SUMMARY MINUTES

CIRCULATORY SYSTEM DEVICES PANEL MEETING

MEDICAL DEVICES ADVISORY COMMITTEE

August 23, 2023
9:00 a.m. EST

Attendees

Chairperson

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

Members

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

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

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

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

Consultants

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

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

Temporary Voting Members

Eric Bates, MD
Professor of Cardiology
Frankel Cardiovascular Center

University of Michigan Health — Ann Arbor, MI

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

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

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

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

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

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

Janet Wittes, PhD
Principal
Wittes LLC — Washington, DC

Consumer Representative

William Vaughan
Consumer Advocate — Falls Church, VA

Industry Representative

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

Patient Representative

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

FDA Participant

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

Designated Federal Officer

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

Sponsor Presenters

Anna Venegoni Dyer
Senior Manager, Regulatory Affairs, Medtronic, Inc. — Portland, OR\

Laura Mauri, MD
Chief Scientific, Medical, and Regulatory Officer, Medtronic, Inc. — Boston, MA

David Kandzari, MD
Director, Interventional Cardiology
Chief Scientific Officer, Piedmont Heart Institute — Atlanta, GA

Felix Mahfoud, MD
Deputy Director of Cardiology, Saarland University Hospital — Homburg, Germany

Raymond R. Townsend, MD
Co-Director of Hypertension Section, University of Pennsylvania School of Medicine — Pennsylvania, PA

Vanessa DeBruin, MS
Senior Director, Clinical Affairs, Medtronic, Inc. — St. Paul, MN

FDA Presenters

Hiren Mistry, MS
Biomedical Engineer, Office of Cardiovascular Devices, CDRH, FDA — Silver Spring, MD

Adrijo Chakraborty, PhD
Statistician, Office of Clinical Evidence and Analysis, CDRH, FDA — Silver Spring, MD

Meir Shinnar, MD, PhD
Cardiologist, Office of Cardiovascular Devices, CDRH, FDA — Silver Spring, MD

David Gebben, PhD
Health Economist, Office of Strategic Partnerships and Technology Innovation, CDRH, FDA — Silver Spring, MD

CALL TO ORDER
INTRODUCTIONS

Dr. Richard Lange, the Panel's chairperson, called the meeting to order and announced the day's agenda: to discuss, make recommendations and vote on information regarding the pre-market application (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. **Dr. Lange** prompted the Committee members to introduce themselves.

CONFLICT OF INTEREST STATEMENT

After introductions, **Mr. Jarrod Collier,** the Designated Federal Officer, read the conflict of interest statement and introduced the proposed indication of the Medtronic system under discussion: for the reduction of blood pressure (BP) in patients with uncontrolled hypertension, despite the use of anti-hypertensive medications, or in patients in whom BP lowering therapy is poorly tolerated. He announced that conflict of interest waivers were issued to Dr. Julia Lewis, Dr. Patrick Nachman, Dr. Randall Starling, and Dr. Robert Yeh regarding their employer's involvements with the sponsor, allowing them full participation in the meeting.

Mr. Collier introduced Dr. Wes Cetnarowski as the industry representative and appointed Dr. Eric Bates, Dr. Matthew Corriere, Dr. Abdulla Damluji, Dr. John Hirshfeld, Dr. Mark Lockhart, Dr. Benjamin Saville, Dr. John Somberg, Dr. Janet Wittes, Dr. Julia Lewis, and Dr. Patrick Nachman as temporary voting members for the day. He also appointed Dr. Richard Lange as the temporary voting chairperson.

MEDTRONIC PRESENTATION

Dr. Laura Mauri, an interventional cardiologist and Chief Scientific Medical and Regulatory Officer at Medtronic, began the sponsor's presentation. She provided background on the global health crisis that is hypertension, citing it as the leading modifiable cause of death worldwide. Nearly 120 million Americans, 48% of the US adult population, have hypertension, and 77% of hypertensive adults have uncontrolled BP according to the American Heart Association. Hypertension was a primary or contributing cause of nearly 700,000 deaths in the US in 2021, and BP has been studied as a valid surrogate of cardiovascular outcome. She emphasized that it is critical to promote BP lowering in all hypertensive patents and addressed

that non-adherence to existing therapy options stuns patient outcomes.

Dr. Mauri described the mechanism of action behind renal denervation (RDN) for hypertension and played a video to show how the Medtronic system works. The catheter and electrodes ablate renal nerves via insertion into renal arteries. The procedure is performed under conscious sedation and decreases renal nerve signaling to the brain, facilitating reduced BP readings over time for the patient.

Dr. Mauri provided an overview of the clinical program, which was done off of medications for an accurate assessment of the procedure's effectiveness. Studies were also conducted to evaluate the effectiveness for patients on medications. Both off- and on-med trials demonstrated that RDN provided clinically meaningful and sustained BP reduction. She emphasized that RDN is meant to complement lifestyle modifications and the use of anti-hypertensive medication, not as a first course of treatment for hypertension. The procedure had excellent short- and long-term safety profiles.

Dr. Raymond Townsend of University of Pennsylvania's Perelman School of Medicine described the current landscape and unmet need that exists for patients with uncontrolled hypertension. He highlighted that adherence is a major limitation of antihypertensive medications, often due to side effects and complicated regimens. He discussed a Medtronic patient preference study that indicated up to 31% of patients would choose an interventional RDN treatment given the outcome of BP reduction and the likely risks.

Dr. David Kandzari of the Piedmont Heart Institute presented efficacy data from the clinical program. Treatment and sham study patients were followed through 36 months, and crossover patients were followed through 24 months after RDN. Inclusion criteria required patients to be off of medication or willing to discontinue at least 3-4 weeks prior to randomization with a baseline systolic BP reading between 150 and 180 mmHg, diastolic readings of at least 90 mmHg, and average systolic reading between 140 and 170 mmHg. Diabetes and other conflicting medical conditions disqualified patients.

80 patients participated in the pilot study and 286 additional patients were randomized in the expansion phase. After 6 months, patients were unblinded and sham-control patients were allowed to cross over to receive RDN therapy, of which 125 patients opted to cross over. Average age was 53 year swith fair racial representation. 50% were from the US; most had hypertension for over 5 years. Comorbidities were comparable between groups except for coronary artery disease, with none in the RDN group and 4% in the control group.

The off-med pivotal study met both its primary and secondary efficacy endpoints. The pilot study saw significantly decreased BP at three months in the RDN group compared to control. The full cohort had a statistically significant absolute reduction of 4.5 mmHg for 24-hour systolic BP and a reduction of 9.4 mmHg for office systolic BP with renal denervation, constituting a clinically meaningful reduction. Fewer RDN patients met escape criteria at the one- and three-month time points. At three-month follow-up, the RDN group experienced significant constant reductions in BP throughout the entire period, including mornings, evenings, and overnight, whereas BP in the sham-treated group was largely unchanged.

The primary efficacy endpoint in the on-med trial was not met, as differences in 24-hour systolic pressures were not consistent between the pilot and expansion groups. However, reductions observed in the on-med trial are clinically meaningful reductions.

Regarding the joint analysis for both on- and off-med studies, the RDN group experienced a mean 9.3 mmHg decline in 24-hour systolic BP and a mean 9.2 mmHg decline in office systolic BP favoring RDN treatment for both measurements. A greater proportion of control patients increased their anti-hypertensive medications, and conversely, a greater proportion of RDN patients decreased their anti-hypertensive medications. More control patients were missing 24-hour systolic data due to higher rates of escape. RDN patients had significantly greater reductions in nighttime ambulatory systolic BP, which is the most significant prognostic marker of cardiovascular morbidity and mortality and is independently associated with increased risk of cardiovascular events such as myocardial infarction and stroke.

Differences between US and non-US patients were thought to be driven by non-congruent medication regime changes. Blood pressure reductions in the on-med sham control and full cohort groups were an order of magnitude higher than for the off-med study despite best efforts to keep patients on stable medication, making on-med data difficult to interpret.

Summarizing, **Dr. Kandzari** offered the following: in the off-med pivotal trial, the primary endpoint was met. Reductions were both statistically significant and clinically relevant for 24-hour and office BP compared with the sham at three months. For on-med, there were significant reductions in 24-hour and office systolic BP at six months compared to the sham-treated 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 BP for renal denervation compared with sham. Importantly, consistent reductions were seen from baseline in the renal denervation treated patients across all of the studies.

Dr. Felix Mahfoud of Saarland University Hospital presented safety and durability data, introducing the procedure and minimally invasive, providing durable reductions in BP, and having excellent short- and long-term safety profiles. He noted that the Clinical Events Committee (CEC) adjudicated the reportable safety events, and safety data was monitored by an independent committee.

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, pre-specified with FDA at 7.1%, was based on expected events and event rates from other renal intervention procedures. The pooled dataset 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. No deaths were reported.

In the off-med study, the RDN group had major adverse events at 0.6% and the sham-treated group rate was 0.5%. One RDN patient was hospitalized for hypertensive emergency. The incidence from enrollment to six months was 1.0% for RDN and 0.8% for sham, and these events were pseudo-aneurysms that resolved without sequalae.

Potential renal artery stenosis was evaluated at 12 months to assess vascular safety. Only one patient experienced stenosis in an accessory renal artery, identified more than three years post-procedure, and no deterioration of renal function was observed.

Renal function was evaluated by estimated glomerular filtration rate (EGFR) as measured by the Modification of Diet and Renal Disease (MDRD) equation. Reductions in EGFR following RDN were within the range of EGFR over time in hypertensive individuals, and

changes in RDN patients were consistent with the decline seen in the sham-control group. Both on- and off-med studies supported the positive safety profile of RDN using the Symplicity Spyral system.

No device related safety events were observed, there was a low rate of procedure-related events, and there was no increased risk of RDN-associated renal artery stenosis. Renal function was sustained over time following RDN.

Long-term results were analyzed from Medtronic's Global Symplicity Registry (GSR), designed to evaluate real-world safety to three years and contains data from over 3,400 patients for over 7,000 patient-years treated with both the Symplicity system and its previous design, the flex catheter. GSR data and clinical trial data demonstrate the durability of BP reductions through three years of follow-up, with more patients reaching target pressure while medication remained stable.

No long-term risks were identified. Medtronic launched a new study, AFFIRM, to follow Symplicity RDN recipients in a real-world population; this study will collect data through 60 months.

Dr. Townsend concluded by re-emphasizing the importance of adherence and the difficulty of medication regimen adherence for many patients. Patients were willing to consider RDN, and given the safety and efficacy, this may be a solution for patients who have difficulty adhering or who do not see results from other treatment methods. He posed that by adding the Symplicity Spyral system to the available treatment options, the number of uncontrolled patients at significant health risk due to high BP may decrease.

Q & A

Vanessa DeBruin, Senior Director of Clinical Research at Medtronic, fielded the Panel's questions.

Ms. Hesser requested quality of life and/or patient-reported outcome data, which **Ms. DeBruin** provided after the lunch break. **Dr. Somberg** requested details on how the sponsor dealt with variability in patient anatomies, such as whether auxiliary renal arteries were ablated. He requested the number and location of ablations performed and asked if there was a correlation between these factors and the outcome. He inquired if there was a training effect seen, wanted ambulatory BPB measurements (ABPM) for per-protocol and as-treated groups, and requested the magnitude of effect for each individual in a waterfall plot. **Ms. DeBruin** clarified that the direction to the sites was to treat any vessel in the range of 3-8 millimeters in diameter, including main renal arteries, accessories, and branches, provided they were outside the kidney parenchyma. She responded that there was no training effect seen. **Dr. Kandzari** agreed to address **Dr. Somberg's** remaining two questions after lunch.

Dr. Yeh requested the distribution of changes be displayed in a histogram format. He requested rates of escape in US versus non-US on-med trials and if escape rates were available for other studies. He further inquired whether there was data regarding lost to follow-up and whether attrition the explain the lower number of patient data at 36 months. **Dr. Yeh** asked the sponsor to explain how patients were selected for follow-up, whether they were self-selecting, and what were the characteristics of patients that stayed in the trial, and whether there is data for patients who had similar enrollment characteristics across different time periods. **Ms. DeBruin** agreed to provide the requested data after the lunch break.

Dr. Lewis wondered what proportion of medication increases in the sham group were related to protocol violations and the proportions of sham and RDN groups due to escape criteria. He further requested data at the three-month time point for the on-med study's primary

outcome, and he asked if intolerance was documented in any way when patients were enrolled. These will be answered after break.

Dr. Allen requested clarification on the number of patients in the on-med RDN versus sham groups and the reported one-to-one ratio. He asked for a comment towards the efficacy of the blinding and expressed concern that the sham group was not truly blinded. He pointed out that he does not see that patients were optimized prior to enrollment to support the indication for use. **Dr. Lange** addressed the first concern, pointing out that in the on-med study, the pilot was on-to-one and the expansion was two-to-one.

Dr. Corriere inquired towards the number of medications permitted and why this was capped at three. He also asked why there is a lack of racial and other demographic information, and he expressed curiosity that the patient preference study relied on interviews.

Dr. Saville wanted to see box plots related to the distributions of the raw data. He also inquired if the primary analysis was a complete case analysis and asked for clarification of imputation strategies. He asked if Bayesian borrowing was implemented as a plan after the data was finalized and wondered if the Bayesian methodology produced a biased result.

Dr. Bates commented that if the primary manuscript for the on-med study were published prior to this meeting, press might have been muted.

Mr. Vaughan requested restrictions on use information for a few countries, which Ms. DeBruin will provide.

Dr. Wittes had trouble understanding the analyses and requested clarification of the data on slides 77 and 78, specifically. He further asked if analyses were done to predict who would benefit from the device and what was meant when it is said that the off-med study met its primary endpoint.

Dr. Lockhart wondered how patients were notified of the existence of renal artery stenosis. He asked if ablations ever crossed the renal artery origin and for details on ultrasound training and CTA MRA training. He also requested information on radiographic slick thickness and the timing of CTA MRAs.

Dr. Zuckerman requested data on results for the Black population specifically.

Dr. Cetnarowski asked if there was patient diary data to corroborate findings in increase of medication use. He asked for medication increase/decrease data out to 24 months.

Dr. Starling wondered what BP measurement was used for escape criteria, if escaped patients were censored, and if there was follow-up data on escaped patients.

Dr. Damluji asked for efficacy data for crossover patients in the on-med study.
All questions will be answered in the afternoon session.

FDA PRESENTATION

Mr. Hiren Mistry, a biomedical engineer in FDA's Office of Cardiovascular Devices and lead reviewer for this PMA, outlined FDA's presentation, presented statistics on the relevancy and seriousness of cardiovascular disease in the US, provided parameters for considering uncontrolled hypertension, discussed the role of renal physiology in BP regulation, re-introduced renal denervation procedures, gave the history of the sponsor's interactions with FDA, reiterated proposed use and design of the Symplicity Spyral system, gave an overview of the Breakthrough Devices Program, and outlined the clinical studies evaluating the system to-date, the off-med (off-med) and HTN-on (on-med) studies.

Key study features noted by **Mr. Mistry** included: after three months, subjects in the on-med studies were able to add medications per investigator discretion to reach a target BP

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.

Key enrollment criteria was presented as: age between 20 and 80 years old, office systolic BP between 150 and 180 mmHg, office diastolic BP over 90 mmHg, and 24-hour ambulatory BPs between 140 and 170 mmHg. Additionally, BP enrollment criteria would need to be met after BP medication washout in off-med, or a BP medication stability period in on-med. In off-med, subjects discontinued BP medications and underwent a three-to-four-week washout period. In on-med, subjects remained on a stable BP medication regimen consisting of one to three medications for six weeks.

Follow-up activities were noted as: measuring office and ambulatory BPs 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 had suspected renal artery stenosis, they may have received additional CTA or MRA imaging at 6 and 12 months.

Dr. Adrijo Chakraborty, a statistician in CDRH's Office of Clinical Evidence and Analysis, discussed the statistical methods used for evaluation of the primary and secondary effectiveness and safety endpoints.

For the primary effectiveness endpoint, a Bayesian approach allowed pilot information to be pulled partially or entirely in conjunction with the expansion data to compute treatment effect. The primary Bayesian cohort consisted of all expansion subjects but may have included partial pilot cohort information. This endpoint was evaluated for each trial individually.

The primary safety endpoint was defined as the occurrence of at least one major adverse event and included parameters for renal artery stenosis. The pre-specified analysis set for the primary safety endpoint was the first 253 evaluable RDN-treated subjects from the off-med and the on-med studies, with additional analyses performed based on all RDN-treated subjects. The safety event rate performance goal was set at 7.1%, derived from a literature review.

Dr. Chakraborty detailed more statistical methods and considerations, noting that the Bayesian method was not used for the rest of the endpoints.

Dr. Mein Shinnar, a Senior Medical Officer at the Office of Cardiovascular Devices, presented the results of the clinical study. He reviewed the on- and off-med designs and the pilot and expansion cohorts, noting that a recurring issue will be whether and how to combine the results of the pilot and expansion cohorts. He discussed subject accountability, blinding, the general similarity of demographic characteristics across studies, and noted the difficulty in obtaining racial data. He presented the results of the different cohorts in great detail. Summarizing, **Dr. Shinnar** made the following remarks: 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 off-med, and on-med 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 off-med and on-med. The off-med study met the primary effectiveness endpoint, demonstrating a between group difference in mean ambulatory systolic BP reduction of 3.9 mmHg at three months in favor of renal denervation. The on-med 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 BP reduction because of confounding factors, such as medication changes, unblinding of study patients, and sham subject crossover to radiofrequency renal denervation that reduced control group sample size. Lastly, the Patriot Preference Study found that some patients may prefer the renal denervation procedure to taking an additional BP pill.

QUESTIONS TO FDA

Dr. Lewis asked for distribution of baseline BPs in the on-med study; **Dr. Lange** redirected this inquiry to the sponsor. **Dr. Lewis** further asked FDA if they considered the 3.9 mmHg BP difference to be clinically relevant and if the 0.02 p-value was compelling in their eyes. **Dr. Zimmerman** declined to give a definitive answer so as not to bias the Panel's recommendations and noted that p-value acceptability is highly circumstantial.

Dr. Hirshfeld inquired about the impact of medication adjustments post-randomization in the sham group and the impact of crossovers on the data; **Dr. Lange** redirected these to the sponsor.

Dr. Wittes asked if the 35 additional patients included in the off-med frequentist analysis were randomized one-to-one and why they were not included in the Bayesian analysis. **Ms. DeBruin** answered that these 35 patients were in screening when the DSMB met and determined the study could stop after 331 patients in the first interim analysis, but these patients were allowed to continue in the trial, so they present as additional data in the frequentist data only. **Dr. Wittes** further inquired specifically about missing data in slides 47 and 48. **Dr. Lange** redirected this for the sponsor to answer later.

Dr. Yeh wondered about the data on slide 48: why the data points beyond 12 months have continually lowering denominators? Do these data reflect crossover patients, and how are crossovers grouped? He also inquired whether medication changes can be considered a useful outcome and if distributions of those changes are meaningful. **Ms. DeBruin** addressed this later.

Dr. Bates asked for slide 54 to be reproduced to show the three month results to better understand how the reductions occurred in the sham-treatred group and asked for a histogram by month showing number of medications for each group, which Ms. Debruin answered later.

Dr. Saville wondered if crossovers were excluded from data on slide 50 at 12 months; **Dr. Shinnar** responded affirmatively. Dr. Saville also asked why the medication index on slide 50 is different from slide 60; **Ms. DeBruin** agredd to answer thay in detail later. **Dr. Saville** further inquired why treatment effect was analyzed by race within a subset of US patients instead of the overall study population; **Dr. Lange** responded that there was no race data collected outside the US. Finally, **Dr. Saville** asked if slide 73's GSR data included participants who had not undergone RDN; **Dr. Shinnar** answered it was only patients who had RDN via either Symplicity or the older flex catheter.

Dr. Nachman asked if patients who did not see a decrease in nighttime pressures had a good response to RDN and for their age distributions. He also brought up that the between-group difference was different for those who dropped many points of pressure as opposed to only a

few, noting heterogeneity in response, inquiring if there is a subgroup of patients who were particularly responsive to the treatment and what characteristics these patients may have shared. **Dr. Zimmerman** asked the sponsor to address this later.

OPEN PUBLIC HEARING

Mr. Collier read the Open Public Hearing Disclosure Process Statement, and **Dr. Lange** announced 14 speakers with 3-5 minutes allotted time each.

Dr. Barry Bertolet, a cardiologist from Mississippi, declared no financial conflicts of interest. He declared the importance of hypertension control in his practice, speculated that the RDN procedure would reduce stroke, coronary heart disease, and total mortality, and reassured that the procedure fits well within a cardiologist's skillset. He encouraged the FDA to follow European lead and approve the technology in question.

Dr. Cara East, a cardiologist and clinical investigator involved in Spyral studies, explained that some patients are resistant to or contraindicated for medication and require alternative methods to control their BP, and she reiterated the efficacy of the RDN therapy, emphasizing that there is significant unmet need.

Mr. Daniel Cash, a high BP patient, gave a personal account of his tribulations with medication side effects and ineffectiveness. He received the RDN procedure and implemented lifestyle changes to manage his BP effectively and conveyed his feelings that RDN was well worth it for him.

Dr. Marcus Schlaich, an Australian hypertension specialist, emphasized the reliable safety profile of the procedure and durability of the anti-hypertensive effect, asserting that the long-term efficacy is of high clinical value for high-risk patients.

Mr. Ken Bradford, a 65-year-old hypertension patient, shared his experience with RDN, emphasizing that RDN did not cure his hypertension in itself, but it certainly helped, and it reduced his need for medication.

Dr. Tiffany Randolph, a cardiologist, advocated for the approval of RDN therapies to aid treatment-resistant hypertension.

Ms. Naomi Saucer, a patient in the RDN trial and Medidata employee, spoke on her own behalf to share her positive experience with the procedure and said she can manage heat better and has seen a 12 to 18 mmHg reduction in BP on average since she received RDN.

Dr. Raven Voora, a nephrologist and hypertension specialist at the University of North Carolina and paid consultant for Medtronic, declared no financial interest in the outcome of the meeting and declared that RDN is something she would not recommend for every patient and should come after lifestyle modifications. But she sees the benefits in approving the technology for some patients.

Dr. Roland Schmieder, a German nephrologist and hypertension expert, warned that the process of RDN needs to be carefully structured and performed only in experienced specialty centers with an interdisciplinary team for case management, backing this with his experience as a European practitioner.

Dr. Michael Shapiro of the American Society for Preventive Cardiology emphasized the burden of hypertension and racial influences in this burden, citing RDN as an important tool to decrease this burden, especially as it pertains to adherence.

Mr. Vincente D'Ingianni, a RDN recipient, shared his positive experience and hopes others can benefit from RDN as well.

Dr. Ali Aburahma of West Virginia University expressed thoughts about the article "Medtronic Denervation Study Misses Primary Endpoint," noting that this evaluation may not have been made by the most appropriate method and does not verify clinical outcomes.

Mr. Scott Snyder testified on behalf of Geneticure, Inc. that RDN did not adequately demonstrate its ability to decrease BP and that multi-organ genetic scoring is related to RDN responses. He provided data in support of this and urged the Panel to consider the issue of genetic non-responders.

MEDTRONIC RESPONSES TO PANEL QUESTIONS

Ms. DeBruin introduced **Dr. Felix Mahfoud** to address some of the questions posed to Medtronic earlier in the meeting.

Regarding the procedure, **Dr. Mahfoud** clarified that all renal arteries above 3 mm in diameter were treated, including accessory renal arteries, which were found in many patients, but did not introduce any statistically significant difference.

Regarding the ablation numbers, an average of 47 ablations were performed with an average procedural time of around 90 minutes. To Dr. Somberg's request, this was clarified as 47 ablations per patient that do not cross the renal origin.

Addressing Dr. Corriere's question, all patients were treated via the femoral route with no formal training performed to the sites.

Addressing Dr. Lockhart's question on duplex ultrasound training, all sites were provided a detailed renal artery and renal parenchyma imaging manual by an independent core lab and were required to perform on-site hands-on training as well as submit test cases for evaluation by the core lab. He asserted that duplex operators were indeed informed about the presence of accessory arteries. For CT and MR training, technicians were provided a details manual and assessed by the core lab. **Dr. Lockhart** requested clarification on contrast timings and slice thickness, which **Ms. DeBruin** could not provide at the moment.

Towards patient preference, **Ms. DeBruin** clarified for Dr. Corriere that interviews were performed to develop the survey to ensure patient comprehension, and the surveys reflected satisfactory patient comprehension.

Dr. Lockhart requested comment on the high inadequacy rate on the CTAs; **Ms. DeBruin** added that a few sites were requested to retrain and declined. She confirmed for Dr. Lockhart that two-thirds were inadequate in MRI.

Dr. Kandzari stepped up to address questions, beginning with Dr. Wittes' question on whether the on-med study was statistically powered to prove a 5 mmHg difference, responding that it was not. Rather, it was designed to demonstrate superiority, not a specific number.

Toward Dr. Lewis, **Dr. Kandzari** provided the distribution of BP with respect to baseline, highlighting an even greater treatment effect for RDN in patients with the highest baseline pressures. Further, he added that intolerance data was not prospectively collected, but 83% of patients in the off-med study were on meds prior to washout.

For Dr. Corriere and Dr. Allen, **Dr. Kandzari** asserted that the study population was replicated as closely as possible for the sham trials to be representative of clinical populations. He cited an older Symplicity study that had difficulties with adherence to regiments of five or more medications, thus the choice for one to three medications. With regard to blinding, he reiterated that the James Index ensures blinding for both providers and participants.

With regard to escape patients, 7.4% met escape criteria, 5.5% in RDN and 9.9% in the sham-treated group. Nine o 12 in RDN had a last observation carried forward in the intention-to-treat analysis, and 6/13 in the sham treatment had the same. He provided patient escape details and a breakdown of US versus non-US escape rates. For **Dr. Lange, Dr. Kandzari** clarified that patients were designated as a safety concern if they experienced severe and dangerous hypertension as designated by the physician. For Dr. Lewis, it was clarified that 18% of patients were escaped among all patients who changed medications prior to the six-month endpoint.

For Dr. Saville and Dr. Somberg, box and waterfall plots of requested data were provided, and the data was discussed at length.

Dr. Mauri next addressed how missing data was handled, clarifying that there was not imputation for missing data, and imputation was only used for those who met escape criteria in the primary analysis. She described multiple other imputation analyses that were performed and the rationale for them. For Dr. Saville, she asked colleagues for data to clarify the magnitude of last observation carried forward. For Dr. Wittes, she clarified that carry-forwards were constant, not imputed and continued with details on when and why data was carried forward. In response to concern from Dr. Wittes statistical expertise, for Dr. Zuckerman, she clarified that FDA independently confirmed the imputation analyses, as they were pre-specified and part of the PMA.

Dr. Hanson, a Medtronic statistician, clarified more details about the Bayesian methods, borrowing, and discounting.

Dr. Mauri addressed data on Black Americans, reiterating that since much of the study was conducted outside of the US, racial data was unobtainable, but that Medtronic is certainly interested in collecting details about historically underrepresented groups. She presented detailed statistics regarding what was able to be collected, and mentioned the AFFIRM study, currently underway, which will focus more on this.

Dr. Lange prompted for any additional, unaddressed questions from the Panel. **Mr. Vaughan** asked for English and Canadian perspectives on RDN that are known to the sponsor. **Dr. Mahfoud** responded that the European Society of Hypertension Guidelines state that renal denervation can be considered as a treatment option in patients with preserved renal function and uncontrolled hypertension that is not well-controlled by drugs or if drug therapy elicits serious side effects and poor quality of life.

Dr. Mahfoud added specific data about stenosis for the Panel to consider, emphasizing that renal function and BP remained stable throughout follow-up in all patients with stenosis and no safety signals emerged.

Dr. Bates asked **Dr. Kandzari** if it is fair to say that proven benefit was degraded by the fact that the sham-treated group had better BP reductions than expected. **Dr. Kandzari** confirmed. It is **Dr. Kandzari**'s belief that benefit was shown adequately by the change in medication data, which decreased for the RDN group and increased for the sham-treated group, rather than BP measurements.

Dr. Lockhart asked, regarding stenosis, if numbers varied because Medtronic only counted them if they were confirmed by angiogram. **Dr. Mahfoud** responded the denominator is different because duplex ultrasound was also allowed as a modality for Medtronic's data interpretation, as patients often opted for less invasive imaging.

Dr. Damluji requested efficacy data for crossover patients beyond six months, which **Dr. Kandzari** provided. **Dr. Lange** noted for the record that this data has not been made available to FDA.

For **Dr. Zuckerman, Dr. Kandzari** clarified data that came from the US versus outside the country, underscoring the differences in medication management between countries and the lack of interaction between US and non-US sites.

Dr. Saville asked why Medtronic thinks there is a difference in medication usage between expansion and pilot. **Dr. Kandzari** attributed this to missing data and due to enrollment occurring during the Covid pandemic. **Dr. Lewis** reminded that the vast majority of medication changes are protocol violations.

The Panel broke and resumed to answer the FDA questions.

FDA QUESTIONS

QUESTION ONE: Given the information on safety, please discuss the 30-day procedural and device safety profile, reliability of post-RDN imaging, and the clinical significance of renal artery arterial responses to RDN treatment.

Dr. Lange commented first. The Panel identified two possible issues, the first related to vascular access through the femoral artery and the second related to renal artery stenosis. **Dr. Lange** prompted **Dr. Lockhart**'s expertise, and **Dr. Lockhart** commented that the ultrasound protocol was well-implemented and likely ruled out significant stenosis, but MRI and CT experienced quality issues and necessitated better training. Ultrasound can miss about 50% of accessory arteries, but this could be mitigated by identifying accessories in advance. **Dr. Lewis** asked if anyone with expertise thought 47 ablations per patient was high; **Dr. Somberg** responded it's not much higher than what electrophysiologists perform, and **Dr. Bates** said this is relative.

Dr. Lange summarized the Panel's discussion by saying that the 30-day procedural and device safety profile appeared to be safe with minimal complications related to vascular damage due to femoral artery access. The imaging protocol was as good as the labs that did them, but in the future, labs should be accredited and verified that they can perform imaging properly.

QUESTION TWO: Please discuss the relative value of ambulatory and office BP measurement in assessing changes in BP and evaluating the effectiveness of RDN.

Dr. Lange summarized the Panel's prior discussion of the sentiment's yesterday: 24-hour ambulatory systolic measurements are the gold standard, and office cannot be relied upon exclusively, though it gives complementary information.

QUESTION THREE: 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 in considering the totality of HTN-OFF and HTN-ON data.

Dr. Wittes commented that she could not figure out what the difference actually is given all the different analysis methods and confidence intervals. She wondered what the best estimate of the difference in question is. **Dr. Lange** reminded it is 3.9 mHg with a p-value less that 0.05.

Dr. Yeh added that it is hard to reconcile these differences, but his impression was that office-based pressure differences matter more and that the difference in the off-med group may be of significance. He found the single point estimate not useful due to biases in the study.

Dr. Hirshfeld felt that the focus on the mean/median values overlooked the granularity of the data and found data sufficient to pronounce that RDN has a real positive effect on patients.

Dr. Somberg found the effect to be more than modest and approximately equal to one drug.

Dr. Saville agreed that the point estimate of 3.9 was not especially useful and preferred the Bayesian distribution from slide 34 of the sponsor presentation. He found benefit displayed in the off-med study. He was concerned by confounding factors and missing data in the on-med study but found value in the reduction of medication use.

Dr. Lewis pointed out that the on-med study could be negative because the null hypothesis was correct and found it potentially inappropriate to ask patients to undergo an invasive procedure for questionable effect. She expressed concerns about the discordant office and ambulatory data.

Dr. Allen echoed the sentiments of **Dr. Lewis** and found the magnitude of difference minimal.

Dr. Starling believed there was a signal of effectiveness.

Dr. Lange summarized: the difference in the off-med trial is real and modest at best, perhaps equivalent to a slight increase in medication dosage. The difference in the on-med trial was negative and the null hypothesis cannot be disproven. **Dr. Zuckerman** noted that the Panel did not address the totality of the data, only the two parts, and asked to discuss this later.

QUESTION FOUR: 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 different groups and the generalizability of these results to the target US population, including US and OUS patients and US Black Americans.

Dr. Lange asked for a show of hands for those convinced by the explanation that medication differences between groups caused the discordant data, and one raised their hand. He also asked the converse, with the majority of panel members affirming.

Dr. Somberg commented that the combined effects of med differences and differences in ABPM sampling may explain the discordance, so he raised his hand affirmatively.

Ms. Hesser felt that the sponsor's explanation was inadequate.

Dr. Lewis added that it was possible the conduct of the study was less stringent in the US. **Dr. Bates** said both major trials were underpowered and can only be hypothesis-generating.

Dr. Wittes thinks the sample sizes were too small to rule out chance or define a reason for discordant results and suggested giving the sponsor a pass on this.

Dr. Saville suggested multiplicity is an issue and variations are likely noise.

Dr. Lange summarized: nobody feels confident that subgroup differences do or do not exist due to subgroup sizes, changes in medications, protocol violations, and missing data. **Dr. Zuckerman** asked if the aggregate data Dr. Mauri showed for Black Americans convinced the Panel that there is no obvious signal of harm or that there was an effect, to which **Dr. Lange** responded no, the population sizes were still too small.

QUESTION FIVE: Please discuss the strengths and limitations of longer-term BP data in patients treated with RDN, including whether RDN provided a durable reduction in BP, the clinical significance of longer term BP changes in RDN subjects versus sham subjects, and the clinical significance of BP medication differences between RDN subjects and sham subjects.

Dr. Lewis observed that there was no evidence of durability and the effect was not clinically significant in her mind.

Dr. Wittes concurred, adding that the selection of the sham group by nature of being the excluded crossover patients no longer represented randomization.

Dr. Saville agreed that randomization was lost with crossover, so up to six months, data was believable, but after that, it was not.

Dr. Lange asked for a vote: does the data provide evidence of a durable reduction? Two believed it did. Five said it did not. Six said they did not know. **Dr. Yeh** contributed that the studies were not designed to answer long-term durability questions.

Dr. Zuckerman asked what **Dr. Yeh** would suggest for a study designed to evaluate that, and **Dr. Yeh** answered that it would be difficult because it is not ethical to leave patients hypertensive, which is likely the reason for the medication protocol breaches present in the study, and that inferences based on number of meds and sustained declines in BP in single arm studies would have to suffice. **Dr. Lewis** contributed that a rank order outcome used for a six-month effect with adequate patient consent would constitute decent proof in her eyes. **Dr. Starling** added that durability measurements should include compliance as well as a patient-reported outcome. **Dr. Saville** suggested a joint model to determine benefit on the different endpoints via a restructured analysis, and **Dr. Yeh** concurred that this could be done with existing data via a hierarchical endpoint that includes escape and/or reaching a BP above a specified amount as part of the endpoint. **Dr. Lewis** compounded that would still be problematic because the BP difference failed.

Dr. Allen pointed out that durability is directly dependent on the rate of re-innervation, which takes a very long time; therefore, it is impossible to measure durability in a six month study.

Dr. Lange summarized: the Panel felt intervention to decrease BP can evaluated by decreased pressure in individuals who are medication-resistant, reduced reliance on medication by dosage or number of meds and/or increased compliance with medications and/or increased tolerance of medication, and patient preference. Durability measurements would be an assessment of those criteria over a period of longer than six months. The Panel was uncertain that the data at hand reliably demonstrated durability.

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

Ms. Hessner contributed that since the patient preference study was performed, methods had been further revalidated, commenting that patients seem willing to take a risk if it offsets pharmaceutical reliance.

Dr. Bates expressed uncertainty that patients were given enough information to make their crossover decisions since the rates varied between the two studies.

Dr. Cetnarowski believed the patient preference study is one important component of the overall risk/benefit assessment.

Dr. Corriere added that patients do not make their decisions in a vacuum and need to be warned about over-utilization of the technology, but he is glad the preference study was done.

Dr. Lange summarized: it is only one component, and it is essential to provide accurate efficacy and risk information for informed consent.

QUESTION SEVEN: 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 in patients in whom BP lowering therapy is poorly tolerated, should be modified or further defined. If modifications are needed, please discuss alternative language.

Dr. Somberg pointed out that the study was not expressly conducted with inclusion criteria to evaluate people who failed medication therapy and suggested the language include mild to moderate hypertension and that it offered the same benefit as one pharmacologic therapy.

Dr. Lewis concurred and wondered why this language was used when treatment resistance was not an inclusion criterion of the study, and **Dr. Allen** echoed this sentiment.

Dr. Bates suggested numerical clarification of what constitutes uncontrolled hypertension, specific phrasing to exclude elderly populations that were not studies, and deletion of the last two phrases to be replaced by 'despite maximally tolerated anti-hypertensive medications.'

Dr. Nachman expressed he does not feel like the data are there to determine what patient population would benefit most from this procedure, but it would be helpful to identify that population and include them in the indication's phrasing.

Dr. Yeh added that more restrictions in use may be in order, such as 'to be used as an alternative/adjunct treatment for patients with mild to moderate hypertension.'

Mr. Vaughan noted that Medtronic is well-known for paying doctors to overuse their procedures and suggests proceeding with such loose indications with caution.

Dr. Hirshfeld commented that the ReCor and Medtronic studies are similar enough in their identified efficacy that they should have the same IFUs, and he echoed sentiments that the designations for uncontrolled hypertension need to be more specific.

Dr. Lewis concluded with some suggestions: define hypertension and include magnitude of effect. He suggested, if another trial is done, that patients with severe hypertension be targeted as a potential IFU, since that group generally saw a better response from the procedure. He added that the ReCor data should not be used to make a comparison here.

Dr. Lange summarized: Medtronic's RDN was not tested in people that have resistant hypertension, and it may play a role in reducing BP and/or medication use. Additionally, the effect was modest, so that should be stated.

QUESTION EIGHT: 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 asked the Panel to vote: eight believed requiring post-RDN imaging in the form of ultrasound should be mandatory for all patients; six did not agree. **Dr. Lange** added that certain patient populations have not been studied, such as diabetics, those over 80 years of age, a GFR less than 60, congestive heart failure, and/or cardiovascular and cerebral vascular diseases, and labeling should mention there is no data to support use in these populations.

Dr. Yeh contributed that imaging can come with downstream consequences and cascade effects and should not be mandated without evidence it will be beneficial.

Dr. Damluji agreed with Dr. Yeh and did not recommend routine ultrasound use.

Dr. Lange took an updated vote: ten believed imaging should not be included as a mandate in the label.

Mr. Vaughan added that the IFU should include the procedure only be performed at specialized centers, which would reduce the need for imaging.

QUESTION NINE: 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. Lewis did not think evidence presented demonstrated enough benefit to recommend the procedure to patients, even despite the minimal risk.

Dr. Starling thinks some patients will have improved adherence as a result of the procedure, which **Dr. Lange** countered that most patients are not going to get off all their medications as a result of RDN.

Dr. Cetnarowski mentioned that there are gaps in medicine's current ability to effectively treat and control hypertension, which complicated the effectiveness profile. **Dr. Zuckerman** concurred and urged the Panel to put their clinical and practical hats on to consider context of use and broader public health implications when making recommendations on the breakthrough device's usefulness. **Dr. Corriere** acknowledged that the discussion should be less stringent in light of the breakthrough designation. **Dr. Yeh** commented that his bar for effectiveness goes down when considering public benefit from breakthrough device approval.

Dr. Yeh further added that the efficacy signal in the off-med trial is undeniable, though the magnitude is debatable. He emphasized the variability of effect and that the mean benefit, which has been the focus of the conversation, underestimates the potential benefit to many.

Dr. Lockhart commented that there is a lot of uncertainty for both safety and efficacy.

Dr. Lewis warned against confounding desperateness of the unmet need with a willingness to throw anything at that unmet need.

Dr. Somberg further emphasized Dr. Yeh's point and noted that he was impressed with the number of people who showed a dramatic response, as evidenced by the box plot. He also noted that there is no training effect in the current iteration of the device, for which the sponsor deserves credit over earlier designs.

Dr. Damluji reiterated that the device is quite safe and thought withholding the device from patients due to a variable benefit profile would be a mistake.

Dr. Saville's perspective as a statistician was that the benefit is small, with unclear long-term benefits and unclear real-world benefit of using it over medicine, adding that no procedure is zero risk. He found it difficult to say if risk or benefit is heavier.

Dr. Lange found it amusing that they seem to be picking out the data that supports their conclusions and ignoring the parts that do not, noting that BP was increased in certain patients. **Dr. Yeh** rebutted that a higher proportion of patients achieved a reduction greater than 15 points, implying benefit.

QUESTION TEN: 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 (PAS). 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. Yeh commented that there's a lot of missing data for long-term follow-ups, which necessitates postmarket study. He noted that postmarket studies are not feasibly randomized. He suggested a reasonable goal would be to assess whether the device has the same effectiveness across racial groups in the US.

Dr. Wittes emphasized that the hypothesis needs to be set out upfront and that sample size needs to be relevant to the hypothesis. She added that there would be many confounding variables that would require adjustment in the assessment of Black versus non-Black populations. She suggested utmost care in the upfront design of why which data is collected for what purpose. **Dr. Saville** concurred at length.

Dr. Somberg suggested developing a pre-established composite endpoint to understand when there are two variables pulling in different directions. He recommended using a registry where those groups are proposed that records who does and does not get the procedure. He further commented that he would like to see either a group of companies perform a study, or an NIH-sponsored program, that evaluates the pathophysiologic basis of reduced efficacy signals seen in these initial studies.

Dr. Bates expressed concern about overuse and conflict of interest in having an industry-run registry, suggesting in its place the TAVR registry administered by the ACC and FDA. **Dr. Zuckerman** added that FDA does not have the authority to mandate that a registry be independently maintained.

Dr. Allen suggested running a trial where patients serve as their own control, in which a patient is enrolled, required to meet goal-directed hypertension management, put on drugs with compliance ensured by drug testing. If the patient has good control, they can get the therapy, and then it can be seen whether or not the patient can come off of some of the medication after receiving RDN. They can then be followed over time. Patients who do not meet their goal can be considered resistant and receive RDN and be followed with that in mind. This would abate the necessity to randomize patients to not get the treatment.

Dr. Saville liked Dr. Allen's idea and added that behaviors can change even within a person, complicating the use of a patient as their own control. He added two points: first, that a single-arm study is most helpful for looking at long-term safety, and second, that propensity score matching in postmarket studies that include registries may provide a more comprehensive look at long-term safety data. **Dr. Lange** clarified that this is an observational study that includes people who have and have not received RDN therapy, which **Dr. Saville** confirmed.

Dr. Nachman considered that a substantial number of patients were excluded due to anatomic restrictions and wondered why they were not analyzed as a control group. **Dr. Yeh** contributed that Dr. Nachman's suggestion constitutes a violation of the positivity assumption — those patients were not eligible for RDN and are therefore an inappropriate control group.

Dr. Yeh further inquired of Dr. Zuckerman: to what extent does FDA collaborate with CMS to think about postmarket requirements for breakthrough devices? **Dr. Zuckerman** responded that this is outside the scope of the day's meeting.

Dr. Lange summarized the responses: subgroups should be pre-specified, and that specification will inform the sample/study sizes. A composite endpoint would be useful because the therapy has multiple effects. A registry and control groups are desirable. Both ambulatory and office blood pressures should be used. Dupplex ultrasound imaging in the postmarket environment is sufficient.

VOTE

Mr. Collier read the voting questions and read the responses into the record.

Voting Question One: 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?

The Panel responded unanimously affirmatively: 13 yes, 0 no, 0 abstain.

Voting Question Two: 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?

The Panel responded: 7 yes, 6 no, 0 abstain.

Voting Question Three: Do 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 Panel responded in a tie: 6 yes, 6 no, 1 abstain. Accordingly, Dr. Lange voted to break the tie and voted no

SUMMARY OF PANEL RECOMMENDATIONS

Dr. Allen voted yes for safety, no for efficacy, and no for risk-benefit. He found that even though the procedure is very safe, efficacy is mild at best and was only evaluated at three months. He cited the overall healthcare burden of devices as unchanged even in cases where devices are very safe.

Dr. Starling voted yes for safety, yes for efficacy, and yes for risk-benefit. He was comfortable with the bulk of the data presented and found the unmet need to warrant more tools.

Dr. Yeh voted yes for safety, yes for effectiveness, and yes for risk-benefit. He felt confident that the off-med trial demonstrated sufficient benefit. He called for the patients who experience the highest benefit to be identified, noting that approval will expedite the identification process.

Dr. Bates voted yes for safety, yes for efficacy, and yes for risk-benefit, noting that he was conflicted. Despite his doubts, he was convinced that the second-generation catheters have a clinical effect. He noted that it would be a shame to lose the breakthrough technology if it can be made to work better and if advantageous subgroups can be pinpointed.

Dr. Corriere voted yes for safety, yes for efficacy, and abstained from risk-benefit. He wanted to see identification of a more specific population that benefits highly and believed more selective labeling and indications for more severe hypertension are warranted.

Dr. Damluji voted yes for safety, yes for efficacy, and yes for risk-benefit, citing the data presented.

Dr. Hirshfeld voted yes for safety, yes for efficacy, and yes for risk-benefit, despite some doubts related to the magnitude of effectiveness.

Dr. Lockhart voted yes for safety, no for efficacy, and no for risk-benefit due to uncertainty in the data.

Dr. Saville voted yes for safety, no for efficacy, and no for risk-benefit, noting that he might change his efficacy vote if the indications were more specific. He would require additional randomized data to change his risk-benefit vote.

Dr. Somberg voted yes for safety, yes for efficacy, and yes on risk-benefit, predicated on the indications being modified to a more specific population reflective of the study population.

Dr. Wittes voted yes for safety, no for efficacy, and no for risk-benefit due to data she saw that said small or no effect and almost no difference in drug use over time.

Dr. Lewis voted yes for safety, no for efficacy, and no for risk-benefit due to one study that is negative and one that is minimally positive. If the device goes to market, he thought it may be a disservice to the public absent a definitive study that better defines the benefit. He worried about the lack of conclusions that will be drawn in the postmarket setting due to the small sample size experienced by each individual physician in practical use.

Dr. Nachman voted yes for safety, no for efficacy, and no for risk-benefit and cited the same reasons as Dr. Lewis. He noted that the procedure is invasive even if it is labelled as minimally-invasive. He worried about opening the gates to perform the procedure on many individuals despite only substantially helping a very small fraction.

Dr. Lange voted only on the last question to break the tie, voting no on risk-benefit. Had he voted on the other two, he would have voted yes for safety and no for efficacy due to lack of clarity in the indications. He cited his reasoning for the no on risk-benefit as due to the negative trial result in the on-med study.

CLOSING COMMENTS

Ms. Hessner voiced her thoughts as patient representative. She felt comfortable with the favorable risk profile. She was undecided about efficacy and risk-benefit, finding the risks to be equal to the benefits at this point in time.

Dr. Cetnarowski, as the industry representative, thanked the Panel for their thoughtful discussion and emphasized that there was a difference between breakthrough device approval and full-fledged approval. He expressed hopes to see the stimulating discussions for this technology continue.

Mr. Brian Pullin from FDA gave the FDA summary at Dr. Zuckerman's request. He thanked Medtronic for their participation and responses to the Panel's many inquiries. He thanked the panelists for their insightful discussion and thanked Dr. Lange for his leadership.

Dr. Lange expressed his appreciation to Medtronic and thanked FDA for their work and for permitting the discussions. He thanked Dr. Zuckerman for his leadership.

Dr. Mauri thanked the Panel for their candid discussion on behalf of Medtronic, stating that Medtronic looks forward to working with FDA to address the Panel's comments.

ADJOURNMENT

Dr. Lange adjourned the meeting.

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

Richard A Lange, MD, MBA

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Date: 2023.10.23 06:44:56 -06'00'

Richard Lange, MD, MBA
Chairperson

Summary Prepared By:

Jennifer Solis
Translation Excellence
3300 South Parker Road, Suite 200
Aurora, CO 80014
(720-325-0459)
September 11, 2023

I certify that I attended this meeting on August 23, 2023 and that these minutes accurately reflect what transpired

Jarrod W. Collier -S

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

Jarrod Collier, MS
Designated Federal Officer