower blood pressure in patients with hypertension, and also that multi-organ genetic scoring is related to response in renal denervation. Background on renal denervation, the importance of identification of non-responders. As we know, we've seen trials that have shown from zero, no change, to a seven-millimeter drop in blood pressure, compared to sham, averaged about 3.61. This as supplemental information, has all been provided, so I'm going quickly. The most recent on med trial missed the primary endpoint. There was a shift of importance from 24 hour blood pressure to office blood pressure that we believe the advisory committee should pay close attention to, and that a two-millimeter mercury drop in blood pressure is really not clinically important, and it's more traditionally around five millimeters plus. Most importantly, 20 to 30% of the patients receiving the procedure had no change or an increase in blood pressure. Even in those that do not have medications, this occurs across all devices, ultrasound, radio frequency, et cetera. We believe it's critical to identify those patients. A lot of the thought leaders in the space agree that it's critical to identify the non-responders and we believe we have a method of doing so. So again, critically meaningful reduction, blood pressure around five. Almost all statistical significance was lost in these two trials, when non carry forward data was used. This slide simply summarized some of our concerns with the publications linked below. You can read into those as, uh, within the supplemental information. I wanted to share a visual representation of the spaghetti plots of responders and non-responders. The two on the left are Medtronic ON-MED, OFF-MED, and then we have RADIANCE. And, interestingly, in the OFF-MED without any medications, we see a subset of populations with no change or an increase in blood pressure. In your supplemental information, you have some background on a small pilot trial that we ran to identify responders and non-responders in renal denervation. Result was a relationship between multi-gene scoring

in response to renal denervation. When we look at patients who matched or who were predicted responders, we see in a median split almost a 14-millimeter drop in blood pressure, and those who we were predicted non-responders, a small subset. You can see out of 12 here had a slight increase in blood pressure. The table on the right simply does the same exercise seeing the widening of these groups. This was with a 96% sensitivity rate and 85% positive predictive value. So, we believe strongly that it's worthwhile to pursue this research to identify genetic non-responders. The identification of these groups is critical for patient safety, adoption of the procedure, but also payer reimbursement. And importantly, patients with a high genetic year score were more likely to have their blood pressure control, which is under control, which is that table on the right. I look forward to your feedback and questions on this and hope that it's considered in the advisory committee meeting.

Dr. Lange: For the record, I wanted to amend my statement. There were 14 speakers that provided prerecorded presentations, but I will now pronounce the open public hearing to be officially closed. We've heard from people from Tupelo, Mississippi to Germany. So, thank you very much for all of your participation. At this time, we'll now begin the panel deliberations, and although this portion is open to public observers, public attendees may not participate except at my specific request. Additionally, we request that all persons who are asked to speak identify themselves each time if I haven't done so. This helps the transcriptionist identify the speakers. Vanessa DeBruin, we've given you a large task, and I appreciate you and your colleagues that have spent time during our break to get the information together. So, I'm going to turn it over to you. And Vanessa, the only thing I'm going to ask is, there are a lot of questions. This is not an opportunity to add to the presentation, but really just to address the questions that the panel members propose. After you've done so, I'll go back to the panel members and ask them if that

answer is sufficient or if they need additional information. So, with that, Vanessa, let me turn it over to you.

Panel Deliberation

Dr. Lange: —turn it over to you.

Dr. DeBruin: Thank you. And just to be most efficient, we group these questions by topic as there was some overlap. We will make sure to address the panelist's name, who asked the question as we go down the list. I'd like to start with, Dr. Felix Mahfoud to address some of the questions regarding the procedure and imaging.

Dr. Mahfoud: Thank you very much and good afternoon. My name is Felix Mahfoud, I wanted to clarify a few aspects regarding the procedure. So first, the protocol required that all renal arteries above three millimeters in diameter were treated, including accessory renal arteries. And, as you can see here, a relevant proportion of patients had accessory arteries identified. And so those were also treated in the OFF- and ON-MED study. But whatsoever there was no statistically significant difference between the two groups shown here on that site. Regarding the ablation numbers that were performed in the often-unmet study, an average of 47 ablations were performed, including ablations in the main and in the branches of the renal arteries. And the procedural time was around 90 minutes on average in these trials.

There was a question raised by Dr. Corriere about the transfemoral access or transradial access in particular, all patients treated in the study were treated via the femoral route. And that excess site gaining and closure was done as per standard of care. There was no formal training performed to the sites.

Let me now come to the imaging questions that were raised by Dr. Lockhart regarding the duplex ultrasound training. All sites were provided a detailed renal artery and renal parenchyma imaging manual by an independent core lab. And also to ensure consistency and quality, all

duplex ultrasound operators were required to perform an onsite hands-on training and to also submit test cases that were evaluated then by the independent core lab. The specific question on whether the duplex operators were informed about the presence of accessory arteries has to be answered with a yes.

And there was also a specific question regarding the CT and MR training and the requirements. Again, the CT and MR images, the detailed manual was provided to the technicians performing all these images and the obtainment of these images. And again, an independent core lab that was blinded to patient characteristics and treatment allocation, assessed all images and the recommendations of this manual are listed here on that site.

Dr. Lange: So, Dr. Lockhart, does that address the questions you have?

Dr. Lockhart: I think it does. I'm assuming contrast timing was during arterial phase and there was a minimum injection rate.

Dr. DeBruin: I'd have to get back to you with the answer on that.

Dr. Lockhart: Oh, I'm sorry. But it is one-millimeter thick slices, which was one concern. And if you're asking them, go ahead and ask, did they also do axial, I mean, coronal and sagittal reconstructions.

Dr. DeBruin: All right. Thank you.

Dr. Lockhart: Thank you.

Dr. Lange: Dr. Somberg, you have a—

Dr. Somberg: I just need a clarification. The 47 number, is that 47 ablations per patient were altogether in the study? I just don't know what 47 meant.

Dr. DeBruin: Yeah, so 47 is the mean number per patient. With the catheter design, you can deliver up to four ablations with each application. So, you could divide that by four, the 47 by

four to get a rough estimate of your actual number of applications. But it was, indeed, 47 ablations. Thank you.

Dr. Somberg: And they don't, and they don't cross the renal origin into the order, right?

Dr. DeBruin: Correct.

Dr. Somberg: Okay. Thank you.

Dr. Lange: Go ahead and continue on Vanessa. Thank you.

Dr. DeBruin: Thank you. I'd like to move on to, I believe Dr. Corriere asked a question regarding patient preference and whether or not we relied on interviews to verify understanding, but was that actually built into the study? So we actually did two things to enhance the study.

First, the interviews were to develop the survey to make sure it was understandable to the patients. In addition to that, we asked comprehension questions when they were actually taking the survey to ensure they understood the final survey instrument. And what we found overall was that comprehension was good within the trial.

And if there's no other questions, I'd like to move on to some other questions regarding general study design and the ON-MED study and—

Dr. Lockhart: Before you do, since you're still in the imaging, can I ask one last thing? I'm just having a hard time getting my head around the high inadequacy rate on the CTAs. Do you have any suggestion or guess of why there were so many?

Dr. DeBruin: So, I think part of it is when we were trying to work with the sites and there were a couple sites that, particularly, we requested retraining because they kept getting non-diagnostics and they refused training, retraining, excuse me. So we had a really hard time with that. In terms of other details, I'd have to get back to you with that.

Dr. Lockhart: There's usually CTAs, not the one where we have that type of trouble. It'd be ultrasound.

Dr. DeBruin: Correct.

Dr. Lockhart: So, in MRI, two-thirds were inadequate.

Dr. DeBruin: Yes.

Dr. Lockhart: Okay. Alright. Thank you.

Dr. DeBruin: Thank you. And with that, I'll turn it over to Dr. David Kandzari.

Dr. Kandzari: Thank you, Vanessa. Good afternoon. I'm David Kandzari from Atlanta, Georgia. We welcome the FDA panel's engagement in this discussion of these data. Dr. Lange, I have a number of items to address and to begin with for study design, I'll first begin with Dr. Wittes who asked with regard to whether the ON-MED study was statistically powered to prove a five mmHg difference. And that is not the case.

The study was designed to demonstrate superiority, thus not a specific number. And therefore the success was defined by a p-value from the Bayesian analysis of change in 24 hours systolic blood pressure, not the exclusion of a difference. Secondly, doctor, if satisfactory, Dr. Lewis had asked for the distribution of blood pressure in both the ON- and OFF-MEDs clinical trials with regard to baseline blood pressure, and here we show related to that outcome. And so, specifically for the OFF-MED full cohort and three-month blood pressure reductions both by ambulatory and office systolic blood pressure, Dr. Lewis, we share for you the tertiles of blood pressure and the numbers of such patients according to baseline 24-hour ambulatory tertile. As consistent and as perhaps Dr. Mahfoud will discuss in further detail, consistently, we observe in these studies an even greater treatment effect with renal denervation therapy for patients with the highest level of baseline blood pressure.

Similarly, we also, pardon me, we also want to share with you, sorry, I'm pulling up the wrong slide here. Bear with me. I also want to share with you the ON-MED full cohort blood pressure distribution based on 24-hour ambulatory systolic blood pressure tertile at baseline, and

again, the outcomes with regard to 24-hour systolic blood pressure and office systolic blood pressure at six months' follow-up.

Dr. Lewis, you had also asked about intolerance in the OFF-MED study. And we did not prospectively capture information with regard to specific intolerances, but notably in the OFF-MED study. To help inform this question, 83% of the patients who were enrolled in the OFF-MED study were on medications prior to a washout period.

Doctors Corriere and Allen also had asked questions with regard to medications in the trial design, for example, optimization of medicines or why one to three medicines were selected in the ON-MED study. In particular, we wish to replicate the study population as closely as possible within the confines of a sham-controlled randomized trial to be representative of those encountered routinely in clinical practice taking one to three commonly prescribed anti-hypertensive medication classes.

In prior experience from the Symplicity HTM3 study, recall, this is a study that enrolled patients from the average of more than five anti-hypertensive medications and for whom the protocol mandated that medications had to be maximized at their maximal doses. This was a study that we've learned from that experience there was substantial non-adherence to medication adherence in that particular trial that led to the redesign of many of the studies both in this program and others with renal denervation therapy. I believe Dr. Allen had also asked with regard to the medication changes and the assuredness of blinding.

And indeed as the FDA showed, the James Index ensures blinding across both providers and the individuals participants in the trial through the study period of up to unblinding. But perhaps keep in mind too, that patients are certainly aware, independent of their blinding status of their blood pressure measurements at home or in other doctor's offices. And further, 80% of the patients in the expansion cohort when we observed such substantial changes in medicines

occurred during the COVID pandemic. Dr. Somberg, Dr. Wittes, and Dr. Lewis also had a number of questions, and Dr. Yeh, pardon me, had a number of questions with regard to escaped patients.

And in particular, I'll begin with sharing you the prevalence of escape patients in the ON-MEDs full cohort and, actually, pardon me, Dr. Yeh I'm going to come back to this in a moment just to start with a preliminary slide and then I'll share with you your question with regard to how many were US and non-US. But, overall in the ON-MEDs full cohort, 7.4% of patients met escape criteria and as represented 5.8% were in the renal denervation group, 9.9% in the sham control group. Dr. Lewis, I believe, had asked with regard to how many of these escape patients did have a last observation carried forward in the intention to treat analysis.

It was nine of 12 patients in the renal denervation group and six of the 13 patients in the sham control group. And, accordingly seven with none and three with none in the sham and renal denervation groups respectively. The reasons for escape are detailed here, and with regard to safety concerns, this was at the discretion of the investigator as the treating physician. Dr. Yeh had also asked if there was a difference in the number of escapes between the United States and the non-United States patient populations. And numerically at least indeed, there were modest differences, 9.6% of US escape patients versus 5.5% of non-US escape patients. And again, with the reasons for such listed below.

Dr. Lange: David, can you just stop for a second? Just to take care, safety concern, it looks like most of the individuals, 50% or more that received that, were escape patients, were safety concerns. What does that mean, just for the panel?

Dr. Kandzari: It could be for a patient who didn't per se meet the criteria of a systolic blood pressure of 180 or greater, but might have, for example, experienced symptoms attributed to by the treating physician to severe hypertension.

Dr. Lange: Okay. Thank you.

Dr. Kandzari: Thank you. And Dr. Lewis, just one other issue related to the escaped patients and related to medication changes, Dr. Lewis had asked of all the patients who experienced medication changes prior to ascertainment of the six month primary endpoint, what percent were related to escape patients? And this was indeed the minority. Only 18% of the patients were escaped patients among all patients who had changed medications prior to the six-month endpoint.

Further, Dr. Saville and Somberg had also asked for additional representations of the results of the ON-MED and the OFF-MED studies, in particular, related to box plots by our statistical colleagues of Dr. Wittes and Dr. Saville and Dr. Somberg by Waterfall plot. Dr. Somberg has also requested for us to demonstrate the magnitude of blood pressure reductions in the prevalence of those reductions represented in this figure is the ON-MED full cohort study with the outcomes at six months for both 24-hour and office systolic blood pressure in the box plot analysis, representing the median with the 25th, 75th intervals, and then the 5% and 95% intervals. And moreover, in the following slide is the OFF-MED full cohort with the outcomes at three months as well. Moreover, for Dr. Somberg and others, I also share with you the ON-MED full cohort with regard to the presentation of the results in two manners. One with regard to waterfall plot analysis, as well as by bar graph analysis. In this instance, in the ON-MED study, visually demonstrating the achieved significant reduction in office systolic blood pressure with renal denervation therapy at six months, the waterfall plots demonstrating not only visibly a greater proportion of patients with blood pressure lowering, but also suggesting a greater magnitude of blood pressure reduction.

And indeed, whereas approximately 61% of the patients achieved with renal denervation therapy, at least a five millimeter reduction in systolic blood pressure at levels of reductions of

10, 15, and 20 mmHg. If anything the magnitude of reductions were greater favoring renal denervation therapy and achieved statistical significance altogether, then the achievement of a targeted systolic blood pressure of less than 140 mmHg was significantly greater among patients receiving renal denervation therapy compared with those in the sham control group by an order of more than threefold. Similarly, yes, sir.

Dr. Lange: David, it's really important data and I just, I don't want to fly by it too quickly. Would you go back two slides to the original box plot and I just want the individuals that asked for that data—

Dr. Kandzari: Yes.

Dr. Lange: —just to take a look at it, peruse it for just a second. So, I mean, again, I appreciate you guys putting together and don't want to go by it too quickly. So let's go back two slides.

Dr. Kandzari: Thank you. Can we go back two slides? Here we go. What I'll share with you first is the OFF-MED full cohort box plots with regard to outcome at three months. Can you help me perhaps with this? AA 12? Thank you, pardon us.

And Dr. Lange, of interest, the last slide I was just going to share in this theme of results was related to the OFF-MED study with regard to the waterfall plots and the magnitude of blood pressure reductions as well. We're bringing up to you now the OFF-MED full cohort outcomes at three months for the box plot data.

Dr. Lange: I'm sorry, David, I blinked. I missed it.

Dr. Kandzari: Yeah, trying again.

Dr. Somberg: While we're waiting, do you also have the waterfall plot for the OFF-MED study? Because I asked for both.

Dr. Kandzari: Yes, sir, I do. And I'll share that next after we complete our discussion of the box plots.

Dr. Wittes: May I ask a question about the box plots? This is great. Now, but there are missing people here, right? Or are they last observation carried forward people?

Dr. Kandzari: These are instances with last observation carried forward.

Dr. Wittes: Okay.

Dr. Lange: But as you said, there are some that are missing. There are some LOCFs and some that are not there.

Dr. Kandzari: There may be some, for example, who did not have the data available and for whom we had no last observation, carried forward as an example.

Dr. Saville: When you say last observation carried forward, do you mean you might have a measurement say at one or two months and it's carried forward to three months because they're missing the three-month observation?

Dr. Kandzari: That's exactly correct.

Dr. Lange: Dr. Lewis, I see your hand up as well. If it has to do with this particular slide or data, Julia?

Dr. Lewis: I appreciate him trying to save time and talking so quickly, but it is going by me very quickly too. I just wanted to clarify that medication changes 18% were due to safety concerns. It means 82% were protocol violations of a major, you know, part of the ON-MED study to not change meds for six months. Is that correct? Did I hear you say that correctly?

Dr. Kandzari: That's correct, Dr. Lewis.

Dr. Lewis: Okay.

Dr. Kandzari: Among all patients with medication changes, 18% were related to patients fulfilling escape criteria, either as we've discussed by the safety concern or by having severely elevated systolic blood pressure.

Dr. Lewis: And I didn't miss the three-month ON-MED results. I didn't miss it when you were going by them, right?

Dr. Kandzari: Three-month OFF-MED or three-month on?

Dr. Lewis: Three-month ON-MED, they had a three-month visit ON-MED. Three month efficacy results.

Dr. Kandzari: Yes. Perhaps I can just verbally address that now. And I believe Dr. Bates had perhaps also asked a similar question. We see overall similar findings at three months in the ON-MED full cohort as we did in the six-month cohort. In part, in the sham control group, the blood pressure reductions are somewhat greater at six months compared with three months. But we already see a larger than expected reduction in three months in the sham control group.

And the reason, principally, for this is that 80% of the medication changes that occurred, as we're discussing in this trial, occurred within the first three months. So already we see the effect of those medication change the potential compounding.

Dr. Lewis: Thank you.

Dr. Kandzari: Thank you. Yeah.

Dr. Lange: So, okay. Dr. Saville, any more about this slide? If not, we'll move forward. I see your hand up still, Ben.

Dr. Saville: Yeah. Question on this slide. So, this is great. This tells me a lot more information than is the difference in mean. Do you have the same graph for the other cohorts? So, broken up by cohort, pilot and expansion cohorts?

Dr. Kandzari: I'm sorry. I do not have it broken down by pilot and expansion. But we can work towards getting that for you.

Dr. Saville: That would be very helpful. Thank you. Super.

Dr. Lange: So, David, this is obviously 24-hour and office and if you go in advance to the next slide, this is OFF-MED full cohort at three months.

Dr. Kandzari: Yes. So I'll share with you, that was OFF-MED at three months and for coming forward is ON-MED at six-month follow up.

Dr. Lange: Okay.

Dr. Saville: And could we get a this broken out by cohort as well, please?

Dr. Kandzari: Yes, we'll work towards that.

Dr. Lange: Super. And David, and I know you said that the three months looks like the six month, if somebody could provide the three month data for Dr. Lewis, that would be terrific.

Dr. Kandzari: We indeed have that and can share that with you.

Dr. Lange: Perfect. Alright.

Dr. Kandzari: Just as a final to Dr. Somberg's request just a few moments ago, Dr. Somberg as your final request, these are the waterfall distribution plot figures as well as the bar graphs for achievement of blood pressure lowering according to the extent of magnitude of blood pressure both for renal denervation and sham in the OFF-MED study, again, highlighting visually a greater proportion of patients having blood pressure lowering with renal denervation therapy and at all intervals, five through 20 mmHg reductions significantly greater with renal denervation therapy and more than twofold higher achievement of a targeted systolic blood pressure of less than 140 with renal denervation.

Dr. Lange: And David, do you have this for the 24-hour ambulatory?

Dr. Kandzari: As I shared a few moments ago, we do not have the waterfall plots available for 24-hour ambulatory blood pressure, but we can certainly work towards getting that for this group.

Dr. Lange: Okay, sir, I'm sorry. Okay. Sorry to interrupt. Go ahead, David.

Dr. Kandzari: No, no, thank you.

Dr. Somberg: Just a clarification.

Dr. Kandzari: Yes, sir.

Dr. Somberg: One second. Were they both, was it EF253? Was that office?

Dr. Lange: Yes.

Dr. Somberg: Or is that ambulatory?

Dr. Lange: That's office.

Dr. Kandzari: The slides I just showed were office. Yes, sir.

Dr. Somberg: Okay. Because we did ask for ambulatory before.

Dr. Lange: Yeah. Dr. Somberg, I'm sorry. You asked for per protocol and as treated and I think he's going to present that.

Dr. Kandzari: Yes, exactly. Thank you. So, finally, Dr. Somberg and I believe Dr. Saville had not only asked for data with regard to the box plots and to the magnitude of blood pressure reduction, but a per protocol analysis. And indeed, we did perform a per protocol analysis which essentially showed similar results to the overall intention to treat population results. Importantly, the per protocol analysis has selected limitations. To begin with, given the frequency of protocol violations, the sample size is reduced by approximately half.

But moreover, the per protocol analysis is agnostic to the magnitude, the frequency, and the asymmetry in medication changes that occur between the two groups. In other words, excluding patients with medication changes has the potential to remove, so to speak, the worst of

the sham patients who had persistently elevated blood pressure and increased their medications. And alternatively, it removes the patients perhaps, who had the greatest blood pressure reductions with renal denervation therapy and had either decreased their medications or their numbers, and perhaps instead an alternative examination of this is, if we could bring up please the US versus non-US for the entire study cohort slide instead. Perhaps, we could share with you that when the medication changes, even though they occur, if they're balanced with regard to medication increases and decreases that we then demonstrate statistically significant reductions for both 24-hour and office blood pressure with renal denervation therapy

More specifically, it is the change in medications that influence largely the results across the group and shown here again in the non-US patient population, which is, albeit a subgroup, a very sizable patient population of 176 patients, which is more than many sham-controlled randomized trials in the space of renal denervation, that here we're able to show in the right-hand panel the significant reductions in both ambulatory and office blood pressure at six month follow-up. I would also highlight, however, as a final commentary that the per protocol analysis is also inconsiderate of missing data. And specifically, if we could bring up please, I believe it's A25. When we look at, I'm sorry, our missing data slide. When we examine patients who had missing ambulatory blood pressure data, during the conduct of the study, but we do have for them available to us a last observed office systolic blood pressure we see quite significant changes between those treated with renal denervation therapy and those patients who were treated with, bear with me, those patients who were in the sham control group. Specifically represented in this figure, we observed an imbalance as previously discussed in missing ABPM data, which was numerically higher in patients in the sham control group.

But again, as this figure demonstrates, when we examine the last observed systolic blood pressure for these patients, there's a 14 millimeter reduction in patients treated with renal

denervation therapy for office systolic blood pressure compared, in fact, with a two millimeter mercury increase in the sham control group. And so, the absence of these data does indeed imply that it attenuated the opportunity to demonstrate a difference in ambulatory blood pressure. And to that end, I'm going to invite Dr. Mauri to address a bit more related to Dr. Saville's questions of imputation of data.

Dr. Lange: Great. Dr. Somberg, you have a question for Dr. Kandzari before he leaves?

Dr. Somberg: Yeah, if you could go back to the CO 55, which he was telling us about, and the imbalance is very critical here in the US patients. But, correct me if I'm understanding this correctly, the percent is, if something is added, 23 versus 37, but that something is not really quantified as how much, so if you went for a mild change, that would, in other words, that disparity in 23 to 37 does not inform you about the importance of the change or not, I think the FDA's analysis in their slide, I believe 50, was trying to imply the significance of the change. And I'm just trying to square those two. Do you have any comment on that? Because it may go from 23 to 37%, but that may not be very meaningful.

Dr. Kandzari: I certainly do. A medication increase or decrease in this instance is importantly represented by medication testing, drug adherence testing. And these medication changes, though, may also represent either an increase in the number of medications, the increase in the class of medications, or the increase in the dose of medications.

And so, we pre-specified medication index two, because it is, I believe, as a clinician, clinically relevant with regard to not only changes in the number of medicines, but changes in the number and or dose of medicines and/or class of medications as well. And moreover, not represented in this figure though, Dr. Somberg, we identified, if we just looked at pure number of medications alone in this trial between sham and renal denervation at three months and at six months there emerged a significant difference just in the number of medications alone. But,

when we then consider the number, and/or dose, and/or class of medications, these differences become even more disparate and statistically significant.

Dr. Somberg: Do you have something to show that? When you take all those things into consideration?

Dr. Kandzari: We can come back and present to you different medication indices. But the point is that the general trends, the directional trends are very similar between these different indices, whether it's medicine, medication index one, medication index two, or pure number of medications as well.

Dr. Somberg: I understand what you're saying, but I'm trying to square the sponsor's presentation where there's a very significant difference in change in medication, which would change my outlook on the ON-MED efficacy endpoint. Compare that to the FDA, where they make a very cogent argument that the changes are highly insignificant. So let's try to address that if we can.

Dr. Lange: So, John, we're going to address that as a group.

Dr. Somberg: Okay.

Dr. Lange: If there are specific questions to the sponsor, if there is information they can provide, we'll do that.

Dr. Kandzari: Yes. And again, as shared, when we consider medication number, dose, and/or class, all of which are independent predictors of adherence, they're quite disparate. Thank you.

Dr. Lange: Yeah. If the sponsor would like to present that data, it'd be great. So we've got Dr. Laura Mauri coming in, I believe.

Dr. DeBruin: Yes. Yes, Dr. Laura Mauri. Thank you.

Dr. Lange: And to talk about some imputation.

Dr. Mauri: Yeah. Thank you. So I want to address questions regarding how missing data might have been handled. I know there were questions about last observation carried forward and when that was used as well.

So, just to be completely clear, the complete case analysis was not the method that was used. The primary analysis that was pre-specified was to consider patients who met protocol escape criteria and use a last observation carried forward. And this was important because we had a three-month time point where patients could have had an ambulatory blood pressure in the ON-MED study before the primary endpoint was reached at six months.

And so if a patient had escaped, but that occurred between three and six months, that data from the three-month visit was used to be the last observation carried forward. In all other cases, if there was not a six-month ambulatory blood pressure available, that data was considered missing and there was no observation considered in the primary analysis. So the data that you saw in the box plots, the data that you see in the primary analysis is the data that uses that method. So there was not imputation for additional missing data.

Dr. Saville: Can I ask, just to clarify, to make sure I understand this, so what you mean is that imputation was only used for those who met the escape criteria in the primary analysis?

Dr. Mauri: Yes. For the primary analysis. That's right.

Dr. Wittes: So, can I ask a question about the LOCF? Because we all know that LOCF has really serious problems including underestimating variability. Did you try to do anything to recover the variability from the LOCF or did you just use single imputation?

Dr. Mauri: We did other analyses as well, and I'll describe them. So, we did do multiple imputation that was pre-specified as a secondary analysis for both studies. And in both cases, the multiple imputation, the method that was used was pre-specified and it didn't significantly change the results either in terms of the treatment effect or the level of significance of the

conclusions. I would add, you know, in addition, in follow up to the observations that you saw from Dr. Kandzari where you can see that there were changes in medications post randomization, as well as the greater amount of missing data for ambulatory blood pressure than office blood pressure, I know that was also a question earlier in the day. There was a consideration of was that imbalance between the two different treatment arms and how do we use the best information available to us to be able to do additional imputation? So we did conduct an additional post hoc analysis to use the best information available in order to consider, I think Dr. Somberg's question of what is really the magnitude of impact of these two aspects of not having complete information for the 24-hour blood pressure.

Although we did have office blood pressure in many of those cases. And you saw that trend which was actually statistic, well, it was quite different numerically where you saw patients in the already untreated arm that did not have a 24-hour blood pressure, had lower blood pressures or a greater change than patients who were in the sham arm who didn't really experience as much change, but was a positive direction of effect, if you looked at their office systolic. The reason that there's more office systolic blood pressure readings available is that it's difficult to obtain a 24-hour blood pressure measurement for a patient who's experiencing hypertension at home, maybe interacting with a physician and doesn't want to wait to come in to the study site, which may not be their primary site of care to be able to adjust their medications if they're quite concerned about a higher blood pressure.

So there are various different reasons that 24-hour blood pressure is difficult to complete. So, I'm going to show briefly how we did this additional analysis that takes each of these factors into account. So, the first is just to show you that we categorize two different sources of impact to the primary analysis, which were first medication changes and two, more importantly, the missing information. There were different reasons for missing 24-hour. It could have been as

discussed, an escape where we didn't have a last observation carry forward from three months because there wasn't one available because many of these escapes occurred before the three-month period, or it's possible that 24-hour blood pressure was missing, but they didn't meet the escape criteria.

And either this was because it was out of window or not available or because we had minimum criteria on a qualifying reading. And you can see that, as a proportion, this was imbalanced with the higher proportion of impact to the sham arm. And what we did was a—

Dr. Saville: Can I ask for a clarification on that?

Dr. Mauri: Sure.

Dr. Saville: In those total counts, go back to that slide. So the 14 and 15, those do not include those who already had elapsed observation period forward per the primary analysis plan. Is that accurate?

Dr. Mauri: That's correct.

Dr. Saville: So, this is missing data beyond those that had already been imputed for last observation carried forward, you said?

Dr. Mauri: Yes, that's correct.

Dr. Lange: I guess to your point, Ben, what you're asking is how much missing data are we missing? I mean, we have a little bit here, a little bit there. In total, how much data are we missing? Is that your point, Ben?

Dr. Saville: Well, yes, but what I'm getting at is she's going to show us some multiple imputation analyses or just varying what's possibly happening with missing data, outside of the missing data it was already to account for with last observation carried forward. So there's kind of two sources of missing data that there's the missing data here, but there's additional missing

data that we've imputed with. Last observation carried forward, which were, remind me of those percentages again, that actually had a last observation carried forward. Do we have that?

Dr. Mauri: I'm going to ask, I'll ask for that to be provided so we can give you the magnitude of last observation carried forward so that it's more visible to you. Is that what you're asking for?

Dr. Saville: Yeah, I just wanted to add the percents because you got seven to 11%. So what additional percentages were last observation carried forward? That would be helpful to me.

Dr. Mauri: Okay. Well, we'll get that for you.

Dr. Wittes: Can I clarify, when I asked about the last observation carried forward being, reducing the variability and then you said you did multiple imputation, did you do multiple imputation, including those LOCF, or, or did you keep the LOCFs constant?

Dr. Mauri: The LOCFs were kept constant.

Dr. Wittes: Okay. So again, I'm concerned about the reduction in variability that is caused by LOCF.

Dr. Mauri: I see.

Dr. Lange: Good. Laura, you were going to talk about the multiple imputations on the next slide, I believe.

Dr. Mauri: Yeah. I'll provide that to you. So on the next slide you'll see the results of imputation and probably just to draw your attention to the last imputation, and I'll walk you through what's included in that. So, we performed imputation where on the patients who, the cohort that I just described, and those patients who had non-evaluable 24-hour blood pressures. We did have sufficient information with a range of observations of 15 out of the 24-hour period. As the minimum of what we actually observed. So, we were able to use that information at the six-month visit. So those data were used when available if they didn't have any 24-hour ambulatory recording.

In many of those cases, as you saw from Dr. Kandzari, we did have the change in office systolic blood pressure between six months and baseline. And so because those differences are correlated, we use that as an imputation for those that had that available. And then the remaining data were imputed to zero, regardless of the treatment arm. And then the overall result was adjusted for medication change. And so, you see overall that has the graded effect of each of those series of imputations of reducing the impact to the sham arm as more information is used in the sham arm. And a difference with ANCOVA of negative three that you see there. Which is rather than, you know, looking at the exact magnitude, I think the focus is on the impact of the missing data. And returning a logical imputation for what it may have been tends to return towards a treatment effect that's more consistent with what we saw in the pilot data, and this being for the full data cohort,

Dr. Lange: Dr. Saville and Dr. Wittes, we will talk about the implications of this, but does this answer the questions that you posed to our sponsor?

Dr. Wittes: To me, it's too complicated.

Dr. Lange: I'm sorry, Janet. You, you don't make the rest of us feel very comfortable when the statistician admits it's too complicated. Don't ever do that again, Janet. *(laughing)*

Dr. Wittes: Okay. Okay.

Dr. Lange: We'll talk about why it's complicated in our deliberations et al.

Dr. Wittes: Okay. I appreciate that.

Dr. Saville: And just so to clarify, you didn't do any sort of multiple imputation using baseline variables that might be predictive of whether they were missing or not. Is that accurate?

Dr. Mauri: We did, we, we did do multiple amputation. That was what we pre-specified in our protocol. I described it, we can certainly show it to you, but the results are, are essentially very consistent. We pre-specified variables into our statistical analysis plan, that had to do with

that. I don't have the full list in front of me, but a list of variables that we would generate the multiple imputation from and those results are consistent. Would you like to see those results?

Dr. Saville: They're consistent with these four methods of imputation I'm seeing here?

Dr. Mauri: They're consistent with the primary analysis as well.

Dr. Saville: Okay. Yes, I would like to see those, if you can show those.

Dr. Mauri: Okay.

Dr. Lange: Alright. I think we've exhausted the non-statisticians on this. Go ahead. Is this the slide? You were asking for Ben? multiple imputation analysis?

Dr. Saville: Yes. So, this is the pre-specified imputation strategy for the primary analysis that's using baseline predictors that, so for those who are missing and this probably does include those who you're already imputing with. Last observation carried forward. I assume you've done last observation carried forward and now you're doing it. Whoever else is missing, you're doing multiple invitation across those.

Dr. Mauri: Yes, that's right.

Dr. Saville: Okay. This is helpful. Thank you.

Dr. Lange: Great.

Dr. Wittes: But, wait a minute. I'm sorry. Can you go back?

Dr. Mauri: Yes.

Dr. Wittes: How, if both are minuses and yet you have a p-value, that's not significant.

Dr. Mauri: I think that that may be a typo. Yeah, it's a typo. It should be minus and plus.

Dr. Saville: Good catch.

Dr. Mauri: Thank you.

Dr. Zuckerman: That's okay. And Dr. Mauri, for the panel transcript, can you clarify, has FDA seen any of these analyses previously? Has FDA been able to independently confirm any of the analyses that you've just shown?

Dr. Mauri: The analyses that we just showed were pre-specified and submitted as part of the PMA.

Dr. Zuckerman: Thank you.

Dr. Lange: Dr. Yeh had asked the rates of escape in the US versus non-US. Did you all present that already?

Dr. Mauri: Yes, Dr. Kendzari presented that. What I would, if that's all right, I think the next we wanted to continue in the line of presenting some of the Bayesian sensitivity analyses that Dr. Saville had asked for.

Dr. Lange: Alright. I'll ask you to do that expeditiously, Laura.

Dr. Hanson: Hi, Tim Hanson, Medtronic distinguished statistician. I'll be as brief as I can. Part of any good Bayesian analysis is a sensitivity analysis and we had a pre-specified sensitivity analysis for the Bayesian primary endpoint, 24 hour for ON-MED, and it was post-hoc for OFF-MED. This is to answer Dr. Saville, your question about whether if we had a common borrowing parameter, whether the results would and indeed they do for ON-MED, for OFF-MED, this is the punchline, things don't really change that much.

For OFF-MED, if we can go to the OFF-MED slide, perfect, these are all remarkably similar. Perfect. I'll just point out to the panel that at the top row is the primary analysis for OFF-MED 24-hour. And the first two rows are two different methods of weighting that have a common discount parameter. In the primary, the main analysis we basically can differentiate differentially discount the sham and the treatment arms.

The next two rows, rows two and three, we basically borrow information equally across, nothing really changes for OFF-MED. And really what we're seeing here is the pool analysis. Right. That's basically what we're getting back. So if we can go to the next slide. Thank you.

Dr. Saville: And in the OFF-MEDs, the borrowing essentially you did was essentially close to one, both those alpha parameters, correct? So it makes sense that not much is changing when you're doing that, those sensitivity analyses.

Dr. Hanson: Exactly. That's exactly right. In fact, some of the borrowing parameters were close to one. Others were like around 0.9. Yeah, that's a good point. And in direct opposition to the OFF-MED, ON-MED, we do see quite a difference when we allow for different types of borrowing. And if we borrow equally across the arms, again, I'll point to rows two and three, really the primary analysis where our posterior probability of success is about 50%. We heavily discounted and things look a lot better if we're allowed to borrow equally, which is what you see in rows two and three. So that posterior probability climbs up to be higher. And again, it's closer to what we would see and what we did see with the pooled ANCOVA analysis, when we're allowed to borrow more liberally, we get results that are closer to the frequentist.

But that's the whole point of this discounting, is that if things are kind of different between the pilot and the expansion, then we want to penalize that because something is changing. So I feel like the discount prior here actually did its job.

Dr. Saville: Yeah. When you say you borrow kind of with a single discount prior there, which one are you choosing? Are you taking the average of the two? Are you taking the one that has less borrow and the more borrowing?

Dr. Hanson: Oh no, there's just one. The way that it was actually developed for example, in Ibrahim's papers and so forth, when they looked at regression, they basically had the one alpha for everything. So, that's what I mean by having the same amount of borrowing across the arms.

So, in rows two and three, there's just one alpha actually in the last row as well, and the fourth row, there's only one alpha.

Dr. Wittes: Doesn't this point to what the big problem is in the fact that the data from the pilot was so different from the data from the expansion. And so depending on how much you use the pilot data, it will change the answer. Isn't that, what this is saying?

Dr. Saville: Yeah, it allows you to borrow more from the pilot data, so it gets pulled more towards the pilot data mean, I'm thinking.

Dr. Wittes: Right? No, that's exactly what I'm saying. So, if you look at these two studies and say, oh my goodness, something happened that in the expansion study, which is much larger than the pilot and, you know, if you were just an old-fashioned frequentist, you'd say that's why you do a second study because you expect the early phase two study, right? To overestimate the effect and so it seems to me what this is saying is that first one is like what a frequentist will do because it says it's really downgrading the pilot and the others are saying we think the pilot and the expansion are basically coming from the same populations. And so we see a big rate in this.

Dr. Hanson: Agree completely. Yeah. I believe that the discount prior was doing its job. The pilot data was discounted. Yeah. Thank you.

Dr. Saville: Thank you.

Dr. DeBruin: Thank you. I'd like to invite Dr. Laura Mauri to address some of the questions regarding our data on Black Americans. Thanks.

Dr. Mauri: Thank you. I just wanted to return to the, just to close the question that you asked about the proportion that had last observation carried forward and it was 4.5 in both groups that had last observation carried forward. So you have a sense of the relative impact. Next, I wanted to address the question that was raised by Dr. Corriere and Dr. Zuckerman. And, you know, we listened carefully to other conversations around the importance of representing underrepresented

populations in our study as well as understanding the impact in our clinical program related to renal denervation. And we're very interested, obviously in the impact of renal innovation in important populations in the United States, including the black population.

One of the first things I mention is that it is true that we have not been able to collect and represent information on race, on all of our subjects. And that is really the fact that half of our study enrollment in on and OFF-MED was conducted outside of the US. And in that situation, we are not permitted by regulations to disclose race and ethnicity even though it's available to us to be able to calculate things like eGFR. So, I wanted to provide that clarification within the United States. When you look across the ON and OFF-MED studies, in the United States population that we enrolled in our study 29%, sorry, 39% of patients, or 129 subjects in total were black Americans. That 39% is higher than the reported rates of black Americans represented in the US hypertensive population which is 14%.

And so this was accomplished by having sites in the United States that enriched for a higher than average representation of black Americans with hypertension into the study. That being said, you know, we also hold the same caveats that the FDA discussed about looking at small subgroups, and I'll walk through the data and show you some of the findings according to black and non-Black American categories.

So, you'll see on the next slide that in the OFF-MED cohort, importantly, we saw consistent findings within the US black Americans versus non-black Americans with a similar magnitude of reduction. Relatively similar effect in the sham arm and no significant p-value for interaction. This is important because the OFF-MED study is, as we've talked about earlier, the simplest way for us to really understand that there's a true biologic effect of renal denervation. And so it's very important if we're thinking about considering varying impacts related to

demographics that we look for that consistency within that cohort of patients who we know remain OFF-MEDications where we had consistent follow-up as well.

Dr. Lange: Laura, do you have the same for ambulatory? That was the primary endpoint for this study.

Dr. Mauri: Yes. I think we did, we represented that in our presentation. And the same is true. There's no inconsistency in terms of the treatment difference on ambulatory. It's a consistent treatment effect.

Dr. Lange: And now ON-MED?

Dr. Mauri: Right. So if we, I can show you the ambulatory here just to close that.

Dr. Corriere: Can you comment on your power to detect a difference with 33 African American patients in that.

Dr. Mauri: The interaction terms across the board are not powered, they're also not adjusted for multiplicity. We used a nominal p-value of 0.15 to consider things that were significant. And the only one that you see that's significant by a pre-specified value is the higher effect with higher baseline blood pressures, but it's underpowered with that sample size. So if we proceed then to show you the ON-MED results here, you can see that in the ON-MED population, pulling it up now, you should be able to see in just a moment here that in the ON-MED population for office systolic, where we had more complete, blood pressure measurements that there was not a significant interaction term here either. Still, the caveat of small sample size. Absolutely. But you can see consistent values in the RDN-treated group as well as consistency of the overall treatment effect.

And it's really the exception that we see in the 24-hour systolic blood pressure result that there was a difference that, that didn't meet the nominal p-value. But granted, with the caveat of having a small interaction term, this was predominantly based on the effect in the sham treated

arm. And we believe that while we know from looking at our results that there were a greater proportion of patients who were African American who did not have 24-hour blood pressure collected and also were represented in escape groups. So that there was a four times higher rate of having absence of the 24-hour blood pressure in that subgroup.

Now granted, these are small numbers and that's why we're very interested in looking at larger sample sets to be able to better understand the impact in African-Americans. And I'll just put up one more slide that shows the pooled analysis across the ON-MED and OFF-MED studies where you can see among African American patients, you see a consistent reduction in the RDN treated arm so that most of the variability comes from that missing information in the sham treated arm, as well as a magnified effect of the changes in medication that Dr. Kandzari described that is present in the African, in the Black American subgroup. So overall, we see that there is a consistent effect when we look at the OFF-MED group as well as across all of the endpoints except for 24-hour within the ON-MED, where there might be a different magnitude of effect there.

That there are more consistent results in all of the other studies where we have more complete data to be relied upon. So, we are very interested though in collecting additional information on black Americans going forward and it's a very important part of the AFFIRM study. As you heard earlier, the AFFIRM study is underway.

It has been since we closed our enrollment and it will enroll up to 1200 subjects. The majority of the sites will be in the United States. And, in addition they do represent sites that will be enriched for the Black American cohort as well as other underrepresented groups.

And we expect that with the rates that we've already achieved of 28% black Americans and 9% Hispanic Americans in the enrollment of 121 subjects to date, that that will continue.

And if anything, be enriched and that we'll have a sizable cohort in the post-approval study to be able to continue to follow patients according to their race and ethnicity.

Dr. Lange: Thank you, Laura. We have 15 minutes left. There were a number of questions posed and I didn't cover them in chronologic order. Are there questions that the panelists had that you were expecting the sponsor to answer, and they have not yet addressed? Let me open that up for the last doctor or excuse me, William Vaughn, go ahead. You had asked for some exclusion criteria from Germany, England, and one other country.

Dr. Vaughn: Canada if possible.

Dr. Lange: Canada.

Dr. Vaughn: The public witness, Dr. Roland Schneider, talked about the German limitations. But do you have anything on England and Canada and what they're saying you can do this procedure on?

Dr. DeBruin: Yeah, we can present on indications and I believe there were some questions about the Global Symplicity Registry that I was going to have Dr. Felix Mahfoud speak to if I may, Dr. Lange.

Dr. Lange: Let's see. Let's address this with William Vaughn and let's see if there are any other questions. Then we'll go to the global registry. I want to make sure that with the current on and OFF-MED, that everybody's questions have been answered. So Vanessa, hopefully we'll have time.

Dr. DeBruin: Wonderful. So I'm going to turn it over to Dr. Felix Mahfoud. Thank you.

Dr. Mahfoud: Thank you. So first, the device is available and approved in 70 countries around the world. The instruction for use states that this device can be used in patients with uncontrolled hypertension. And what we do in clinical practice then, is that we refer to published guidelines. You have heard about the publication, the most recent publication of updated guidelines, and this

is the European Society of Hypertension Guidelines, where this stated that renal denervation can be considered as a treatment option in patients with preserved renal function and uncontrolled hypertension, that despite the use of anti-hypertensive drugs in combination are uncontrolled or if drug therapy elicits serious side effects and poor quality of life.

Dr. Lange: Thank you. Thank you.

Dr. Mahfoud: I want to address before moving into GSR just to comment and address all potential concerns regarding renal artery stenosis following renal denervation and the discrepancy between the rates that we were reporting and that were provided by the FDA and their presentation.

So in total, it's important to recap that in this study and this study program, patients with stenosis at baseline of up to 50% were allowed to be included. And the protocol defined as significant renal artery stenosis as an angiographically-confirmed stenosis of more than 70%. And this was not observed in any of the patients.

When we then look further into the data, we have 474 patients with diagnostic imaging, either duplex, ultrasound, CT, or MR and long-term follow-up here at 12 months, indeed. We have one patient that had renal artery stenosis detected by MR at three years of follow-up and an accessory renal artery. This will provide a renal artery stenosis rate of more than 70% of 0.2%. And when decreasing that threshold, then, to 50% stenosis as used by the FDA, there were two additional patients with potential stenosis, one of 60% in accessory renal artery detected by CT, another patient that had a progression from baseline, 40% to 60% at follow-up. And this will provide a possible rate of stenosis of three out of 474, which is 0.6%.

Importantly, renal function and blood pressure remains stable throughout follow-up in all of these subjects. So in summary, I guess it's important to reiterate that there were no safety signals in terms of stenosis, rate of stenosis observed following denervation, and that the

incidents of renal artery stenosis is indeed similar to that, what we see in patients with hypertension as they age. Let me now—

Dr. Lange: I'm sorry, Dr. Bates, you have your hand up.

Dr. Bates: Yes. Could I have David Kandzari come back to the microphone?

Dr. Mahfoud: Sure.

Dr. Bates: I've been overwhelmed by the statistical analyses, the subsets, the subsets of subsets, the 200 slides. It seems very simplistically, and correct me if I'm wrong, that you got the expected result you thought with the catheter treatment, but that was degraded by the fact that the sham group had a lower, had a better reduction of blood pressure than you expected. So it narrowed, it degraded your benefit. Is that fair?

Dr. Kandzari: It is. And I might also add that I believe the absolute reduction in renal denervation in the ON-MED study, again, achieved with renal denervation if anything could be conservative or muted. Given that in the pilot study, we saw even greater differences and the ABPM, while it is our standard for primary endpoint, is equally influenced by changes in medicines and if renal denervation patients, for example, decrease their medication dose and/or number, then similarly, their ABPM results will be affected as well. Although we still demonstrated a significant difference in nighttime ABPM. But yes, overall, Dr. Bates, I support your conclusions.

Dr. Bates: So, maybe you just did that, but I wanted to give you your best final closing argument on why the sham patients had a greater reduction in blood pressure than you expected. All of your rationalizations, all of your interpretations, your best argument for why the difference that we expected to see, we did not see in the final report.

Dr. Kandzari: Thank you for that opportunity. And from one clinician to another I appreciate this that consistently across the program, independent of the Observational Global Symplicity

Registry, but supported definitely by it, we see consistent themes of reductions in office systolic and diastolic blood pressure, ambulatory systolic and diastolic blood pressure with renal denervation therapy in the context of quite extremely favorable safety.

But specifically to your comments too, Dr. Bates, in the expansion phase where we saw quite a remarkable imbalance and asymmetry in medication changes with the sham patients significantly increasing their medications compared to the renal denervation group and the renal denervation patients significantly decreasing their medicines in comparison to the sham control group. This, along with as shared by our statisticians and Dr. Mauri with, in part, missing data combined to attenuate the opportunity to demonstrate the significant result in that particular trial, notwithstanding the totality of evidence that we represent shown here.

Dr. Lange: Thank you, Dr. Kandzari. Dr. Lockhart.

Dr. Lockhart: Thank you.

Dr. Lange: Then Dr. Damluji.

Dr. Lockhart: So, going back to that last slide that they just showed of the renal artery stenosis, can we pull it back up?

Dr. Lange: Sure. Should we get Felix back to the mic?

Dr. Lockhart: Yeah. Felix, if he'll come back up please.

Dr. DeBruin: Yes.

Dr. Lange: Alright.

Dr. Lockhart: So just hearing your words, I think you were saying that your numbers were different than theirs, partially due to the definition that you only counted them if they were angiography confirmed.

Dr. Mahfoud: So, the protocol defines significant renal artery stenosis as angiographically confirmed stenosis of more than 70%. The denominator is different because we also allowed duplex ultrasound to be an imaging modality of value to assess for potential renal artery stenosis

Dr. Lockhart: As a confirmation or as the initial detection?

Dr. Mahfoud: As the initial detection and as for confirmation.

Dr. Lockhart: But part of the difference in the numbers is because so many people refute this to get angiography and because you had so many non-diagnostic CTAs and MRAs. Right?

Dr. Mahfoud: So, an angiography invasive follow-up was only recommended in case patients had a suspected renal artery stenosis on either one of these imaging modalities. Most of the patients opted then for non-invasive imaging.

Dr. Lockhart: Okay.

Dr. Lange: Thank you. Dr. Damluji and then Dr. Zuckerman. And then we'll just about bring us to break. Go ahead. And then Dr. Saville. Sorry, go ahead.

Dr. Damluji: Yeah, keeping it brief. Thank you, sir. I don't know if the sponsor has the data for those who crossed over beyond six months in terms of efficacy.

Dr. DeBruin: Yes, we do have that. And I'd like to have David Kandzari come back and speak to that.

Dr. Kandzari: Thank you, Dr. Damluji, Dr. Lange I have the crossover results, but others had also asked about durability. Is that still of interest, durability, and medications over long-term? Some had also asked about 12 month results of the ON-MED study.

Dr. Lange: Sure. Let's do both. Let's look at first of all, again—

Dr. Kandzari: Okay.

Dr. Lange: —the crossovers, and we'll look at that and I'll turn off to Dr. Zuckerman and Dr. Saille. Go ahead, David.

Dr. Kandzari: Thank you. Dr. Damluji, our best evidence to date for crossovers stems from the follow-up of crossover patients from the ON-MED pilot study. To date from the full cohort, we don't have completeness of data for the crossover patients, and so I share with you the results of the crossover results from the ON-MED pilot study which we now have available through 12 months of follow-up. Not again, withstanding the sample size, we see, relatively consistent reductions through intermediate term follow-up, at least with renal denervation in these crossover patients, both for office and ambulatory systolic blood pressure. To that end, to expand on that with long-term follow-up I'll first share with you the—

Dr. Lange: So, David, hold on, hold on.

Dr. Kandzari: Yes, sir.

Dr. Lange: Excuse me a second. I just want to make sure, because the crossover didn't occur until six months. So—

Dr. Kandzari: Crossover was permitted at six months but given variability in getting patients back and with covid and everything, the time point here, let me clarify. The time point here at the time of crossover to three month follow up post crossover—Dr. Lange: Thank you.

Dr. Kandzari: —six months and 12 months. If that clarifies it.

Dr. Lange: Yes. Yes sir. Thanks for that clarification—

Dr. Kandzari: Sorry about that.

Dr. Lange: Go ahead.

Dr. Kandzari: To expand on the questions related to durability and medications I'll share with you results from OFF-MED, ON-MED pilot and then ON-MED full cohort, being sensitive to the panel's time. To begin with for the OFF-MED full cohort, we now have data through two years of follow-up.

We present here again after the timing of unblinding and the reintroduction of medications in the sham group. We see a greater magnitude of blood pressure reduction for both the renal denervation and sham groups that is sustained through two years of follow-up. But importantly, despite similarity in blood pressure reductions over long-term follow-up with renal denervation therapy, we witnessed the complementarity of renal denervation with medications, given that blood pressure reductions are achieved at a significantly lower medication index, again, clinically relevant differences with regard to medication dose class and/or number. And we see the disparity in the escalation of medicines in the sham control group to achieve similar magnitudes of blood pressure reduction through two years follow up.

Dr. Lange: And that's the med index two, not the med index one, just as far as everybody understands.

Dr. Kandzari: Yes, sir. Although, med index one also follows a similar trend. Yes. And similarly—

Dr. Lange: Go ahead, David.

Dr. Kandzari: Pardon me. And similarly for the ON-MED pilot study we have now follow up through 30 years of surveillance for these patients, again, demonstrating, meaningful significant reductions through 24 hours and for office with renal denervation therapy compared with the sham control. Although we now see a greater reduction in the sham control group than we did at six months because of reinstatement of medications. And although the medication index is not represented here by any metric as FDA shared, the medicines were similar at all time points through three years, if not at occasional time, points significantly higher in the sham control group compared with the renal denervation patients.

And put in another perspective through long-term follow-up with regard to durability is if we examine the so termed “always on” effect, we see that it's sustained, it's sustained and

continued it through three years of follow-up among patients treated with renal denervation. And despite the reintroduction and escalation of medications in the sham control group, still through three years, we don't see similar reductions through three years of follow-up over a 24-hour period that we do with renal denervation, combined with medicines, again, showing the additive complementary effect of renal denervation plus medicines.

Again, in this instance between the groups, similar, if not greater degrees of medications, in the sham group compared with the denervation cohort. And finally Dr. Lewis, I think had asked for the ON-MED full cohort. I just shared with you the pilot study, but the ON-MED full cohort through 12 months. Keep in mind that patients have crossed over at this point to renal denervation and therefore are not represented in the sham control group, nor in the renal denervation group.

So, in the initial as treated group through 12 months, we see amplified reductions for both 24-hour systolic blood pressure and for office systolic blood pressure for both the renal denervation and the sham control patients. But notably, the sham control numbers are, are achieved at a significantly greater medication burden 3.9 versus 5.5 for medication index two, which is statistically significant, but follows again a similar pattern for other medication indices.

Dr. Lange: Thank you. And I appreciate the facts noting it's not been submitted to the FDA. I just want to make that for the record—

Dr. Kandzari: Yes. Thank you for reminding me these data have not yet been submitted to FDA—

Dr. Lange: Dr. Zuckerman and then Dr. Saville, I'm sorry, David, we're just running out of time.

Dr. Kandzari: Sure. Excuse me.

Dr. Zuckerman: Okay. Dr. Kandzari, going back to Dr. Bates' hypothesis, which is that there's a problem with the sham and also when you look at US versus OUS, it seemed to be that the problem was centered in the United States, but in the slides that you've just run through now, have you cut those US versus OUS? Is there a consistent effect? Because the main slide that we've seen is one that you've shown where there seemed to be more medication changes in a total bar graph in the US and similarity in OUS between medication changes.

Dr. Kandzari: Dr. Zuckerman, were you asking with regard to long-term follow-up between US and OUS differences?

Dr. Zuckerman: No, just the acute primary effectiveness endpoint for the ON-MED trial. The point that Dr. Bates was trying to help us understand,

Dr. Kandzari: I believe, Dr. Zuckerman, you're referencing these data showing—

Dr. Zuckerman: Yes,

Dr. Kandzari: —you're, yes, sir. In which, again, in the United States population, we had a considerably, significantly higher number of patients in the sham control group escalating their medication dose and/or number and nearly one in five patients in the renal denervation group decreasing their dose medication or number in the US cohort.

But as I shared earlier, when we look at these data in the non-US population of 176 patients, randomized, that we see when there are more balanced changes, even though there's a prevalence of medication changes in both groups, when it's more balanced, we see the opportunity to demonstrate the benefits of renal denervation as represented in the right-hand panel within this subgroup analysis. Significant reductions in both office and 24-hour ambulatory blood pressure. And importantly in the OFF-MED trial, the OFF-MED pivotal study, we saw no interaction between non-US and US sites. So it further underscores this influence of medication changes between perhaps the geographic populations. And moreover, in the ON-MED pilot

study, once again, we saw no interaction between non-US and US sites. So it clearly identified something was different about the expansion phase and, more particularly, in the US population.

Dr. Zuckerman: Thanks. And these are overall aggregate results. I don't know if you had any further backup slides that look at this in a more granular matter as to what went wrong possibly in the US.

Dr. Kandzari: Only in the context that most of these medication changes, as I've shared earlier, occurred within the initial three months of follow-up.

Dr. Lange: David, if you've got that grant—

Dr. Zuckerman: Thank you.

Dr. Lange: —or data, go ahead and have someone prepare it and share it, so if you would. Last question, Ben, or last comment Ben? Dr. Saville.

Dr. Saville: Thank you. My question's really along the same line. I mean, the one big question I have in my head, I understand how you get the results and why you're explaining that based on this differential medication usage. But I don't understand why, I'm interested in a sponsor explanation on why they think the sham had a higher usage of meds and the expansion for the intervention group across two studies. So, in my mind, is this random variability? You got different results between the two studies. Is there systematic differences in the population, the protocol? What do you think is driving the difference results that we saw, for example, on slide your course slide 51? That's the big question in my mind.

Dr. DeBruin: Yeah. I'd like to invite Dr. Laura Mauri as from a sponsor perspective to address this. Thank you.

Dr. Kandzari: Sorry. So, I think the question is why still do we see this higher prevalence of changes in the sham group if blinding existed, is that correct?

Dr. Saville: The question is more why is there a difference between the expansion and the pilot in terms of the medication usage? You know, the differential between the intervention and the sham? There's clearly something different between these studies. What's different?

Dr. Kandzari: Yes. As Dr. Mauri described, in part it's missing data, but to a large extent it is, as you've suggested, as we've been discussing the medication changes and why they occur in the expansion group is speculative. But keep in mind that 80% of these patients were enrolled during the COVID period. There's a wealth of data external to renal denervation therapy, describing different patient behaviors with regard to blood pressure control. And again, while this is speculative, that may be one contributing reason.

Dr. Saville: Alright.

Dr. Kandzari: But it is, as I've shared it, it is a unique finding that we had not observed in three separate prior sham-controlled trials that successfully achieved their primary endpoint.

Dr. Lewis: So, since this is supposed to be the panel deliberation time, can I just remind them that their vast majority of the medication changes are protocol violations.

Dr. Lange: Yes.

Dr. Lewis: So that is a very telling statement, I think.

Dr. Lange: Right. And with that, Julia, we're going to stop because we're going to take a 10 minute break. We're going to come back and we'll answer the FDA questions and in the context of that, address the issues that you all have already brought up regarding study, medications, protocol violations, explanations, and then finally get to a vote.

So, we'll reconvene at 3:45. We've got 11 minutes and I'll ask Jim to set the timer. Thank you. Again, please don't discuss any of this with anybody until we get back.

FDA Questions

Dr. Lange: Good afternoon. It is now 3:45 Eastern time and I would like to call this meeting back to order. At this time, we're going to focus our discussion on the FDA questions directed to the panel. Panel members, copies of the questions have been sent to you electronically and posted online for the public.

I would ask each panel member to identify him or herself each time he or she speaks to facilitate transcription. I will turn it over in just a second to Mr. Hiren Mistry to read the FDA questions to the panel. There are 10 questions, embedded in there are 17 different queries. So, some of these we addressed yesterday.

In the interest of time, I'm going to take my prerogative to the chair. If there's something that I thought we addressed yesterday, I'll summarize it. If there's a dissenting view, please voice, that it's not meant to quash any discussion, but I want to move on to the things that will be unique to this particular study that the FDA is going to particularly want us to pay attention to.

So with that, Mr. Hiren Mistry, if you'll read the FDA questions to the panel.

Dr. Mistry: Great. Thank you Dr. Lang. I'm sharing my screen now. One second. Can you all see my screen?

Dr. Lange: Yes, sir.

Question One

Mr. Mistry: Great. Go ahead and start. So, question one is regarding safety. The primary safety endpoint was a pooled analysis of composite major adverse events through 30 days and new renal artery stenosis defined as greater than 70% diameter stenosis confirmed by angiography through six months in the first 253 evaluable HTN-off and HTN-ON RDN treated subjects.

The primary event rate was 0.4% with a one side upper 95% confidence interval of 1.9%, which met the 7.1% performance goal. The safety event rate in all pooled HTN-OFF and HTN-

ON pilot and expansion cohort subjects was 0.4% with a one side upper 95% confidence interval of 1.2%. Overall, the safety results were similar in HTN-OFF and HTN-ON pilot expansion and full cohorts. Renal artery stenosis was recorded if it was greater than 70% diameter stenosis confirmed by renal angiography,

Medtronic use, sorry, slide did not advance. Renal artery stenosis was recorded if it was greater than 70% diameter stenosis confirmed by renal angiography. Medtronic used protocol-driven duplex ultrasound and implemented a site-training program for initial screening of renal artery stenosis. No potential stenoses were identified with first-line DUS at six months using the threshold of greater than 60% diameter stenosis.

However, DUS imaging quality is operator dependent and lacks sensitivity to identify non-hemodynamically significant stenosis less than 70%. Medtronic performed 12 months CTA or MRA on 206 RDN subjects. There were no subjects with a greater than 70% stenosis, diameter stenosis lesion confirmed by angiography. Potential lesions with greater than 50% diameter stenosis were detected in 13 renal denervation subjects. When considering subsequent confirmatory imaging performed for these subjects, this rate could be up to 2.9 to 3.9% at 12 months. The study protocols did not include renal imaging after 12 months. Also, there were no clinically significant changes in eGFR or serum creatinine.

Please discuss the 30 day procedural and device safety profile of renal denervation, reliability of post renal denervation imaging, and the clinical significance of renal artery arterial responses to renal denervation treatment.

Dr. Lange: Alright, I'm going to take the first stab at this. We identified two possible issues. One is obviously related to vascular access and that's true of this and every other device that's inserted through a femoral artery, and I think that's the same. I don't think it's any different for

this, which goes in through a six French sheath. Dr. Lockhart, you're the expert on imaging, and I'd like for you to address a couple issues to the FDA with regard to this particular study.

Dr. Lockhart: Okay.

Dr. Lange: We've seen other studies where everybody had CT and/or MRI imaging at six and 12 months. You could clearly define whether somebody had renal artery, stenosis. This particular study, it wasn't routinely mandated. There are some issues that you brought out regarding reliability of the test. Do you feel comfortable that you could identify with whether the renal artery stenosis rate is acceptable or not with the current information? And how would you do things differently?

Dr. Lockhart: So, I think they said and did what they were supposed to in terms of the ultrasound, the protocol looked good. They did training and the cutoffs that they used have the high sensitivity. So you're hopefully not missing any, but you'll have the false positives, which then you go on to the other study. So I thought, you know, short of the only thing they didn't say is that they were accredited laboratories, which in the post-marketing, I would hope if they're mostly in the US they'll use accredited laboratories.

But the ultrasound, I thought they did pretty well. And I think if they did the direct and then indirect approach, they probably didn't miss any significant stenosis by the ultrasound if they did the full one, like they described. What just was disturbing more, you know, you, he just read off about the variability of ultrasound, but in this study, the variability and the operator dependence was the MRI and the CT, which I'm a little dumbfounded about because everybody thinks CTA and MRA are just easy. And yet, they were the ones that had the quality issues more than the ultrasound. So, I felt like they did a good job with the ultrasound and I feel like they probably did a good job of excluding significant stenosis during the ultrasound process. Does that answer what you're—

Dr. Lange: I'm not looking for a particular answer. I'm looking for your opinion. I guess what I'd summarize to the FDA is the type of imaging, starting with ultrasound and then advancing was fine, but any future ongoing studies you would want to document that the labs are proficient in whatever technique they're using or all the techniques they're using. Is that fair?

Dr. Lockhart: So again, emphasizing training like they did, emphasizing a protocol that was direct and indirect with the ultrasound and using accredited laboratories, I think—

Dr. Lange: —accredited, okay.

Dr. Lockhart: —need to all be part of the requirements.

Dr. Lange: Okay.

Dr. Lockhart: And then, obviously they're going to need better training on their CT and MRA than what was in this one.

Dr. Lange: Great. Dr. Lewis.

Dr. Lewis: I wonder if one of the interventionalists or Dr. Lockhart could comment their thoughts about the 47 ablations per patient and the long-term potential safety issues around that. It just seemed like a huge number to me, but I'm not in that business.

Dr. Lockhart: I don't do these, so I'll have to defer to the interventionalists.

Dr. Lange: Dr. Corriere, were you about to say something? I saw you moving up to the mic.

Dr. Corriere: I haven't personally done these, but I'd be curious if they had any, you know, data about the duration of the procedures.

Dr. Lewis: I think they said 90 minutes.

Dr. Lange: It is, the average was 90 minutes, 47 ablations. Keith, I see your hand, Dr. Keith Allen, go ahead.

Dr. Allen: Yes, hi. So, I think we have to be careful about extrapolating a class effect. I mean, what we talked about yesterday and today are very, while the end result is denervation,

they achieve that from two different mechanisms. And I use RF in surgical cases every week. And I see complications from RF energy versus say HIFU or ultrasound or cryo. And I am a little bit concerned about the potential for injury and the number of ablations that were done. I also think that even though they only go down to a three millimeter vessel the variability of seeing lesions in small arteries with ultrasound can be very problematic. So, I do have some concerns, but in general, a 30-day procedural and device safety profile is not a big concern of mine.

Dr. Lange: Okay, great.

Dr. Lockhart: Yeah, Dr. Allen's right, so that's why I asked them if they identified the accessory arteries in advance because if they didn't, you can miss about 50% of accessory arteries with ultrasound. But if they told them they were there in advance, hopefully that would help. The other one negative of using ultrasound for this specific trial is it's more likely the ablations were occurring further downstream in the artery, and ultrasound does not do as good post-osteum, that's why I was asking if they ablated the origin. So it's better at the origin once you get beyond into the mid and distal and branches, ultrasound doesn't do quite as well. So just, just to get that in there.

Dr. Lange: Right. Dr. Somberg?

Dr. Somberg: Yeah, I just wanted to respond in terms of Dr. Lewis's question, it's 47 ablations, but that's on both sides. So, it's half. So let's say it's 50, it's 25 on each side, and each time they turn the radio frequency generator on it goes to the electrodes. So it's about, what, five? They move the catheter about five times to do. They do one ablation per site. And this is about it's not too different than a lot of these atrial fibrillation ablations in the, you know, the pulmonary artery. So, the numbers sound a lot, but in actuality, it's not much more than electrophysiologists do. But they're doing it in a vessel. The others are doing it on the, well they're doing the pulmonary artery as well as the atrium, which are also very thin structures.

Dr. Lange: Dr. Bates?

Dr. Bates: Yeah, I think you have to give a relative answer. If you take a hundred people and 50 get an intervention and 50 don't, there're going to be some complications when you invade the arterial space. This is a young population. If you do this in thousands of patients, you're going to get a guide catheter dissection of an osteorenal artery.

Sometime you're going to perforate with a wire sometime if they say there's a one to 2% complication rate. I think that's very reasonable. And within the bounds of an interventional procedure. But it's higher than in the patients who don't get an interventional procedure.

Dr. Lange: Mark, my question to you specifically, and the FDA's interested, is it's a different procedure than what we heard yesterday in terms of ultrasound versus RF number of procedures, sites that are ablated.

But you felt comfortable with the information that that provided that the renal artery stenosis rate is low. In other words—

Dr. Lockhart: I do. I was concerned when I was first reading this because it's ablation and they didn't have that similar system that the ultrasound had, but it is water cooled in the tubing to try to protect the wall. And again, if the ultrasound was done well, we should pick up a significant stenosis on these. You know, I hear ablation of the artery and I think higher risk of wall damage and later on having stenosis, you know, 12 months. But, based on what I'm seeing here, it seems safe. You know, maybe it is 2%, maybe it's not 0.4% like they're saying, but I don't think it's 10%.

Dr. Lange: Okay. So, in response to question number one, it appears that the 30 day procedural and device safety profile appears to be safe. And that is a low complication related primarily to vascular damage from access to the femoral artery. And the imaging protocol is as good as the labs that do them. And the responses in the future is to make sure they're accredited

labs verify that they can do the imaging study correctly. Does that address your questions, Dr. Zuckerman?

Dr. Zuckerman: It does very well, Dr. Lange. Thank you.

Dr. Lange: Thank you. Let's move to question two.

Question Two

Mr. Mistry: So, question two is regarding the effectiveness and the blood pressure measurement method. Data were presented using both 24-hour ambulatory and office blood pressure measurement. Ambulatory blood pressure has been shown to have greater prognostic value compared to office blood pressure, and was identified as a preferable method at the 2018 panel meeting.

This may be due to the large number of measurements made for ABPM that are free from potential confounders in HTN-OFF at three months. The 24-hour ambulatory and office systolic blood pressure results at three months followed similar trends with statistically significant reductions favoring RDN, although the OSBP analysis was not adjusted for multiplicity. OSBP to reductions with greater in magnitude versus ASBP in both RDN and sham groups. In HTN-ON at six months, the 24-hour ASBP and OSBP reduction in the pilot cohorts and the OSBP reduction in the expansion cohort favored RDN over sham.

However, in the HTN-ON expansion cohort, the 24-hour ASBP reduction was similar between groups. Please discuss the relative value of ambulatory and office blood pressure measurement in assessing changes in blood pressure and evaluating the effectiveness of RDN.

Dr. Lange: Right. And I'll summarize the discussion we've previously had regarding this. One is the feeling, is the ambulatory systolic blood pressure or inventory, blood pressure is the gold standard. People don't feel comfortable relying only on office, although both can give complimentary information. Ambulatory gives both daytime and nighttime information, which

office doesn't. It's agnostic with regard to when people take their medications. So it's not based upon timing of medication. You don't have white coat syndrome with it. And then, yeah. And those were the comments that were expressed yesterday. And I don't think they've changed, but I'll open it up. If I've not accurately represented our discussion yesterday. Dr. Nachman, I see your hand up already.

Dr. Nachman: I just want to ask maybe Dr. Zuckerman to comment. I mean, yesterday we had quite a bit of discussion about a target of five mmHg reduction in the ABPM and none of the—

Dr. Lange: We're going to get to that in question three, doctor.

Dr. Nachman: So, I'll keep my mouth shut then.

Dr. Lange: No, no, no. You're not, you're actually setting us up for the next question. And then I believe that we mentioned yesterday that home blood pressure recordings and transmitted telephonically can provide probably complimentary or better information than just the office systolic blood pressure. So, Dr. Zuckerman, we discussed this yesterday. I think I've summarized what we said yesterday. Does that adequately address question two for the FDA?

Dr. Zuckerman: Yes, you've summarized it well, and in contrast to yesterday's discussion, you further emphasized the use of 24-hour ambulatory blood pressure recordings rather than just an average daytime ambulatory blood pressure recording. That's very helpful information.

Dr. Lange: Thank you. Alright, let's move on to question number three, and we'll let the FDA read it and then we'll let Dr. Nachman direct it towards any of us.

Question Three

Mr. Mistry: So, question number three is regarding effectiveness and the magnitude of blood pressure reduction. Based on FDA's interpretation, the 2018 panel considered a five-mmHg difference in ambulatory systolic blood pressure reduction between treatment groups to be clinically significant. The primary endpoints were baseline adjusted differences in mean 24 hour

ASBP reduction between RDN and sham groups using a Bayesian power prior method. HTN-off measured ASBP at three months while medications with were withdrawn. HTN-ON measured ASBP at six months while medications were kept stable. In HTN-OFF because of the similarity in the pilot and expansion cohort ASBP results, most of the pilot cohort data were used in the Bayesian analysis and there were a statistically significant between group difference of 3.9 mmHg favoring RDN versus sham. The primary effectiveness endpoint was met.

In HCN-ON pilot cohort, ASBP results were discordant with the expansion cohort results. Consequently, very little pilot cohort data were used in the Bayeseian analysis, which demonstrated a between group difference of only 0.03 mmHg, the primary effectiveness endpoint was not met. Medtronic noted potential confounders for the different outcomes between the HTN-ON pilot and expansion cohorts. Please discuss this clinical significance of the observed difference or effect size in reducing 24 hour ASBP between the RDN and sham groups and HTN-OFF, HTN-ON and considering the totality of HTN-OFF and HTN-ON data.

Dr. Lange: Great. Dr. Wittes has her hand out first and I'm going to call on Dr. Yeh and then Dr. Lewis. So, Dr. Wittes?

Dr. Wittes: Yes. So this is Janet Wittes. It seems to me that I can't figure out actually what that difference is. It says 3.9, but there's so many different analyses depending on how they're dealing with the missing data and the lower bound of that confidence interval is 1.9 minus 1.9. So, I think for me on the table is still what is the best estimate of the difference that we are seeing that the HTN-OFF study showed?

Dr. Lange: Okay, Dr. Yeh, let's assume it's 3.9. So, and again, there's a statistical significance of a p less than 0.05. What is the clinical significance? Dr. Yeh?

Dr. Yeh: You know, my thoughts on this are related to both the last question in this question, which is, you know, I know there was agreement on ambulatory blood pressures being the gold standard because of its greater prognostic significance and its greater accuracy.

Those data and that decision was made prior to these most recent meta-analyses. In my reading of those meta-analyses is that the five point difference is clinically significant, not just measured by ambulatory blood pressure, but by office-based blood pressure as well. I mean, I'd like to be corrected by the hypertension experts here, but looking at those trials that comprise the meta-analysis where they just determined that at Lancet in 2021, many of those studies used office-based blood pressure in determining those measurements.

So, you know, part of me wonders, the other thought I have is that even though it may be more accurate, I can't think of a way that office blood pressure would be biased, even though it's more variable perhaps, but not biased between sham and controls. So, the differences that we're seeing in office-based blood pressure between the two arms, I think are real physiologic effects, not some sort of random occurrence.

So, it's a little bit hard to reconcile why those two outcomes look, you know, so different in at least, you know, a couple of the trials. But my impression is that the office-based pressure differences matter that they're reflective of an actual difference in treatment effect. And therefore, I'm inclined to think that the clinical significance and based on what the, the meta-analysis actually studied, that the clinical significance that we see in hypertension off is actually perhaps, you know, actually of significance.

On top of that, for many reasons that we've talked about, all of the various biases that are in these studies, they all have the single same direction of effect, which is to bias the effect, estimate to the null. Whether it's the informative censoring that's generated from the escape, whether the escape was handled, whether it's differences in co-intervention, which clearly bias against the

treatment. So I'm just thinking that that point estimate that we're seeing is not that useful. Maybe I have the same impression as Dr. Wittes, I just don't put that much stock in that single point estimate. Because it may be underestimated on top of being the measurement that is, you know, is sort of more likely to be neutral.

Dr. Lange: Okay. Dr. Hirshfeld?

Dr. Hirshfeld: Well, I felt all along that the focus on the mean value or the median value of the delta is overlooking the granularity of the data. And I think for this second time through in this process, we knew to ask for the waterfall plots and the box and whiskers plots. And I thought, you know, visual inspection of those plots clearly indicated that there was an effect of the RDN. I think it may, if you tried to stack it up against what we saw yesterday, and this is not necessarily an apt or an appropriate comparison, I think the effect was slightly more modest than what we saw yesterday. But I think nonetheless, there was a real effect and there were clearly patients on the left-hand side of the waterfall plot who derive a substantial benefit from the procedure.

Dr. Lange: Okay. Dr. Somberg,

Dr. Somberg: Okay. So, with that said, two comments. One is that ABPM samples so much more than office blood pressure that it's very valuable and it's been correlated with a lot of surrogates for adverse cardiovascular outcome.

Yes, that matter analysis is informative. And I certainly stated yesterday that I wouldn't throw out office blood pressure. It certainly encompasses sympathetic reactivity, which this approach to denervation deals with. So it's something to consider, but I think if the FDA was having to choose one, and they don't have to choose that, but ABPM should be paramount.

The second thing I just wanted to comment on, it seems that any way you look at it, the effect size with this device is there, but is diminished or modest. And I see, my impression is that the ON-MED data suggests that the effect is very comparable to pharmacologic therapy.

So, I mean, some people have a belief that this is going to be a replacement for pharmacologic therapy, and I think it's an adjunct in patients that can't tolerate, can't, possibly be compliant and other reasons. But that this is going to obviate pharmacologic therapy, I think is incorrect that it's a modest effect and it's approximately equal to one drug.

Dr. Lange: Okay. Dr. Saville?

Dr. Saville: Yeah. So, to kind of answer these questions here, my interpretation of the offset results, I also don't put a lot of stock in a single point estimate of 3.9. What I put a lot of stock in is that Bayesian post distribution, so the sponsor showed slide 34 from core presentation that shows essentially the model-based distribution. And even though it's centered at minus 3.9, there's a lot of mass to the left of that. It could go as high as six. There's a fair amount of mass to the right of that as well, goes as low as two and somewhere between minus six and minus two. There's clearly some benefit herein the ON-MED study. And I think you see that both in whichever endpoint you look at in terms of the ambulatory systolic blood pressure or the office systolic blood pressure.

Dr. Lange: Now that's in the OFF-study. What about in the ON-study?

Dr. Saville: I'm sorry, that was the off, I said that wrong. Yes, so that was the off. The on study, that also has a similar distribution, but it's centered right at zero. Right? But you have all these confounding factors, you have missing data. The biggest issue, and we looked at some imputation of missing data that's maybe says maybe it should be shifted a little bit to the left and maybe there is some small benefit.

My interpretation of the on study is that you really have two correlated endpoints. You have both the systolic blood pressure and you have the number of medications. Those are both post randomization outcomes and it's hard to interpret one ignoring the other. And that's what we're trying to do when we, you know, try to estimate what's the drop in blood pressure and the

fact that you've, you know, you have a systolic blood pressure that's about the same between the two groups, but you have lower drug usage, lower medication usage.

That to me means something as well. It also indicates that there's a benefit here. You maybe not benefiting the, the blood pressure group, but you're certainly benefiting on the number of meds that are required to get there.

Dr. Lange: Okay. Dr. Lewis, Dr. Allen, Dr. Starling, and then Dr. Lange.

Dr. Lewis: Okay. Well, regretfully mostly for the patients who are participated in this trial, but also for Medtronic's, I think we're in a position where the hypertension on trial is negative and you can come up with all kinds of reasons, it might be negative, but it might be negative because the null hypothesis is correct. And there's no getting around that. They have a lot of hypothesis-generating data and could do another trial that was sham-controlled rather than the 1200 single arm study. In hypertension off, the effect is modest. I realize that, you know, there are people that the distribution is different than what the mean is. That's also true for all the data that suggests that greater than five mmHg is clinically significant. I don't know that I would vote for a blood pressure medicine that had even a small amount of side effects that only had a mean of 3.9.

I think most blood pressure medicines are 5, 10, 15. So, I think this is a very small effect. And you have to think of all the people who are going through, and I know you guys are interventionalists and device people, but speaking as someone who's gone through these procedures many times, it's not a walk in the park to ask a patient to go through something that may have no effect or very little effect on them that is positive.

And aside from the safety data, just the experience, let alone what the safety data will be like in the wild. So, I think we have a one study with an at best modest effect.

Dr. Lange: Thank you, Dr. Lewis. Appreciate it.

Dr. Lewis: Oh, and also, I have one, one other quick comment and a discordant office blood pressure and ambulatory, which is not what we see. And we, and I don't really think we're supposed to talk about yesterday, so I'll just talk about the other analyses for today. You know, it is not typical to see that kind of discord between the ambulatory and the office. So even in the OFF trial, there's just something off. And I'm deeply disturbed by the protocol violations, which I bet you were COVID-related, and so this was just a hard break for them. Not that the people had COVID, but that COVID disrupted their clinical trial operations because not changing meds is a very important protocol thing in the ON-trial. And that, you know, they had a large number of people who did change meds is a problem.

Dr. Lange: Okay. Thank you, Dr. Lewis. Dr. Allen?

Dr. Allen: I'm going to, I'm going to echo what Julie just said. And, you know, my brief summary would be in the hypertension off there is, I'm not going to even use the term modest, there is minimal delta difference in the hypertension off at three months and at six months, once meds are brought back in, there's essentially no difference.

Hypertension on did not meet its primary endpoint. It was negative. It echoes what John said earlier in that medications are very good at managing hypertension. I also have a real problem, and I know we're going to talk about this when you get to the IFU, but these were not medically-resistant patients or people that couldn't take medicines. There's been no evidence that that's the type of patient that's been studied here. And so, I really think the magnitude of the blood pressure is quite minimal.

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

Dr. Starling: Dr. Lange, Randy Starling. I'm clearly in the camp that looking at the composite data that's been presented, I believe there is a signal of effectiveness. I'd also like to point out that this discrepancy between ABPM, which I agree is the gold standard and office-based, we saw

this yesterday. I don't think we have a physiologic explanation for, but it's a consistent finding, which is quite intriguing.

Dr. Lange: Right. I'm going to summarize what we have to date and then if people want to voice a dissenting or different opinion, or if you want additional with regard to the significance of the observed difference in hypertension off. Individuals believe it's real, it is modest at best and less than the effect of what one would see with the addition of a medication. Perhaps just a slight increase in the dosage of a medication. With regard to the on trial, it was negative, and I think Dr. Lewis described it well, there are obviously confounding factors, but what you can't get away from is you can't say that the null hypothesis isn't correct. And at the end, it's a negative study and regardless of whether that's due to the confounding factor or the fact that it just doesn't do what they'd hope for it to do. I'm not sure any additional discussion is going to provide any more insight into that. Does that sufficiently address or answer the question, Dr. Zuckerman?

Dr. Zuckerman: It addresses A and B. And then Part C is how do you put those two trials together, the totality of the data?

Dr. Lange: And do you want to discuss that now or part of the safety and efficacy, Dr. Zuckerman? Discuss it now?

Dr. Zuckerman: I think we can defer it to until we get to the benefit risk safety efficacy question.

Dr. Lange: Dr. Dr. Lewis. I want to get back to something you mentioned. The protocol violations bother me a lot as well. And as we're changing medications, I have a hard time ascribing it to COVID because patients don't change their medications, generally, doctors do. That's who changes it. And I don't think that my activity or my care of patients during COVID was any different than, than pre or post covid. So I realized that's the time this study took place.

But there are other studies that took place during COVID as well, and we didn't see these protocol violations in the studies. So…

Dr. Lewis: Yeah, I think that there were some patients who during COVID were willing to come out from their homes to see their own doctors, but not go to clinical trial centers. I think some of that went on, but in any case, I don't think it matters. It's a negative study. So, I mean, it's unfortunate.

Dr. Lange: Yeah. Alright, let's move on to question number four.

Question Four

Mr. Mistry: So, question number four, just regarding effectiveness in subgroup analyses. In HTN-ON there are numerical differences in 24 systolic blood pressure in Us subjects, in African American versus non-Americans in the US. In HTN-ON in six months, US subjects had 1.5 mmHg reduction in 24-hour systolic blood pressure in favor of the sham group. While OUS subjects had a 4.8 mmHg reduction in 24-hour systolic blood pressure in favor of renal derivation. The US sham group had a higher percentage of subjects who increased blood pressure medication burden as measured by medication index one. In OUS subjects, blood pressure medications were generally similar for both groups.

In HTN-ON at six months, black Americans and the sham group had greater reductions in 24-hour systolic blood pressure while the renal denervation group had a greater reduction in office systolic blood pressure. If, for Black Americans in the sham group, medications increased by 0.3 of one full medication dose and was unchanged in renal denervation group for black Americans. Please note the small sample size of a black American subgroup. For US, non-Black Americans and non-US subjects, the ASBP and OSBP had the same directionality. Please discuss the clinical significance of the HTN-ON discordant results between 24-hour ASBP and OSBP results for renal denervation versus sham treatment in the following groups and the

generalizability of these results to the target US population, including US and OUS patients and US Black Americans.

Dr. Lange: We've heard one of the possible explanations being medications, differences in medications being US, OUS, and US black Americans. Just a show of hands, how many of you are convinced that that's the reason? Hands up. One. How many of you are not convinced if that's the reason.

Alright, so, alright. Dr. Somberg, Dr. Lewis., Dr. Somberg, Deneen. You got your hand in first, then Bates, Lewis. And, go ahead, Dr. Somberg.

Dr. Somberg: Well, I just wanted to say that you posed the question sort of in a strange way that I'm convinced that I would like to rephrase the question that between the medication differences and also the sampling of ABPM differences those two have a good chance of explaining the difference. And, and I would add to that, easily when you have a small treatment effect, if you have these other variables going on at the same time, it will obscure the treatment effect. So I think that's why I voted yes. Obviously, you can't be certain because the study is not done.

Dr. Lange: Dr. Thank you, John. Deneen.

Dr. Hesser: My vote, my hands up was really based on, I didn't have an adequate explanation from the sponsor.

Dr. Lange: Okay.

Dr. Hesser: These were two things that popped right out of the data sets, and I did not hear something that explained what they were going to do about this or why it occurred. So I just don't have the confidence there.

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

Dr. Lewis: So, these are both subgroup analyses. We always, I think as the US FDA want to see a positive effect in the US. However, we do have, by chance alone, you know, the study is

not powered for the either of these subgroups. The other possible explanation is that the conduct of the study, for whatever reason, was less stringent in the United States. I actually would give the benefit on this one. I wouldn't say, well, because it didn't work in the US and it didn't work in our black Americans. That, you know, that's a prohibitive problem.

Dr. Lange: Okay. Dr. Bates.

Dr. Bates: I would say both major trials were underpowered. One of them was negative because of the protocol violations and the crossovers and other discordant challenges we've had to the data. This whole data set appears to be observational and I don't think we can have any conclusion from any subset analyses. I think they can only be hypothesis generating the sample sizes and the subgroups, I'm surprised the statisticians haven't objected to.

Dr. Lange: Don't give me any fuel, Eric. Alright, I got the two statisticians in line now. Okay. Dr. Saville and Dr. Wittes. Dr. Wittes first, I think you had your hand up first and then Ben.

Dr. Wittes: Yeah, I put it up and down because I heard what everybody was saying. I read, these are very small sample sizes. Okay. When you're talking about a study that needs to be several hundred people and then you look at 40 people I think a parsimonious explanation is this could all be by chance and the other explanation could be, well, there may be a reason, but it's too small to know. So, I'm with those who said, give them a pass on this.

Dr. Lange: Alright, thank you. And then Dr. Saville last word on this.

Dr. Saville: Yeah. Not only is it small sample sizes in these groups, but you also have to think about multiplicity. How many different subgroups are we looking at? Rather than a lot of different subgroups. You're always going to find a couple things here there that look like they vary. Are they real, are they noise? Chances are they’re probably just noise.

Dr. Lange: Okay. So, Dr. Zuckerman, to summarize, when we talk about the clinical significance that there, nobody feels very confident that they can, that there are subgroup

differences or that there are not because of the subgroup sizes change in medications, protocol violations, and missing data. This could be a hypothesis generating, but certainly it's something that the sponsor would need to address in the future. Does that adequately address your…

Dr. Zuckerman: Yes. That adequately addresses these small subgroup analyses. A question to Dr. Lange, the sponsors, specifically Dr. Mauri, then showed a larger sample size for black Americans that was an aggregate from all the trials. Did that help convince you that there wasn't an obvious signal of harm or no effect in Black Americans?

Dr. Lange: Personally, I, again, I think the data size was too small, and I agree with Ben in terms of looking at multiplicity. I think it needs to be addressed and I, as they discussed their plan to enrich their population with African-Americans and hopefully Americans as well. But no, there's nothing I've seen that really assuages, that convinces me that the effect is similar in that group as it is in the general population.

Dr. Zuckerman: Thank you.

Dr. Lange: Great. Number five.

Question Five

Mr. Mistry: So, question number five is around the durability of effectiveness. When considering blood pressure changes over time for the HTN-OFF study, the 3.9 mmHg, ASBP reduction difference at three months favoring RDN was not seen at six or 12 months. Although, RDN subjects had a lower medication burden on average of about one fourth or one full blood pressure medication dose. Data beyond six months are not available for the HTN-ON full cohort. And the HDN-ON pilot cohort sustained decreases in 24-hour systolic blood pressure are noted at 12, 24, and 36 months. The number of medications was similar between pilot cohort RDN and sham groups during longer term follow-up.

Limitations with interpreting longer term data include the addition of blood pressure medications, unblinding of subjects, small sample sizes, particularly for HTN-ON and crossover, reducing the control group sample size.

Please discuss the strengths and limitations of longer term blood pressure data in patients treated with RDN, including whether RDN provides a durable reduction in blood pressure, the clinical significance of longer term blood pressure changes in RDN subjects versus sham subjects, and the clinical significance of blood pressure medication differences between RDN subjects and sham subjects.

Dr. Lange: Alright. Dr. Lewis, I don't know if you have your hand up or if that's residual.

Dr. Lewis: I do have my hand up.

Dr. Lange: Go ahead, Dr. Lewis.

Dr. Lewis: Yeah, I think that there is no evidence of durability and a quarter of one medication in my mind is not a clinically significant effect.

Dr. Lange: Thank you for that. Dr. Wittes.

Dr. Wittes: Yes, I agree with what was just said, but I also want to add that the problem with the sham group in this case is not just the reduction in sample size, but it's the selection which was said before. So, that comparison it seems to me it's just not a comparison and it's just that can be defended by randomization.

Dr. Lange: When you say selection, what do you mean? I'm sorry.

Dr. Wittes: Yeah, those who decided to go into the active group, right? So the people left over in the sham are people who are different from the total group

Dr. Lange: You're talking about the, I'm sorry, you're talking about the crossover patient?

Dr. Wittes: The crossover people, yeah.

Dr. Lange: Okay.

Dr. Wittes: There's a statement that the crossover, the reason it can't do the crossover is the sample size is so small, but it's more fundamental than that. It's not a comparison that reflects the randomization anymore.

Dr. Lange: Okay. I'm going to take a, go ahead doctor Saville. I'm going to take a bonus on something. Go ahead Ben.

Dr. Saville: Yeah, just to follow up quickly on that. So, I think that the randomized study, you lose that once you allow crossover, just I wanted to emphasize that. So you lose that randomization and it's hard to interpret what happens after that point. So really, up to six months, if I understand those right, up to six months, you can believe. And after that it's really difficult unless you use some more complex tool methods to analyze those.

Dr. Lange: Okay. With regard to number one, I'm going to ask a question whether it provides a durable reduction. I'm going to take a vote straight up. If you believe it does, I'm going to ask a show of hands, if you believe it doesn't, show of hands, or if you believe you can't know from the data. So those of you that believe there is a durable reduction in blood pressure, show of hands. For the record, that's two. Those of you who believe it, it doesn't show a durable, one, two, three, William? You scratch your 10. That's four. Okay. That's four. And those that say I can't, and Steve Allen's five and those of you who say, I just don't know. One, two, three, four, five, six. Okay. Just for the record. So Bram, hopefully that will at least provide some insight in how the panel feels about it.

And that is they either feel it isn’t durable or there’s just not enough information. They can make that decision based upon the data. With regard to the clinicals of the longer term blood pressures and the treated versus the sham subjects, I think Dr. Saville and Dr. Wittes, as you mentioned, it is that at that point you lose randomization and it’s very difficult to make anything of that data. And now you have two different patient populations, not the ones you originally

randomized to. And the clinical significance of blood pressure medication differences between the subjects and the sham. I'll get to you in just sec, Dr. Yeh, because I, I don't want to have the final word, but as Dr. Lewis mentioned, it's a quarter dose change in one medication. And the feeling is that's probably unlikely to account for the convergence of the two blood pressures. Dr. Yeh?

Dr. Yeh: Yeah, I was going to, let's just say reiterate that the studies really can't answer those questions because they weren't designed to answer those long-term durability questions. So it's really not, you know, I think a failure of the study to not be able to discern those. But the, the one thing I would say is that there were some data that Dr. Kandzari, I think presented at the end, which appeared to show, I mean, it went by a little fast, but appeared to show a more durable and larger magnitude difference in medications. I forget which study it was, but he showed these curves of medications over time and it did show, I think, a sustained difference in medication use between the arms that appeared to be maybe slightly bigger in magnitude than what the FDA had shown. So, I just can't quite remember the data and why those are different.

Dr. Lange: It was the HTN-2 OFF data and it was the MDI-2, which is not a linear relationship, so it's li different than the MDI-1 index that we're using. That's why.

Dr. Zuckerman: So, Dr. Yeh, absent a randomized study, do you have any suggestions for how a more robust demonstration of durability can be shown with this type of device?

Dr. Yeh: You know, I think it's really a tall task because it's really not ethical to leave people hypertensive. It's also not something clearly that patients want to be and their physicians want to keep doing when we have effective medications out there. And I think that's really what you saw in the on study, which is probably people were walking around hypertensive didn't like it, and they and their physicians decided to escalate medications against protocol. So, you know,

and I think in many ways, if you think about those things, that's, that's probably good clinical care. So, you know, this is one of those situations where. Offering good clinical care actually hurts your ability to find treatment effect over a long, the longer you try to study this, the more difficult it will be, because it just means that you're sustainably, you know, not offering good clinical care to patients.

So I don't have, you know, a magic bullet here. And I think you'll have to make inferences based on number of medications and sustained declines in blood pressure in single arm studies or find, you know, potentially find control groups that you can work on in a study that's not so protocolized.

Dr. Lange: Dr. Somberg, Dr. Lewis, and Dr. Wittes.

Dr. Somberg: Well, I agree with what Dr. Yeh just said, how you would design the study and you let people titrate the medications, but you just don't have to look at the number. I think Dr. Kandzari made a good point when he showed us that it wasn't just the number, it's also the class and the amount of the medication.

So if you, go from 25 to 50 of hydrochlorothiazide, it's not the same as you go from dropping amlodipine and adding mineralocorticoid perone or spironolactone. So, I think there's a scoring system you can develop here. I thought the data was suggestive that the medication actually the complexity of it was higher in the sham than the denervation group. And the denervation remains low, lower blood pressure over time with less medicines. And I think we're just being much more rigorous, maybe because of fatigue than we were previously.

Dr. Lange: Or maybe not, John. I'm not tired. Dr. Lewis,

Dr. Lewis: Sorry about that. So, I think that you could, I think the on trial, if it had shown, it allowed people to have blood pressures up to 180 for six months. And I think it's speculative what Dr. Yeh said about, you know, it failed because doctors and patients walked away from it.

Patients signed consent forms. And the patients came into those studies, I assume, with blood pressures that were not under control for sure. And may have even been that high. And I also think, and that's the part where I think I'm tired, but it's not a call to composited outcome, but, and I'm just blanking on the, what they call it now, but you could have an outcome that includes patients that need to escape, as a, like a negative the way—

Dr. Lange: A rank order outcome?

Dr. Lewis: A pardon me?

Dr. Lange: A rank order outcome?

Dr. Lewis: Yeah. A kind of rank order outcome. So I think it is really doable and I would buy a six month as a durable, at least a good sign of a durable effect.

Dr. Lange: Okay.

Dr. Zuckerman: Thank you. Those comments are very helpful, Dr. Lewis.

Dr. Lange: Yeah. And so in that rank order, we talked about medications and quantifying that type dose number. We talked about escape, obviously other clinical signs or symptoms, heart failure, pulmonary edema, those kinds of things as well. And then blood pressure as well. So, Dr. Wittes and Dr. Starling.

Dr. Wittes: Yeah, so I was going to say something very similar. I think that, and it's similar to what Dr. Saville said, that we have to think of it not as just blood pressure or drug.

There has to be an endpoint that somehow combines them, whether it's a rank order or whether it's some scoring system, but something that combines them both. And that way you don't have to compromise the safety of the patients. They can be treated well, and you can do the analysis, but it's a complicated, it would be a complicated endpoint, but I think would capture what everybody is saying.

Dr. Lange: Okay, Dr. Starling.

Dr. Starling: To address Dr. Zuckerman's question. I think any measure of durability also should include compliance as well as a patient reported outcome. Because the patient is the one taking the medication. Thank you.

Dr. Lange: Thank you. Great comment. Thank you Randy. Dr. Saville and Dr. Yeh. Then we'll close this up.

Dr. Saville: Yeah. Just to pick back up on Dr. Wittes' comment. So it could be an innovative endpoint, but it also could be an innovative analysis where maybe it's a joint model trying to figure out what's the effect or what's the benefit on these different endpoints? And maybe you don't have to restructure endpoint, but maybe you restructure the analysis.

Dr. Lange: Great. And then Dr. Yeh.

Dr. Yeh: Maybe this was the comment that Dr. Saville was trying to make, but those things could be done with the existing data. One doesn't have to run an entirely new randomized trial. One could do a secondary analysis and make a hierarchical endpoint that includes, for example, escape as part of the endpoint or reaching a blood pressure above X that's clinically dangerous as part of the endpoint because those data were collected in the existing trial. So, that type of analysis might be informative.

Dr. Lange: Great. Thank you. The last two comments—

Dr. Lewis: Can I just make a quick response to Dr. Yeh?

Dr. Lange: Sure.

Dr. Lewis: I think the problem with the existing data is that in the on trial, you know, one of the most important things, which is the blood pressure difference failed. So, I think that you would have to rank them in some way. And I think that would be problematic. I mean, I think it would be interesting to see it all put together. But I think it would be problematic.

Dr. Lange: Okay. Dr. Allen, last word and I'm going to summarize.

Dr. Allen: So, I would want to push back a little bit on kind of durability based on clinical results because the durability is really directly dependent upon the rate of reintervention whether that occurs or doesn't occur. And I'd give you multiple clinical examples. So, for example, cryoablation of intercostal nerves during surgery. It takes well over six months for those nerves to become reinnervated. Nerves typically regenerate at a rate of one millimeter per month. Reinnervation takes a long, long time.

So this idea, that you're going to arbitrarily pick three months or six months, and then you're going to know whether this is durable or not is fantasy.

Dr. Lange: Right. So Dr. Zuckerman, I'm going to summarize the use of an intervention to decrease blood pressure is designed to do one of three things: either reduce the blood pressure in individuals in whom it's high-resistant is a responding medications.

Two is use as an adjunct to medication, either to reduce the number of medications or compliance with medications or dose of medications or tolerance of medications. And the third is related to patient preference and what their outcome is. And so, looking at durability would be some assessment of those things, as Dr. Allen mentioned, over a period longer than six months. So does that, you've heard the entire deliberation Dr. Zuckerman, does that summarize and do you need additional information?

Dr. Zuckerman: No. That's a good summary for possible next steps.

Dr. Lange: Okay.

Dr. Zuckerman: But for right now, the question regarding durability of blood pressure reduction with the data at hand, there's great uncertainty or do you want to rephrase that conclusion?

Dr. Lange: Yes. There was only one person that felt that the results were durable and everybody else felt that it was either not durable or couldn't be answered with the current information.

Dr. Zuckerman: Thank you.

Dr. Lange: Great. Number six. Keith, put your hand down if you would.

Question Six

Mr. Mistry: So, question number six is regarding the patient preference study. Medtronic conducted a patient preference study using a discreet choice experiment with 400 patients to ascertain preferences for renal reinnervation procedure compared, compared to pills only. The study aligned with the CDRH PPI guidance document the results suggest that between 15.1% to 30.9% of patients with select renal denervation system intervention.

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

Dr. Lange: Deneen, I'll let you speak to that first, and then I'll summarize. We talked about yesterday, so maybe I'll let you go first.

Dr. Hesser: Okay. I just wanted to add that the results of this DCE were published back in January in Circulation, and there was a lot more information provided in the journal article than there was today. They really went out of their way to validate their methods and revalidate. So it was an impressive study, but even though there were limitations to it, they still reflect the same thing that we saw yesterday, that patients are willing to take a risk if it means offsetting some of their pharmaceutical reliance. No, I'll leave it at that.

Dr. Lange: Okay. Dr. Bates.

Dr. Bates: I liked the concept, but I'm struck by the fact that in the first study, 66% of the patients crossed over to the intervention when they were given that option. In the second study, 74% crossed over to the intervention and the explanation was patient interest.

So, what I'm concerned about is whether the patients had the accurate information upon which to make this decision since this is still an unapproved device and we're arguing amongst ourselves whether it has any clinical importance or not.

Dr. Lange: Thank you, Dr. Cetnarowski.

Dr. Cetnarowski: Thank you. So the question here is what is the impact patient preference study within the risk-benefit assessment? And I think it is an important component for sure, but it's only one component. So, when we talk about the risk-benefit, we see that patients here do have a preference for at least being able to be offered an alternative treatment. But again, just one component of risk-benefit we're talking about, we should consider the gap that we have and being able to effectively treat hypertension. There are differences in the requirements of CDRH here to determine efficacy and safety in a device. There is the safety of the device that data that's been presented. There's the efficacy data. So all that together should really be the risk benefit assessment. And patient preference is certainly an indicator that the patients want an alternative treatment and it's an important component of the risk benefit.

Dr. Lange: Thank you. Dr. Corriere, I'll let you have the last word on this.

Dr. Corriere: I just wanted to say that the, the language here, I'm glad they did a preference study. I'm glad it's published. But, you know, it's important to acknowledge here that shared decision making never occurs with a patient in a vacuum, just choosing a treatment. And this percentage that would choose ought to have also a cautionary tale of, you know, potential over utilization if it's pitched that way without the right context and consideration of alternative therapy. Thank you.

Dr. Lange: So, to summarize the response to question number six, everybody feels like patient preference is important, but as Dr. Cetnarowski mentioned, it's only one component and probably the most essential thing is to provide them with the most accurate information regarding how effective it is and what the risks are so that they can make that informed consent be involved in the sheer decision process. So, do you need any other clarification, Dr. Zuckerman?

Dr. Zuckerman: No, that's very helpful, Dr. Lange.

Dr. Lange: Thank you. Number seven.

Question Seven

Mr. Mistry: So, question number seven is regarding labeling and indications for use. In the clinical trial, the sponsor evaluates subjects with mild to moderate uncontrolled hypertension in the HTN-off and more severe uncontrolled hypertension in the HTN-ON as detailed in the table below. The proposed indications for use statement is as follows, the Symplicity Spyrall, multi electrode renal denervation catheter and the Symplicity G3 RF generator are indicated for the reduction of blood pressure in patients with uncontrolled hypertension despite the use of anti-hypertensive medications or in patients in whom blood pressure lowering therapy is poorly tolerated. Please discuss whether the available clinical data support, the proposed indications for use, and please discuss whether the phrase, despite the use of anti-hypertensive medications or inpatients in whom blood pressure lowering therapy is poorly tolerated, should be modified or further defined. Modifications are needed, please discuss alternative language.

Dr. Lange: Dr. Somberg and then Dr. Lewis.

Dr. Somberg: Well, I'd just like to point out that, for consistency, many, as Dr. Zuckerman said, many an application has been approved on the basis of one pivotal trial with a device. And I do

think the HTN-OFF which is the cleanest way to study this, off-medication, does show a small treatment effect.

However, to answer this specific question, the first part of it is that it's certainly not for people who resist in hypertension, who failed medications, because that wasn't the inclusion criteria of the off study. So I think how you would word this, we have to think about it, but I think if it was approved, the indication would have to suggest that it's mild to moderate hypertension and that it offers the same benefit as possibly one pharmacologic therapy, appropriately escalated.

Dr. Lange: Okay, Dr. Lewis.

Dr. Lewis: I have basically the same thing I said yesterday with a little bit added to it, but I agree totally with Dr. Somberg that they didn't study these people. They didn't document intolerance. They're not necessarily resistant. So, the magnitude, again, as I said, of the effect, were you to label it, and I don't think we've gone into the benefit-risk thing, would have to be somehow incorporated into the indication.

I also wonder why this language is in here. Because honestly, if it was an effective treatment, I could see many people who have never been on medications and don't want to become a 20-year-old on a medication, unlike all the other 20-year-olds, and want to have a procedure done that makes them not become one of those people. So, I can see treating even very mild people with something like this intervention, given its safety profile, not necessarily this one, but a intervention. So I don't know, you know, like is there some worry that the FDA or the sponsor had that they only wanted to treat like really desperate people with this? I mean, it just seems strange, but in any case, there's no evidence to support it.

Dr. Lange: Okay, thank you, Dr. Lewis. What I'm going to ask you to do, Dr. Lewis, I've got five other people, six others are going to make comments, but I'd be thinking about how you would reword this, what we recommended to the FDA.

So I've got Dr. Allen, Bates, Nachman, Yeh, William Vaughn, and Hirtsfeld. So Dr. Allen, and I'll ask you guys to summarize in about a minute or two.

Dr. Allen: I'm just going to echo what I said yesterday. There is a huge disconnect between this current IFU and what was studied. They're just simply this IFU is not what was studied. You know, what was studied was how does renal denervation work in a patient who has, you know, mild or moderate blood pressure and its effect. And that effect is quite small at three months and goes away. It seems to go away at six months with medications.

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

Dr. Bates: Yeah. I would quickly offer some wordsmithing suggestions, assuming this is a rough draft.

Number one, I think we have to define uncontrolled hypertension as 140 or 135 or 130. And I'm surprised thinking about this, these were 50-year-old people with diastolic blood pressure that were studied. I don't think we have any data on systolic hypertension in the elderly. Number two, the last two phrases I would delete and say despite maximally tolerated anti-hypertension medications.

Dr. Lange: So, you would get rid of the phrase despite the use of anti-hypertensive medications? Is that what—

Dr. Bates: Despite the use, I don't like and poorly tolerated, I don't know what that means. But if they, if you put them on me, it's like coronary disease, you put them on the maximally tolerated medication profile, they can accept. And if then, they still have whatever you think is

uncontrolled chest pain or uncontrolled hypertension, then an interventional procedure is reasonable.

Dr. Lange: Okay. Thank you, Eric. Dr. Nachman?

Dr. Nachman: Yeah, thank you. I just want to, I don't want to be contrarian to everything that was said, because I do agree with it, but I do want to point out that unlike yesterday the subgroup analysis did show still a response which may have been more marked in the patients with the highest tertile of blood pressure which is reassuring to me and I think with all the noise that we talked about, there is a signal there that could be a patient population that would benefit the most from this procedure. Although, the data's not sufficient to prove that, but I think that's a path forward that in my opinion, is well worth reviewing.

Dr. Lange: Okay. So, in other words, what you're saying is you don't feel like the data are there to make that an indication now, but some additional work that would be something that they would need to strive for with a proper study. Is that fair?

Dr. Nachman: Yes. Perfect. Thank you.

Dr. Lange: Okay, Dr. Yeh.

Dr. Yeh: I had the similar thought to Dr. Lewis when I, you know, I first read this and I think I made that comment yesterday, which was, it almost appeared more stringent that they needed to be based on what they studied and like thinking about how both sponsors have put together very similar indications for use. I think with the single exception of this is the word ‘is’ here. And yesterday, what was like a ‘maybe’, I think they're really identical, and I suspect it's an acknowledgement of what we've been discussing, which are nobody thinks that this treatment should be a replacement for medications. And so even though it's not the population studied, I suspect it's an acknowledgement that medications ought to be first-line treatment.

And so maybe the responsible use of a technology like this were, it to be approved would be delimited in those situations where the patients somehow can't take first-line treatment for anti-hypertensive medications, which I think everybody in this panel agrees should be. So, it's one of those, I think, acquiescence to the fact that data are not maybe as strong or compelling as they would be for, you know, as one might have hoped for, but that it still may be an effective therapy for those patients, even though it's not the patient population that was studied.

So, it's a difficult balance there because you could see that they could have an indication for use that was patients with mild to moderate hypertension. And I was thinking as an alternative or an adjunctive treatment for patients with mild to moderate hypertension, that's actually much broader, more sweeping than what they've proposed here. Maybe more faithful to their inclusion criteria, but also maybe, you know, opens the door for I think what people are concerned about here, which is more broad use. So, I understand the rationale for it after taking two days to understand the rationale for it. And maybe it's a response to be more restrictive for use.

Dr. Lange: Okay. Thank you William Vaughn, Dr. Hirshfeld and Dr. Lewis. And then I'll try to summarize.

Dr. Vaugh: Just the thought as a consumer taxpayer representative that Medtronic people we've seen today are brilliant and all, but I think we've all read that some of their advertising and marketing people have paid millions of dollars in fines in recent years for encouraging doctors to overuse a procedure, and if we're not careful, in a couple years we'll have you know, if your blood pressure's 121 come see us and get operated on. And how do we prevent that on the consumer community?

Dr. Lange: Okay. Good point. Good point. Mr. Vaughn, Dr. Hirshfeld and Dr. Lewis.

Dr. Hirshfeld: Two quick comments. It seems to me that these, the two products we reviewed yesterday and today are similar enough in terms of their identified efficacy that they really should have the same IFU, I think that would be inconsistent to have different wordings for two different products that are really intended to do the same thing and have similar levels of evidence supporting their efficacy.

Second thing, I think in response to the comment just made, I think it's worth being more precise about what constitutes uncontrolled hypertension in the indications that there are societal definitions of that, and we can adopt that as well. So, I think in terms of making it a rigorous call, that would be one way to do that.

Dr. Lange: Thank you. Okay, Dr. Lewis, you have the first word and now the last word.

Dr. Lewis: Yeah. Well, you asked me to come up with it, so—

Dr. Lange: Great.

Dr. Lewis: —I understand, but I do have a couple words too. I think it's, you could put that it's indicated for the reduction of blood pressure and patients with hypertension, and I would define hypertension and then put in there and that part, I'm not going to say the exact words, but put in with as long as the, you know, something about the patient and the doctor are aware of or something or even just put in the magnitude of the effect.

I agree with Dr. Nachman, by the way. I had notes when I reviewed the briefing document that there was suggestions that it worked better in higher blood pressure patients and the FDA and the company could consider that when designing, if they do design another trial. I disagree that we should make the decision that medicines should come first, because I think the patient per patient performance, whatever it's called, those studies that they did talking to patients both yesterday and today, support that patients really, actually many of them would want a procedure to either not take a med or take one less. And lastly, I don't think the efficacy results

are comparable between yesterday and today. I don't actually think we should be talking about yesterday. And I don't think that we should assume that because yesterday's device efficacy results were good, that means that this device is also benefits from their efficacy results. It's—

Dr. Zuckerman: Okay. Let me pause you there. Dr. Lewis, excellent comments and certainly the FDA has gotten a good general sense of where an appropriate indication might lie, Dr. Lange. But now, and especially going into the future questions, it's extremely important that we concentrate on today's data, today's PMA and assess a benefit-risk and not think about any other devices. This is a PMA that must stand on its own data. Thank you, Dr. Lange.

Dr. Lewis: I agree completely.

Dr. Lange: You've heard all the comments. The feeling is that they really didn't test it in people that have resistant hypertension, despite medications that it may have a role in mild to moderate hypertension and either lowering blood pressure or reducing medication use. And that effect is modest and should be so stated. Any other direction or comments, Dr. Zuckerman, the FDA needs?

Dr. Zuckerman: No.

Dr. Lange: Okay. Thank you for that. Again, a really good discussion. Number eight.

Question Eight

Mr. Mistry: So, question number eight is regarding labeling. Please discuss whether labeling should contain recommendations for post RDN renal artery imaging, and if recommended, please discuss labeling language should be included. Also, please identify any other labeling recommendations.

Dr. Lange: Dr. Lockhart, do you want to weigh in on this?

Dr. Lockhart: This is a broader question than just the safety of the follow-up imaging. This is whether or not it should even have follow-up imaging.

Dr. Zuckerman: That's correct. Dr. Lockhart.

Dr. Lockhart: Yeah. So whether it should even have, I'll probably leave to the whole group, but if you were to do imaging, it would probably just be with ultrasound rather than CTA based on what we saw from their data.

Dr. Lange: So, Dr. Lockhart, as part of the group, I'm going to give you the first vote on this, and then I'll take a vote. Do you, believe, obviously your an imaging expert believe that there ought to be post renal artery imaging?

Dr. Lockhart: I do.

Dr. Lange: On all patients. I'm going to ask the panel. Show of hands those of you that believe the same thing, there ought to be in routinely mandated in all patients. One, two, three. Keep your hands up. One, two, three, four, five, six, seven, eight. Those of you who do not believe should be mandated. One, two, three, four, five. So the panel is, and six, the panel is split, but mostly saying that it wouldn't be indicated. It is not necessary unless indicated as a decline in renal function or some other reason. And if it was to be done, the recommendation would be to start with duplex, ultrasound or ultra-sonography and use that as a screening tool. It's non-magnetic. There's no radiation involved. And then if there's an abnormality to follow that up with MRI or CT.

With regard to labeling recommendations, we mentioned that there are a number of patients in whom this hasn't been yet tested or evaluated. And those would include diabetics as William Vaughn suggested people over the age of 80 in this particular study. Yep. We're not going to mention you by name in the labeling William, we can't do that. Okay. But diabetics, congestive heart failure cardiovascular disease, cerebral vascular disease these unfortunately are individuals that haven't been studied and so it'd be hard to, the labeling should mention is that at this particular time, there's no data to support its use in those patient populations.

Dr. Nachman: Or GFR less than 60.

Dr. Lange: Thank you, Patrick. I was just about to say that. So Dr. Hirshfeld and Dr. Yeh.

Dr. Hirshfeld: My hand is no longer up. My apologies.

Dr. Lange: Alright, Dr. Yeh?

Dr. Yeh: I was just going to say, it seems like there's an intermediate step, which is if we need more information about the safety with imaging, there's post-market requirements that we could discuss. And this is already jumping to the labeling, which obviously has more sustained impacts. And I just think that asymptomatic imaging is potentially fraught with all sorts of issues that people know about, and downstream consequences and cascade effects. I don't think you want to necessarily put that in a labeling for device without evidence that it's going to be beneficial.

Dr. Lange: So, noted. Thank you Dr. Yeh, for mentioning that. Dr. Bates, myself, interventionalists, who end up chasing things we wish we weren't. Dr Damluji.

Dr. Damluji: Yeah. Just to echo this, you know, routine use, that means every person who's going to get this will get an ultrasound and that will lead to, you know, issues down the line. Initially, what I was thinking of how you utilize imaging, probably if there are symptoms is probably, if there is deterioration or kidney function on follow-up, probably imaging would be indicated. But routine use, I don't think it's a good idea.

Dr. Lange: Okay. Now, based on those comments from you, I'm going to take one more vote. I'm not asking you to change your mind, I want to present this to the FDA. How many of you believe that labeling not a post-market study, not to be a post-market study, but it ought to be in the labeling, is that you would like to see imaging recommended in everybody? Show of hands. One, two. Okay.

Those who would not like to see it in the labeling, one, two, three, four, five, six, seven, eight, nine, ten. I didn't mean to change anybody's mind, but the conversation did. That's why we have these conversations, so they would not leave it as a part of the labeling. William Vaughn, I'll let you make a comment and then I'm going to go on question nine.

Dr. Vaughn: Just on, on this point, the German people had talked in Germany, they have it at centers of excellence, if you will. And if that's one of the recommendations that this not be done at every little community hospital or surgery center, that might help. And you wouldn't need to do follow-up scans to see how much injury was being done.

Dr. Lange: Your point's well taken. Thank you. Very well taken. Thank you. Question number nine.

Question Nine

Mr. Mistry: Question number nine is regarding benefit risk. Given the totality of the evidence presented regarding the safety and effectiveness of the device, please comment on the benefit risk profile of this device.

Dr. Lange: Obviously, we're going to vote on that shortly, but Dr. Lewis, you want to lead us off? Then Dr. Starling's going to follow.

Dr. Lewis: Well, I'm sure it's not going to surprise anybody when I say that I, unfortunately, do not think that the evidence presented today in these two studies demonstrate enough benefit despite the minimal risk in terms of the safety data to recommend that patients go through it.

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

Dr. Starling: Editorial comment, this discussion reminds me a lot of the evolution of AFIB ablation. So, I think benefit in the context of one we haven't defined who's going to be a responder, but medicine compliance is a reality that we've seen, and patients have aversion to

taking medication. So I think in that context, there, there will be patients that will benefit from this.

Dr. Lange: I'm going to counter that and there may be a small number but most patients on this don't get off don't get off of medications. They may be reduced somewhat, but there are very few individuals that, with hypertension, they get this, that are off-medication. So, I just counter that, Randy. But I'm not trying to argue or dissuade you, just a counter opinion. Part of this discussion is to be able to have those frank discussions.

Dr. Starling: I would just counter that with compliance is the issue. We don't really know who's taking medication. Thank you.

Dr. Lange: Point well taken, thank you. Dr. Detnarowski.

Dr. Centarowski: So, I think my comment was premature earlier, and it probably belongs here. So for the record, I think the risk benefit discussion has to incorporate more than just the safety that we've seen, the efficacy that we've seen, but has to incorporate the patient preference for an alternative treatment. It's got to incorporate the requirements and/or the differences for requirements of CDRH versus CDER. It's gotta incorporate our acknowledgement that we've got gaps in our ability to effectively treat and control hypertension. And, I think that's it. I'll stop. Thanks.

Dr. Lange: Okay. Thank you, Dr. Cetnarowski. Dr. Corriere.

Dr. Zuckerman: Could I just add to what Dr. Cetnarowski just stated, because this would be of most help to the FDA? Number one, this is a breakthrough device designation and also specifically CDRH has a benefit-risk guidance document. And the bottom line is, as Dr. Cetnarowski stated at CDRH, in addition to the data on the table, the context of use and some of the broader public health implications need to be taken into account when a breakthrough device is being considered. So, I'm going to ask all the panel members really to put on their clinical hats

and practical hats as Dr. Cetnarowski was suggesting when making their subsequent comments. Thank you.

Dr. Lange: Thank you. Dr. Zuckerman. Dr. Corriere?

Dr. Corriere: No, I was going to just say the previous couple folks had me in a little tension about how stringent to be given that it's a breakthrough device. But Dr. Zuckerman kind of stole my thunder about making that point about how stringent we should be about effects in the context of a breakthrough device application.

Dr. Lange: Okay. Dr. Yeh? Thank you. Dr. Corriere. Dr. Yeh?

Dr. Yeh: Yeah. I think. You know, separate from the, the regulatory designation. I mean the regulatory designation is a result of the public health need. And I think when we think about that and the fact that people won't take medications, maybe my bar for effective demonstration of effectiveness goes down a little bit when I think about the additional new therapeutic option that will be offered to some patients who can't otherwise achieve control.

Now, when I think about effectiveness, I think it's impossible not to look at the OFF-MED drug and see at least some signal of effectiveness there. I think it is effective and the magnitude we can debate, but there is a physiologic effect there. And it may be, as Dr. Nachman pointed out, greater among those patients who start with a higher blood pressure. But what is also clear is that there's variability of effect. And I think that we've really anchored on the mean treatment effect in this discussion today. But we saw figures showing that greater than 15% reduction of blood pressure was nearly twice the rate of achieving that among patients who got the procedure than not in, I forget if maybe it was the OFF-study. So ,there are these, you know, this just like we saw yesterday. I mean there's treatment effect heterogeneity here, there's variability. So there are some patients who benefit more and I'd love to be able to, you know, for the community to figure out who those patients are. But I don't want to anchor solely on the

mean treatment effect because then I think that underestimates the potential benefit to a large proportion of patients.

Dr. Lange: Okay. Dr. Yeh, Thank you Dr. Lockhart.

Dr. Lockhart: So, there is evidence of benefit, but it's low and it's in one of two studies. There's evidence of safety, but there's also uncertainty of it. So I think we're left with a lot of uncertainty.

Dr. Lange: Thank you. Dr. Lewis.

Dr. Lewis: I think we have to be cautious not to confound the desperateness of the unmet need with a willingness to throw anything at that unmet need. It's not going to help people's blood pressure or their cardiovascular outcomes to have a procedure that is potentially either not effective or minimally effective. So that's—

Dr. Lange: And Dr. Lewis, I would say I'd go even further. I'd say not just a procedure, but a particular device for a procedure because we're not talking about renal artery denervation as a procedure. We're talking about this particular device and studied, and what's the risk-benefit profile of this device, not of renal denervation.

Dr. Lewis: And I will point out, remember, this device has a history. It had to be modified because the initial device, even though it also would've, you know, potentially benefited people, whatever, had negative studies. So, whatever the breakthrough device designation is, it says when you read the statements in the briefing document, that it doesn't change the standard of safety and efficacy. I mean, that's what it says, and they read that this morning as well. So, I think we, you know, just can't confound the, I mean, we don't help people if we don't help them.

Dr. Lange: Dr. Somberg, Dr. Damluji, then Dr. Saville.

Dr. Somberg: Well, I just wanted to further emphasize the point Dr. Yeh made that there is a population that we saw that benefited. And when the sponsor presented the box graph and also

the waterfall I was impressed with the number of people who did show a pretty dramatic response.

I also want to state, and I'm not speaking, you know, I'm not an expert for the sponsor, et cetera, but I think the reason the device was modified and my understanding being on the panel back five years ago and being involved in a number of symposia in this area was that, and writing an article on the subject, was that I'm looking at some of the early studies that actual denervation was variable. The number of notch lesions, the number of other signs that one saw with denervation with the first device was variable depending upon the expertise of the operator. We heard today that it's not operator dependent. There's no training effect. And I think the sponsors deserve note that they solved that problem. So, I think that's why that was undertaken a change in the device.

Dr. Lange: Thank you, Dr. Somberg. Dr. Damluji, and then Dr. Saville.

Dr. Damluji: Yes, sir. Thank you so much. I agree also. I initially raised my hand and then Dr. Yeh expressed it very well. But just to reiterate, the device itself is quite safe. I mean, there's no major adverse cardiovascular outcomes after the procedure. And if you look at the data in aggregates, there may be a mild benefit on average, and in select patients, there is a large benefit if you look at the box and whisker plot. So, you know, not approving, you know, a breakthrough device based on a mild benefit may withhold treatment from people who may benefit from ablation therapy. That's my opinion.

Dr. Lange: Okay. Dr. Seville, and then I'm going to sum up.

Dr. Saville: Yeah, so just from a statistician's perspective, I think there's clearly a small benefit. I think the off study is clean and it shows a small likely a clinically meaningful benefit. I think the long term benefit is unclear, but again, the study wasn't designed to show that. I think the real world benefit is in context of using meds, is unclear, that's shown with just how messy

the results were of the on study and the fact that it achieved the primary endpoint there. I think, yes, the study, I mean the procedure looks safe again from a statistician's perspective, but I think with any procedure, the risk is not zero. So, I recognize that there's always going to be some risks. And in the context of a breakthrough device with an unmet need for me as a statistician, the scale for benefit and risk looks pretty even to me it is difficult for me to say that one is heavier than the other.

Dr. Lange: Okay. So we're going to adjudicate, I won't have to summarize this. We're about to take a vote on it. But, to summarize again, small benefit, durability uncertain, real world benefit uncertain. I, I'm always drawn to, I'm always amused at the argument. There's a small group that benefited a lot from it. There's a small group that was harmed a lot from it. Their blood pressure went up 20 or 30 millimeters.

So, to say that's why we look at a population at large. By the way, that population of blood pressure over 157 is 52 patients by the way. So, I'm always amused when we pick out that part that supports, if I wanted to say it was harmful, I'd pick out the group of individuals in whom it raised their blood pressure, 20 or 30 millimeters. And if you want to say it's helpful, you pick out the group that it really benefitted. I find that amusing. So let's go to number 10. Dr Yeh, go ahead.

Dr. Yeh: I'm sorry. Can I just rebut that comment Dr. Lange? I think that, and I'm not sure that's really fair and that's what we're trying to express here, Dr. Damluji, Dr. Somberg and I in our opinions, yes, you can find in a single treatment arm, individuals who looked like their blood pressure went up and went down. However, when you look at the number of patients who achieved a blood pressure reduction of greater than 15, it's a higher proportion, which is a substantial benefit. It's a higher proportion in one arm in the other. So that's a randomized treatment effect that is different for that particular endpoint. And so that's the remark. Not that of

course, there are in the waterfall plot, there will people who go up and people going down. But the randomized size of the randomized treatment effect in different subgroups differs. That's what we're referring to. Thank you.

Dr. Lange: That comment is welcome and appreciated and I appreciate the clarification for the record and for all, everybody that's listening. Thanks Rob. Good. Alright. Let's go to number ten.

Question Ten

Mr. Mistry: So, question number ten is regarding the postmarket study. Medtronic has proposed a postmarket registry that will continue to follow subjects in HTN-OFF and HTN-ON through five years. And the AFFIRM continued access study cohort with enrollment of up to 1,200 subjects. The study will collect ambulatory and office blood pressure procedural results, medication burden TTR and proportion of subjects require repeat RDN Medtronic plans, pre-specified analyses for subjects with isolated systolic hypertension, chronic kidney disease, and diabetes mellitus type two.

Please comment on the sample size and proposed endpoints. Please discuss whether sample sizes for additional subgroups or diverse patient cohort subgroups should be pre-specified and evaluated in the post-approval study. Please discuss the strengths and limitations of a single arm study design for the PAS and please discuss the adequacy of the 12-month imaging performed by either duplex, ultrasound, CTA or MRA in the post-approval study to confirm long-term denervation safety.

Dr. Lange: Okay, John, I'm going to come to you in just a second. Before I do that, Rob, I want to call on you first. I know you've given some thought to this. I wanted to call on our two statisticians. John, I'm going to come to you. So Rob, let's talk about what a PAS would look like. Let's give the FDA some recommendations. Some guidance.

Dr. Yeh: That's me. Yeah. The, you know, I think that when it's hard not to think about the study, I know there's been advice, not to think about this, the postmarket, but just thinking about postmarket requirements in general for this space, for durability, you know, they presented what is effectively a large post-market study that they've been doing in Europe. And we've seen, I think we didn't get a full chance to fully discuss some of those limitations as the group, but it was pretty clear that there were significant limitations of those data when we looked at them for assessing long-term durability, mostly because of just the potential missing data, you know, as you went on for long-term follow-up.

So, you know, this is a challenging one. I think there's, on the table, there's single arm studies that look at, you know, baseline blood pressure and then look down the road to see what continued blood pressure measurements look like. And those, of course, have the difficulty of not having a comparison group. But I think we also recognize in a potent market setting with this number of patients, it's going to be really hard to do a randomized, really not feasible to do a randomized sort of study. So, I think one can be creative about thinking about control groups, registries that include control groups. But I think if the goals are to look at whether or not this is as effective in, say, black Americans as it is in other populations, well there, the control groups are sort of built in. You can do a single arm study of patients who, you know, that includes sufficient numbers of black Americans like they propose and other, you know, individuals to see if those effects sizes. The delta blood pressure is the same over time. I think that's probably the most likely scenario, but I'd be interested in thinking about potential creative control groups to include.

Dr. Lange: Okay, great. Let's see. Dr. Wittes. And then Ben, and I've got Dr. Somberg, Dr. Bates, Dr. Bates. Sorry, Eric.

Dr. Wittes: All right, so this is Janet, and I'm going to echo what Ben said yesterday. It's important. One arm study is always difficult to know what you can learn from it. So, it's very important if there's going to be one that it be, that the hypothesis be set out upfront that the sample size being relevant to the hypothesis. And I'm not sure I hear that you could do African Americans versus non-African Americans and see whether there's a difference in control, but there's going to be all kinds of other variables that you have to correct for in doing that. So, yes, this could be useful, but only if it's designed upfront with a real care about why are you collecting what data for what purpose.

Dr. Lange: Okay, Ben?

Dr. Saville: Dr. Wittes stole my thunder. I was going to say the same thing. So, I do like these endpoints. I like the fact they're going to collect both ambulatory and the office blood pressure. I think again, the important thing with these studies is to size the study to answer whatever the question is. And so, first you gotta decide on what the question is. What do we want to accomplish? What's the objective of this postmarket study? Once we know that, then we can talk about the size. But it, it is difficult to just say, you know, I'm going to do a thousand subjects and here's the thing I'm going to collect and I'll show you what I have. Yeah, if you do that, basically that's the end result, you're going to end with a bunch of more questions and not really any answers. So, I would start with the objectives and what questions you want answered and work backwards from there.

In terms of the pre-specified subgroups, I agree with, with Janet, this idea that maybe you can do some, some comparisons between say, black Americans and the non-blacks. That yes, you can do those, they're going to have to be carefully thought through ahead of time and with very clear hypotheses and analyses specified in terms of how you want to do that, because those may or may not show anything depending on how the study is set up.

Dr. Lange: Okay, Dr. Somberg.

Dr. Somberg: I think the most important thing is to try to develop a composite endpoint to evaluate. We see here all the data, it's confusing because of the introduction of medications. It's very similar to, let's say, benefit of an anti-platelet, drug with MACE, but an increased bleeding and you, or with NOAC or something like that. So I think what you have to do is develop some sort of composite endpoint where that's pre-established so you can have an understanding when you have two variables pulling in different directions. Also, if possible, I would recommend the registry where those people are proposed and those who get it versus those who don't.

It's not a perfect control group but it gives you some information on the course of hypertension over time in those people who don't get the therapy. And finally, I wanted to say about African Americans. I was surprised today by seeing Dr. Mauri show that there was, in the expanded group, more benefit, because over the history of denervation studies that's always been one subpopulation where there's been a reduced signal compared to others. And I think there's a pathophysiologic basis of that. So, I think, and in that area that either a group of companies get together or an NIH-sponsored program would be recommended to do a controlled study in this area because that's the only way you'll get a definitive answer.

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

Dr. Bates: So, number one, I'm very concerned about overuse if one or two catheters gets out into the market. Number two, I don't think I trust industry with their financial conflict of interest to run a registry that'll be useful to answer all the questions you want. So, I would suggest we think about the left atrial appendage occlusion registry and the TAVR registry that the ACC have in concert with the FDA, where it can be iterative, it can have outside experts.

You can ask questions and figure out what extra information you want to gather and you can control the release of this until you have better proof that it's actually being used. It worked

very well with TAVR. And that would be the, the precedent I would suggest might be the best way to gather clinical information if these catheters become available. And I'd make industry pay for it. If they really want the catheters out there, let them get somebody independent to test the catheters.

Dr. Lange: Thank you very much, Eric. Dr. Allen.

Dr. Allen: I think about this discussion. You know, I think doing more—

Dr. Zuckerman: Before, Dr. Allen continues, I just want to respond briefly to Dr. Bates. Dr. Bates, from a public health perspective and FDA is first and foremost a public health agency. We're always concerned about diffusion of technology into the US real world. But we don't have the regulatory authority to say that a registry must be conducted by a professional society versus the industry.

Rather, what we need here are the ideas that need to be incorporated such that FDA and a sponsor can carefully look at a diffusion of an important new technology so that it is not abused in the real world US population. Thank you.

Dr. Lange: Dr. Allen.

Dr. Allen: So, as I think about that, you know, some type of a postmarket study or another study to get around randomized trials, I've not heard anybody think about it. Maybe it's thinking too much out of the box. But why not run a trial with patients that serve as their own control? And the way you would do that would be to enroll a patient and he has to meet goal-directed hypertension management, and he gets on drugs. You make sure he is taking his drugs through urine testing. And if he's resistant, you know he is resistant, but if he has good control, he could still then get the therapy and you'll learn then whether or not you can now come off some of the meds that he was on. So, you get somebody that starts out with a blood pressure of 150, they get down to 120 and they're on three meds.

Now they get their device and you can follow them and see what happens over time. Similarly, if they don't meet their goal and you know, they're on goal-directed therapy, by definition, they're resistant. They still can get their device and you can follow those patients. This also allows you then to look at subgroups using patients as their own control.

There won't be all the noise about, you know, this group has less medicines, or this group is black. You'll know that black patients that got it, who were controlled with medications, they drop their medication burden by, you know, one and a half pills. That may be a way that you could answer some questions without actually randomizing patients to not get the therapy.

Dr. Lange: Thank you. Dr. Saville.

Dr. Saville: I like that idea, Dr. Allen. I think one thing you have to think about is behaviors can change even within a person. So, even though they can serve as their own controls, when you're following people over time their behavior, things are changing in their lives, and so it's not as clean-cut as maybe it's out made out to be.

I wanted to just state maybe two quick things. Number one, I think a single arm study is primarily helpful for looking at safety, long-term safety and these rare safety events. And also, maybe for descriptive summaries about the effectiveness, but they're not really great for hypotheses. If you really want to answer questions or hypotheses regarding efficacy that weren't addressed in the randomized studies, then these, you know, a registry type study, postmarket study where you have both those who have the intervention and those who don't have the intervention and you're following both them across time.

And you're able to do some, some perhaps some complex analyses where you're doing propensity score matching. You're trying to find your own control. So it's more an observational study, but that may be your best chance to really look at long-term or more real-world benefit

because we're not seeing, it's hard to really figure out how this works in the real world with the data we have right now in these randomized trials.

Dr. Lange: So, you're not talking about a single arm, you're talking about an observational study that includes people that have the intervention of people that haven't, is that what you're saying, Ben?

Dr. Saville: Exactly. That's what I'm saying, yes. Okay. And then you have to find the control that kind of matches your intervention. Similar, you know, patient characteristics, baseline things, and then baseline descriptive summaries and follow them across time and see what happens.

Dr. Lange: Okay. Dr. Nachman and Dr. Yeh, then I'll close it out.

Dr. Nachman: So, I'm not an interventionalist, but it seems to me from the description of the patient population of people who were considered to participate in the trials, there were a substantial number of patients who were excluded because of anatomic restrictions. They would've been good candidate for denervation, but their anatomy precluded the use of the renal denervation. And my question is, why isn't that a good control group? The patient would have met blood pressure criteria, would have met denervation candidacy, but couldn't get it for an anatomic reason. You can follow them on medication only. Is that, could that be used as an OFF-MED? Sorry. Pure medical treatment of renal denervation control group.

Dr. Lange: In fact, they'll never become the crossover group, will they? Pat? So, good point. Very good suggestion. We'll include that. Dr. Yeh.

Dr. Yeh: Just a quick response to Dr. Nachman, actually, my epidemiology colleagues would tell me that that violates what's called the positivity assumption, which is those patients, by definition, were not eligible for renal denervation, so probably shouldn't serve as a counterfactual control group. But, actually my main question is to Dr. Zuckerman. To what

extent as a breakthrough device are you, is FDA working in concert with CMS to think about potential postmarket requirements? I know this is legislation or rulemaking in flux. So can, is there an update that you can have for us and should, I know there's a lot of concern about use and cover, you know, what sort of evidence might need be needed in LAO, et cetera. Those types of things came out. I think CMS regulations. So, to what extent are is FDA and CMS collaborating on these discussions?

Dr. Zuckerman: Okay, so let's pause a moment, Dr. Yeh. Certainly, there's been effort over the last few years to better connect the dots between FDA and payers, including CMS.

But for the purposes of this panel meeting today, what we have to consider is what would be the most use to the FDA is working within the framework of the FDA regulations, which by virtue of a breakthrough device we want to establish a reasonable assurance of safety and effectiveness. And if there is a handle, questions of uncertainty or important questions about diffusion of technology for either acute results or more long-term results in a required FDA post-approval study. Now, any sponsor may simultaneously talk with payers and include CMS because those are different entities. And in a PAS study, they may have different goals. In fact, that is always the case. And post an FDA approval decision, we can be flexible to incorporate other objectives and goals. But, I must emphasize for the purpose of this panel meeting, we really want to center on the FDA regulations and how we can best accomplish what's asked in points A through D here. Does that help you?

Dr. Lange: I'm going to summarize what I've heard. To date, we've had about eight or nine people respond. One is pre-specify the subgroups, and that pre-specification will inform the sample size, the study size. And again, I would say, and I would certainly include their knowledge, pre-specified subgroups of patients that have not previously been enrolled, if we're going to extend the therapy to them. Again, people we mentioned, type one diabetics,

uncontrolled diabetes, congestive heart failure reduce GFR, cardiovascular disease. There's the thought there should be a composite endpoint because this therapy doesn't just do one thing. It doesn't just reduce blood pressure, but it may change the number or types of medications.

It may improve patient preference or patient compliance. It may prevent some hard endpoints. Then, it may be needed to be provided people that have poorly-controlled hypertension. So, a composite endpoint. There is a desire to have some sort of a control group, whether that be a registry, as Dr. Yeh mentioned. I like the idea of individuals that their anatomy isn't quite suitable, and I just make sure I send that manuscript not to an epidemiologist, he'll nix it, but those of us that take care of patients would say that's okay. And, so don't send it to Rob, send it to me when you get ready for that manuscript.

Again, using the ambulatory blood pressure in addition to the office blood pressure. And then with regard to imaging, if imaging is going to be required in the PMA or post-marketing study again, the consensus is that DUS would be sufficient. 12-month was an adequate time. And then there would be follow-up imaging if the DUS suggests that in fact there is a significant stenosis. And I think I've got most of the comments. Is there anybody that I dissed you accidentally? Dr. Zuckerman, does that provide enough guidance regarding how the group feels about a post-marketing study?

Dr. Zuckerman: Yes. This has been a very helpful discussion, in summary, Dr. Lange.

Vote

Dr. Lange: Alright. At this point then we're ready to vote on the panel's recommendation of the FDA for the Medtronic Symplicity Spyral rendered renal denervation system. The panel is expected to respond to three questions relating to safety, effectiveness, and benefit versus risk. Mr. Collier will now read two definitions to assist in the voting, and I'll remind the panel members and those that are watching or observing, is that after the definitions are read and the

voting questions are read, the voting members will leave the public forum. A vote will be taken, it will be tallied. We'll return in about 10 minutes to share the results of that vote, at which time the panel members will also discuss how they voted. We'll hear from our consumer patient industry reps and the FDA will have the final word. So, Mr. Collier, would you please read the definitions?

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 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, forced, 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 Symplicity Spyral, multi-electrode renal denervation catheter and the Symplicity G3 RF generator are indicated for the reduction of blood pressure in patients with uncontrolled

hypertension. Despite the use of anti-hypertensive medications or in patients in whom blood pressure lowering therapy is poorly tolerated.

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.

Voting question number one reads as follows. Is there reasonable assurance that the Medtronic Symplicity Spyral 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 number two reads as follows. Is there reasonable assurance that the Medtronic Symplicity Spyral 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 number three reads its follows, do the benefits of the Medtronic Symplicitie Spyral 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.

Dr. Lange: Oh, at this time. I'm going to add—

Dr. Collier: At this time. Please give us a moment as we tally and verify the official votes. Thank you.

Dr. Lange: Thank you. At this time, I'm going to ask the panel members to go backstage and at which time our audio visual will share in the chat, the place to go to register your vote. So if you'll go backstage at this time, and if the public will wait, we'll return in about 10 minutes.

Mr. Veizis: Okay, good. We're clear. Everyone, all voting panelists should have received a link. So, Janet, did you receive a link? Dr. Allen, did you receive a link?

Dr. Allen: Yes, I got it on chat, and I voted if you could confirm you got it.

Mr. Veizis: Good. Okay. Yeah, very good.

Dr. Wittes: Yeah, I got it on chat too and voted.

Mr. Veizis: Okay. Thank you. I'm going to go backstage now. Thank you.

Dr. Lange: Welcome everyone. I want to thank you for awaiting while we allowed us to vote and tally the votes. The votes have been received and Mr. Collier will now read the votes into record.

Vote Results

Mr. Collier: Thank you Dr. Lange. For question one, the panel voted 13 yes, zero no, and zero abstain that the data shows reasonable assurance that the Medtronic Symplicity Spyral Renal Denervation System is safe for use in patients who meet the criteria specified in the proposed indication.

For question number two, the panel voted seven yes, six no, and zero abstain that there is reasonable assurance that the Medtronic Symplicity Spyral Renal Denervation System is effective for use in the patients who meet the criteria specified in the proposed indication.

Last question number three. The panel voted six yes, seven no, and one abstain that the benefits of the Medtronic Symplicity Spyral Renal Denervation System outweigh the risk for use in the patients who meet the criteria specified in the proposed indication. The three voting questions are now complete and I'll now turn it back over to Dr. Lange. Thank you.

Dr. Lange: If you can put the votes back up for just a second and we will walk through votes. First one please, I just want to make sure for the record, we, number one is 13 Yes and zero no, zero abstain. For question number two, reasonable assurance it's effective. There are seven yes, six no, and zero abstain. And for the third question, the voting panel members, do the benefits outweigh the risk for use in patients who meet the criteria. There is six yes, six no, and one abstain. At this point, that vote is a tie. The chair votes only in the instance of a tie. In that case,

my vote would be no. That would make the final tally six, yes, seven, no and one abstain. At this particular time, two things I want us to remind everybody listening is, the panel doesn't vote on whether a device is accepted or not a vote. The panel votes on the questions that were submitted to the FDA and the final decision rests with the FDA at this particular time now, I'll ask the panel members to discuss their votes, and if you answered no to any question, please state whether the changes to labeling restrictions on use or other controls would make a difference in your answer. Again, I'm going to ask you to state your name and how you voted for each question for the record. And I'll start with Dr. Allen.

Summary of Panel Recommendations

Dr. Allen: This is Keith Allen. I voted yes for safety, no for efficacy, and no for risk-benefit. I think while this is a very safe procedure, the efficacy was mild at best and only was that three months, once medicines were re-engineered or reintroduced that went away at six months. And the ON-MED trial was a negative trial. While I think sometimes we like to think that the threshold for efficacy should be lowered when the device is very safe, we still have to think of the overall healthcare burden of particularly devices that are going to be used in patients and whether it's appropriate or not.

Dr. Lange: Thank you, Dr. Allen. Dr. Starling.

Dr. Starling: For safety, I voted yes. For the second question, I also voted yes. And for question number three, regarding the benefits outweighing the risk. I voted yes, and my voting was influenced by two things. One, the bulk of the data presented, I was comfortable with my voting. And number two, the unmet need and the fact that hypertension is not effectively treated with current tools and more tools are needed to treat blood pressure.

Dr. Lange: Thank you, Dr. Starling. Dr. Yeh.

Dr. Yeh: Thanks. I voted yes on safety. I voted yes also on effectiveness. I voted yes on risk-benefit balance. My effectiveness and risk-benefit balance were principally rooted in, again, very similar to Dr. Starling, the totality, the evidence, and especially the OFF-MED trial, which I think clearly demonstrates at least some effectiveness. I think we can quibble about the magnitude. I think there was variation in the effectiveness. I think there will be patients who would benefit. I do think it will behoove the community to identify who those patients are, but I thought making the device available will help the community figure out who those patients are and accelerate treatment of patients in need.

Dr. Lange: Thank you, Dr. Yeh. Dr. Bates?

Dr. Bates: I voted yes on all three questions. I'm as conflicted as I was yesterday. I take Dr. Lewis's concerns about the trial and if I were on a guideline committee seeing a small positive trial and a negative trial, I would say this has no clinical utility and we're going to have that discussion when the ON-MED trial was published because every journal's going to have a meta-analysis showing a three to four millimeter reduction in blood pressure with the five trials that we reviewed, I suspect. Yet, this is a breakthrough device evaluation. I think I am convinced that the second generation catheters have a clinical effect.

The delta evaluation is significantly impacted by the sham population reduction in blood pressure. And I think there are problems testing blood pressure the way they did in the small number of patients they did with the crossovers and the medications. And my vote is a vote to continue research, not to release this to the general public. I think if there is a group that benefits, like those that have the positive gene profile mentioned after lunch or the hypertensive urgency patients that come to the hospital, we don't want to lose the technology if we can make it work better and pick out the subgroups where it might work.

Dr. Lange: Thank you. Dr. Bates. Dr. Corriere.

Dr. Corriere: I voted yes on the safety question. I voted yes on the efficacy question. And I abstained on the risk-benefit question. And the reason for that for me was we had some very broad criteria. I do think on that third question, I abstained, I do think there's potential benefit for this device. The question is, we don't know which patients are most likely to have a benefit that outweighs the risk. And along the lines, under my abstention I do think that more selective labeling and indications for the product and more severe instances of hypertension, not things like one drug hypertension would potentially tip that balance more in favor of the benefit outweighing the risk. And I apologize if my abstained vote has thrown a wrench in any of this.

Dr. Lange: No. By the way, no votes throw a wrench in anything. I appreciate the fact that people have a very robust and rich discussion. That we don't all agree. We all listen, we consider, and we vote our conscience in our heart. So, Dr. Corriere, thanks. Dr. Damluji?

Dr. Damluji: Yes sir. Thank you. I voted yes for safety. There are no major adverse cardiovascular events related to the procedure in the short term and the long term up to six months. The device is safe. I also voted yes for efficacy, and my vote was based on, the question is, can I say this device is ineffective and the answer is no.

If you look at the, the data in aggregate, I agree with Dr. Yeh, there are, the magnitude of benefit is, you know, you can argue on it on drugs, off drugs, but there is some signal and related to the benefit risk analysis. I also voted yes because there are subgroups who showed sustained benefit with 10, 15, 25 mmHg. So just withholding this device from them might not do them. Good. So I voted yes to three of them. Thank you.

Dr. Lange: Thank you, Dr. Damluji. Dr. Hirshfeld.

Dr. Hirshfeld: I voted yes, yes, and yes. Most of my rationale. Was very nicely summarized by Drs. Yeh and Bates, which shows that we interventionalists think alike. I was very close to joining Dr. Corierre and abstaining on three because of the very modest effect size, it was

generated and it was demonstrated. But nonetheless, I felt that there was a sign that at least in a subset of the patients who were treated, there was evidence of efficacy and benefit. So I finally tipped away from abstaining to yes.

Dr. Lange: Thank you, Dr. Hirshfeld. Dr. Lockhart.

Dr. Lockhart: I voted yes on safety. I think it's got a good safety profile. I voted no on effectiveness. I think a small-shown probable effect on one of the two trials is probably real, but there's just too much uncertainty. And then, while I can't prove it's ineffective, I don't think the data's there for me to say it is effective, which is a different viewpoint. And then risk cost effect or no, effectiveness to risk? I voted no because again, I think there's too much uncertainty that there is actual, a real clinically-relevant benefit to outweigh even the small risk of an invasive procedure like this.

Dr. Lange: Okay. Dr. Saville?

Dr. Saville: I voted yes for safety, no for effectiveness, and no for the risk benefit. So, I voted yes for safety even though I think there are risks associated with any procedure. And, and we talked about some of those risks here. I voted no for effectiveness, primarily because of the precise wording of the indication. I did not think that effectiveness was demonstrated for patients in the proposed indication.

I do think there's a small benefit. The OFF-study was, was clean and I think shows a small, but likely a clinically meaningful benefit. So my answer for effectiveness could change to a yes with some appropriate change in the language for the indication. I voted no for the risk-benefit. For me, it's even if, if we change the, the language of the indication to you talking about the same population of the trial, that we actually studied for me, that the scale that of benefit risk is still very even. And I worry about this idea of generalizing this to the hypertension population, and I don't think my answer would change, even if there's a change in the wording of the

indication. For me, I think I would need additional randomized data to convince me that the risks outweigh, I'm sorry, that the benefits outweigh the risks.

Dr. Lange: Thank you, Dr. Saville. Dr. Somberg.

Dr. Somberg: I voted yes for safety. I voted yes for the benefits. But that was predicated on my understanding that the indications would be modified to in accordance with what the population was studied and not for population of resistant hypertension, which wasn't studied in this program. And I voted yes on the risk-benefit ratio because I do think there is a population that responds. And I disagree that you can always find some people that respond. I think there was additional data presented in the presentations that showed that more people showed benefit, especially with higher initial blood pressure readings. And I think that was very important to my vote. Thank you.

Dr. Lange: Thank you, Dr. Somberg. Dr. Wittes.

Dr. Wittes: So, I voted yes for safety for the reasons that everybody says. I voted no for efficacy for the reasons that Dr. Allen and Lockhart described. Even if the change in language were made about the criterion for entry, that wouldn't change my mind because I saw in one study a small effect in the other study, maybe no effect. And then every, hardly any difference in the drug use over time. And then I voted no for risk benefit because I think the benefit was not so great that it outweighed the potential risk.

Dr. Lange: Thank you, Dr. Wittes. Dr. Lewis?

Dr. Lewis: I voted yes for safety and no for the subsequent two questions. I feel like we have one study that's negative and one study that is minimally positive, and I have no reason to be biased or have a view that one is more valid than the other. So as far as I'm concerned, we still don't know the efficacy of this. And I think if it gets on the market, the anecdotal small sample size of each individual physician using this intervention will not allow them to select out the

patients it'll benefit from those who won't benefit, and to not have a definitive study that better defines that it is efficacious and in whom is actually a disservice to the public.

Dr. Lange: Thank you, Dr. Lewis. Dr. Nachman?

Dr. Nachman: Yes. Thank you. I voted yes, no, and no, and Dr. Wittes and Dr. Lewis really summarized my thinking on the effect of efficacy. The OFF-MED trial did show a small benefit, and I worry about a clinical benefit slide basing our, you know, benefit on smaller and smaller magnitude of benefit, that's on the one hand. I am convinced that there is a subgroup of patients who would benefit from this, and I worry that that subgroup is A, not defined, but B, could possibly be a minority of patients. And for an invasive procedure, we may call it minimally invasive, but it is invasive procedure. I worry about opening the gates, do a lot of procedure to benefit only a minority of patients. So that's why I voted no, even though I heard the same argument for a yes vote. So, and for the risk benefit it's just same argument essentially. Thank you.

Dr. Lange: Right. I'll register my vote. Then we'll talk to our patient rep, consumer rep, and our industry advocate as well. I voted just on the last question to break the tie. Had I voted on safety, I would've voted yes. Had I voted on question number two, effectiveness, I probably would've voted no. And for the same reason that Dr. Seville mentioned that is for the indications proposed, I don't think it was proved, shown to be effective. And had those indications changed, my vote perhaps would've changed, and I voted no for the same reason, Dr. Lewis, Dr. Saville, Dr. Allen, Dr. Nachman we're faced with a negative trial, unfortunately, and we can try to explain it away, but in the end, it's a negative trial. And so, I can't honestly look patients in the eye and tell them that I believe that the benefit outweighs the risk in the patient population at large. Let's move to our patient advocate, Deneen Hasser, I'd like to hear from you.

Dr. Hasser: If we had been designing a trial at this point, I would've been 100% in support of moving forward and getting answers to the questions that we couldn't wrap our heads around now. As far as risk is concerned, I was comfortable with that. That would've been a yes vote. I have flip-flopped back and forth all afternoon on whether or not it's effective. I agree that it looks like there is some group in there. But whether or not that deserves FDA approval, I don't feel confident answering whether or not the benefits outweigh the risks. I truly thought that they were equal at this point in time. Thank you.

Dr. Lange: Thank you, Deneen. William Vaughn is our consumer advocate.

Dr. Vaughn: I would've gone yes, no, no. And I really liked Dr. Nachman's point that there probably are some people that if the FDA could define or work with CMS to make sure the payer community holds it to that group that'd be worth doing. But until there's some gate on this process, no.

Dr. Lange: Thank you, William. Our industry advocate or representative is Dr. Wes Cetnarowski. I'm interested to hear from you, Wes.

Dr. Cetnarowski: Thank you. So, I really appreciate the voting panel members' discussion and consideration today from an industry perspective, this was very encouraging.

I think as was acknowledged there was certainly one very positive trial. And, what I appreciated was the recognition that there is a difference, or at least the beginning of the recognition amongst the panel members that there is a difference in the requirements both from a breakthrough technology and a device standpoint, difference in requirements for approval, a consideration for approval. So, I thank the members for that and hopefully we can have some additional stimulating discussions to that end in the future.

Dr. Lange: Thank you, Dr. Cetnarowski. I'm going to turn to over to the FDA, you have up to 15 minutes for summation comments or clarifications. Let me open the door to you, Dr. Zuckerman, or your representative.

Dr. Zuckerman: Mr. Brian Pullin will talk on behalf of the FDA.

Dr. Lange: Okay.

Mr. Pullin: Hi, this is Brian Pullin from FDA. I'd just like to thank Medtronic today for their presentation and for really quickly addressing numerous requests from the panel. In addition to the FDA throughout the process, I know there was a lot to go through and appreciate their efforts. I'd again like to thank the FDA panel staff and the review team for all of their work. I mean the amount of work that goes into a single panel meeting is noteworthy, but preparing for two meetings in two days for, for two different products, especially with the complexity of these studies is really significant. And this isn't even to mention the years of work that has gone into the renal denervation space that has brought us all here today. So, all along, they really kept the health of the US public at the forefront. And really personally, it's been impressive to witness their dedication. So, thank you to them.

I'd like again to thank you the panelists for lending your time to a very full two-day schedule. We've been looking at this data for months. But it's been impressive how you've been able to digest it so quickly and provide a very insightful discussion. And it's been truly helpful to FDA. So thank you.

And finally, Dr. Lange, I mean, your leadership has been incomparable over the last two days. You've kept the meeting moving without sacrificing the discussion. And it's been great to have you back as chair. So, we know that you're always willing to serve in this role, and we're grateful that, and I, you know, we hope to see you there again. So thank you all again. I don't want to spend any more time, let you move on, but thank you again.

Dr. Lange: Okay. So, before we leave, I want to express my appreciation to Medtronic. What I've told is this is a project you've been working on for years, and you've worked very closely with the FDA, their laudatory work with you and you bringing this to the panel. I want to thank the FDA for allowing us to be involved in this discussion. I want to remind everybody listening that the panel is not voting on this product or this device. The panel is voting on the questions that were posed to us by the FDA, the FDA takes those votes and this very rich and candid and thoughtful discussion we had and the FDA will work with the sponsor and make a decision about what will transpire in the future. I've served in the FDA panel now for over 12 years, and I've seen a marked change in how industry and the FDA work together for the common good of the consumers. I realize that many people at Medtronic are my colleagues as well, and have been and continue to be. I want to thank you all again for excellent presentations, excellent response. The FDA, same, excellent presentations, an excellent response to well as well. It's a privilege to serve on this panel. And I want to thank you, Dr. Zuckerman, appreciate your leadership as well. So, with that, Bram will give you the last word and then we'll sign off.

Dr. Zuckerman: Yes, Dr. Lange, before I sign off, I believe that Medtronic may want to have a closing comment by virtue of Dr. Mauri. Is that correct, Dr. Mauri?

Dr. Mauri: Thank you. Thanks, Dr. Zuckerman. Thank you, Dr. Lange. It's a very simple comment. I know it's been a long day. Just really want to reiterate the thanks to everybody here today on behalf of investigators on Medtronic, as well as the patients who've been in these studies. It's a large amount of information as you heard today. And we really appreciate your candid discussion, and we're looking forward to working together with the FDA and taking into account all of the comments that we heard today. So, thank you very much.

Adjournment

Dr. Lange: Thank you, Laura. With that, this concludes the second day of panels. I want to thank everybody that participated. The fact that you came back a second day was really encouraging to me this morning, and I appreciate it. By the way, don't come back tomorrow. All right? So, thank you all.

Dr. Yeh: Thank you.