24 Hour Summary of the Circulatory System Devices Panel Meeting
August 23, 2023

Introduction:

The Circulatory System Devices Panel of the Medical Devices Advisory Committee for the Food and Drug Administration met on August 23, 2023, to discuss, make recommendations, and vote on the benefit-risk profile of the Medtronic Symplicity Spyral Renal Denervation System, including whether the device demonstrates a reasonable assurance of safety and effectiveness in the treatment of hypertension patients considering the proposed indications for use.

The sponsor has proposed the following indications for use:

> The Symplicity Spyral multielectrode 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 antihypertensive medications or in patients in whom blood pressure lowering therapy is poorly tolerated.

Panel Deliberations/FDA Questions:

QUESTION #1: Acute and midterm procedural and device safety profile.

The panel agreed that the device appears to be safe, with a low procedural complication rate associated with transfemoral access and a low renal artery damage rate. The panel agreed with the sponsor's methodology used for post-rfRDN renal imaging involving both direct and indirect assessment with ultrasound and with emphasis on training; however, they noted the unexpected lack of quality for computerized tomography (CT) and magnetic resonance angiography (MRA) imaging. The panel emphasized the need for high quality imaging performed by accredited laboratories with accompanying verification of their imaging ability.

QUESTION #2: Blood pressure (BP) measurement method

The panel agreed that ABPM is the gold standard method of BP measurement due to reduced variability and its greater prognostic value for cardiovascular events. No panelists thought that OBPM alone would be sufficient; however collecting both ABPM and OBPM remains of interest. The panel emphasized the importance of collecting 24-hour ABPM as compared to the use of daytime ABPM measurements only due to nighttime dipping. The panel also believed that home blood pressure measurement transmitted telephonically can provide additional supplemental information.

QUESTION #3: Magnitude of blood pressure reduction in the clinical trials.

The panel agreed that the observed difference (effect size) from the HTN-OFF study is modest and is less than the effect of one medication. The panel noted that the sensitivity analyses and additional analyses for BP reductions for ABPM and OBPM trended in the same direction. Some panelists expressed that focusing on the between-group difference in BP reduction overlooks the granularity of the data, and noted that the distribution of BP reduction, which showed that more patients benefited in the rfRDN group, is also valuable.

The panel noted that the HTN-ON study did not meet its primary effectiveness endpoint and that while multiple confounding factors make interpretation difficult, it is unclear if the confounders alone are responsible for the negative result. Some panelists expressed a concern with the number of subjects in the rfRDN and Sham arms that changed their medications between treatment at 6 months when medications were supposed to remain stable. The panel noted that while ambulatory systolic BP (SBP) was similar in the HTN-ON Expansion cohort, the office SBP showed a difference, and the panel was uncertain of the meaning for the discordant results.

QUESTION #4: Subgroup Analyses in HTN-ON considering US vs OUS and US Black Americans

Overall, the panel was unable to conclude whether or not there were differences in BP responses in these subgroups based on limitations in lack of statistical power due to small subgroup sizes, the lack of adjustment for multiplicity, and potential differences in medications changes between the groups. The panel emphasized the need to further study these subgroups.

QUESTION #5: Whether rfRDN provides a durable reduction in blood pressure, considering changes in longer-term blood pressure and changes in antihypertensive medications.

The panel recognized that the studies were not designed to assess durability, and most panelists were either uncertain about durability or considered the treatment effect not durable based on the data available. Limitations for interpreting the longer-term blood pressure changes included medication changes beyond the primary endpoint assessment timepoint and limited sample sizes due to missing data and crossover. The panelists were uncertain whether the small differences in medications between rfRDN and Sham were clinically meaningful when the between-group BP reductions were similar at later timepoints.

QUESTION #6: Degree of importance that the patient preference study results should be given when considering supplemental benefit-risk assessment information

Panelists appreciated the patient preference information (PPI) for consideration and how well the PPI study was designed and conducted. Panelists noted that patients were willing to accept the risks of the interventional procedure for a potential reduction in BP and reduced reliance on pills. The panel agreed that the PPI is important, and that it is one component of the overall benefit-risk assessment for this device. The panel emphasized the need for patients to have accurate information and be adequately informed about the device's effectiveness and risks, so that patients can make informed treatment decisions.

QUESTION #7: Indications for Use Statement

The panelists recommended substantial changes to the proposed indications statement. The panel expressed concern that the terms 'uncontrolled HTN' and "poorly tolerated" were not defined in the indication. The panel agreed that the indication should reflect patient population enrolled in the clinical trial, which they do not agree represented uncontrolled hypertension despite medication use or population for which medications are poorly tolerated. The panel noted that the device may have a role in mild to moderate hypertension, but that the effect size was modest in this population. Most panel members agreed that the device would not be appropriate as first line treatment, but several believed it should be a treatment option. Panel members suggested that the indications for use could include blood pressures to define the type of hypertension and identify the expected magnitude of effect.

QUESTION #8: Labeling Recommendations (post-treatment renal imaging and general)

The majority of the panel agreed that the device labeling should not require post-treatment renal imaging. The panel agreed that duplex ultrasound could be used as an initial screening tool, while other modalities could be used if abnormalities are detected. The panel also recommended that the labeling clearly indicate the populations that were not included in the clinical studies and cohorts with limited data such as African Americans, females, elderly, patients with diabetes, congestive heart failure, cardiovascular/cerebrovascular disease, and p[patients with impaired renal function (eGFR < 60mL/min)).

QUESTION #9: Benefit-Risk Profile

The panel indicated that the device demonstrated a small benefit, but that uncertainty remains regarding the magnitude of the benefit in a real-world population and durability of the treatment effect. A few panelists noted that size of the treatment effect differs in various subgroups, and although treatment responders (and non-responders) were not clearly identified, there may be some patient populations that could benefit.

QUESTION #10: Post Approval Study (PAS)

The panel discussed the need for a post-approval study to be designed with a sufficient sample size to enroll pre-specified subgroups (e.g., African Americans, US subjects) as well as evaluate study endpoints. The panel also discussed the utility of a composite endpoint which assesses variables including but not limited to: blood pressure, medications (number, type, dose), patient compliance, patient preference. The panel agreed that although a single-arm study can provide safety information, interpreting effectiveness would be difficult. They hypothesized possible comparators for the rfRDN treatment arm, including registries, patients as their own control, and patients excluded due to anatomy. However, the panel did not achieve consensus on a recommended comparative arm. The panel also continued to emphasize the use of ABPM and inclusion of OBPM. Regarding follow-up imaging, they panel agreed with a 12 month timeframe, the use of duplex ultrasound as initial imaging with further evaluation by other modalities if abnormalities or stenoses are detected.

VOTE:

The Panel voted on the safety, effectiveness, and benefit-risk profile of the Medtronic Symplicity Spyral Renal Denervation System.

Voting Question 1:
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 voted as follows:

- Yes: 13
- No: 0
- Abstain: 0

Voting Question 2:
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 voted as follows:

- Yes: 7
- No: 6
- Abstain: 0

Voting Question 3:
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 voted as follows:

- Yes: 6
- No: 7*
- Abstain: 1

*The Panel Chair broke the tie for this question with a vote of "No"

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Transcripts may be downloaded from:
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