

Panel Questions for the Advisory Committee Meeting for the Medtronic Symplicity Spiral rfRDN System – August 23, 2023

DISCUSSION QUESTIONS

Safety

1. The primary safety endpoint was a pooled analysis of composite major adverse events (MAEs) through 30 days and new renal artery stenosis (RAS, defined as a >70% diameter stenosis confirmed by angiography) through 6 months in the first 253 evaluable HTN-OFF and HTN-ON rfRDN-treated subjects. The primary safety event rate was 0.4% (1 event) 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 Cohorts subjects was 0.4% (2 events in 537 subjects) with a one-side upper 95% confidence interval of 1.2%.

Medtronic used protocol-driven duplex ultrasound (DUS) and implemented a site training program for initial screening of RAS. No potential stenoses were identified with first line DUS at 6 months using the threshold of >60% diameter stenosis (DS). However, DUS imaging quality is operator-dependent, lacks sensitivity to identify non-hemodynamically significant <70% DS, and the assessment of renal artery branches distal to the main artery is not commonly performed. Medtronic performed 12 months CTA or MRA on 206 rfRDN subjects. There were no subjects with a >70% DS lesion confirmed by angiography. Potential lesions with >50% DS were detected in 13 rfRDN subjects based on initial 12-month CTA or MRA imaging. Considering the results of the subsequent confirmatory imaging performed for these subjects, the per subject rate of a >50% DS could be as high as 2.9% to 3.9% at 12 months. The study protocols did not include renal imaging after 12 months. There were no clinically significant changes in eGFR or serum creatinine.

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

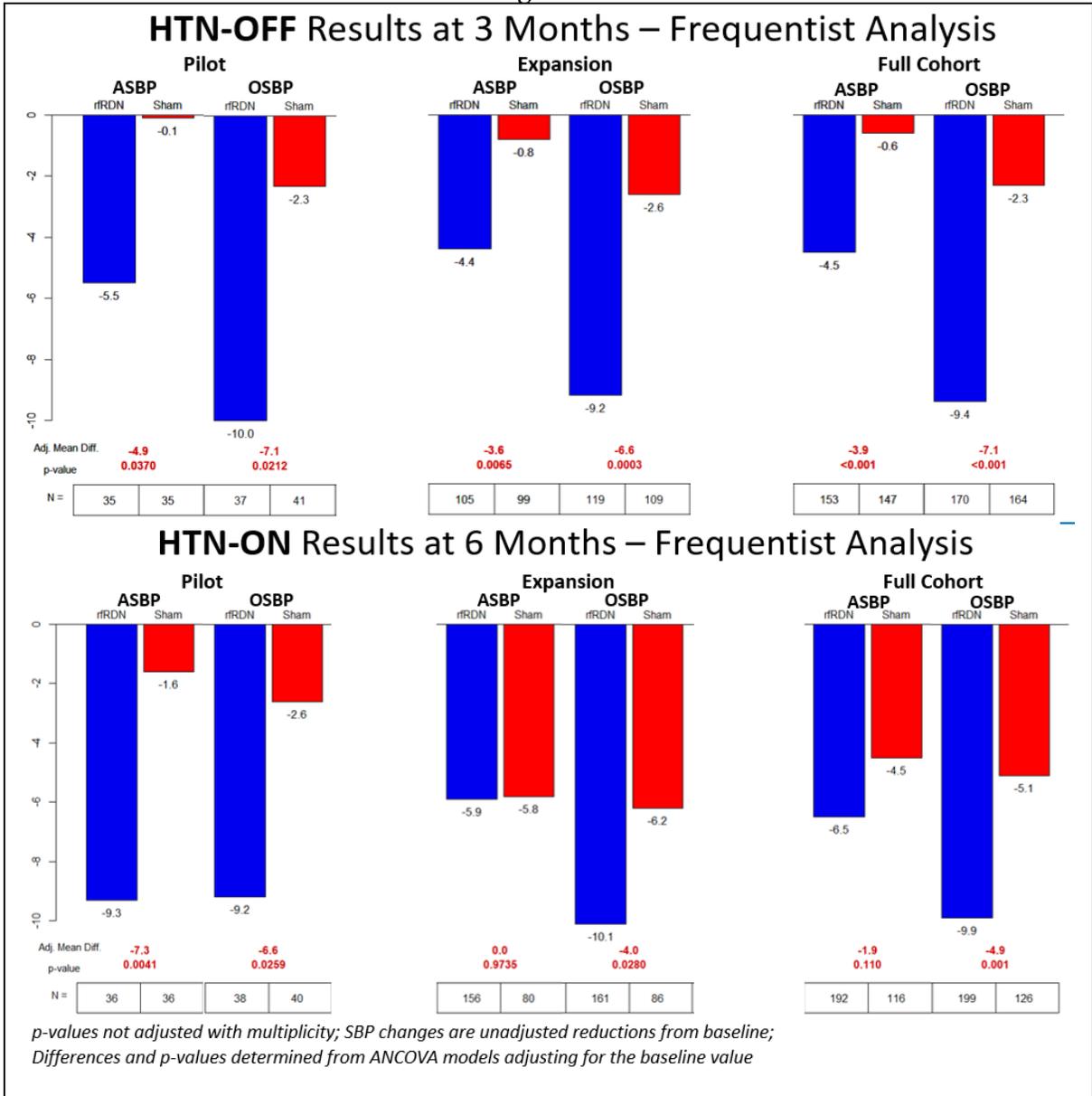
Effectiveness

2. *BP Measurement Method.* Data were presented using both ambulatory blood pressure measurement (ABPM) and office blood pressure measurement (OBPM). Most prior hypertension trials have used OBPM. However, ABPM has been shown to have greater prognostic value compared to OBPM and was identified as the preferable method at the 2018 Circulatory System Devices Advisory Panel Meeting. This may be due to the large number of measurements made for ABPM that are free from potential confounders (e.g., the white coat effect).

In HTN-OFF at 3 months (Figure 1), the 24-hour ambulatory systolic blood pressure (ASBP) and office systolic blood pressure (OSBP) results at 3 months followed similar trends, with statistically significant BP reductions favoring rfRDN over Sham (although the OSBP analysis was not adjusted for multiplicity). OSBP reductions were greater in magnitude vs. ASBP reduction in both rfRDN and Sham treatment groups.

In HTN-ON at 6 months (Figure 1), the 24-hour ASBP and OSBP reduction in the Pilot Cohorts and the OSBP reduction in the Expansion Cohort favored rfRDN over Sham. However, in the HTN-ON Expansion Cohort, the 24-hour ASBP reduction was similar between the rfRDN group and Sham group.

Figure 1



Please discuss the relative value of ABPM and OBPM in assessing changes in blood pressure in evaluating the effectiveness of rfRDN.

3. *Magnitude of BP reduction.* FDA and the Sponsor reviewed the discussions during the 2018 Circulatory System Devices Advisory Panel, and there is debate regarding the Panel’s opinion regarding the relative importance of absolute BP reduction vs. baseline (associated

with a specific treatment) compared with the relative BP reduction between treatment groups. In FDA's interpretation of the Panel's discussions, they considered a 5 mmHg difference in systolic blood pressure reduction (measured by ABPM) between treatment groups to be clinically significant.

In HTN-OFF, antihypertensive medications were withdrawn through 3 months post-rfRDN or a sham procedure, and the primary effectiveness endpoint was assessed at 3 months. In HTN-ON, subjects were maintained on a stable BP medication regimen for 6 months post-rfRDN or a sham procedure, and the primary effectiveness endpoint was assessed at 6 months.

The primary effectiveness endpoint was the difference in the mean reduction in 24-hour ambulatory systolic BP (ASBP) between rfRDN and Sham groups using a Bayesian power prior methodology.

In HTN-OFF, because of the similarity in the Pilot and Expansion cohort ASBP results (as shown in Figure 1), most of the Pilot Cohort data were used in the Bayesian analysis, and there was a statistically significant between-group difference of 3.9 mmHg favoring rfRDN vs. Sham; the primary effectiveness endpoint was met.

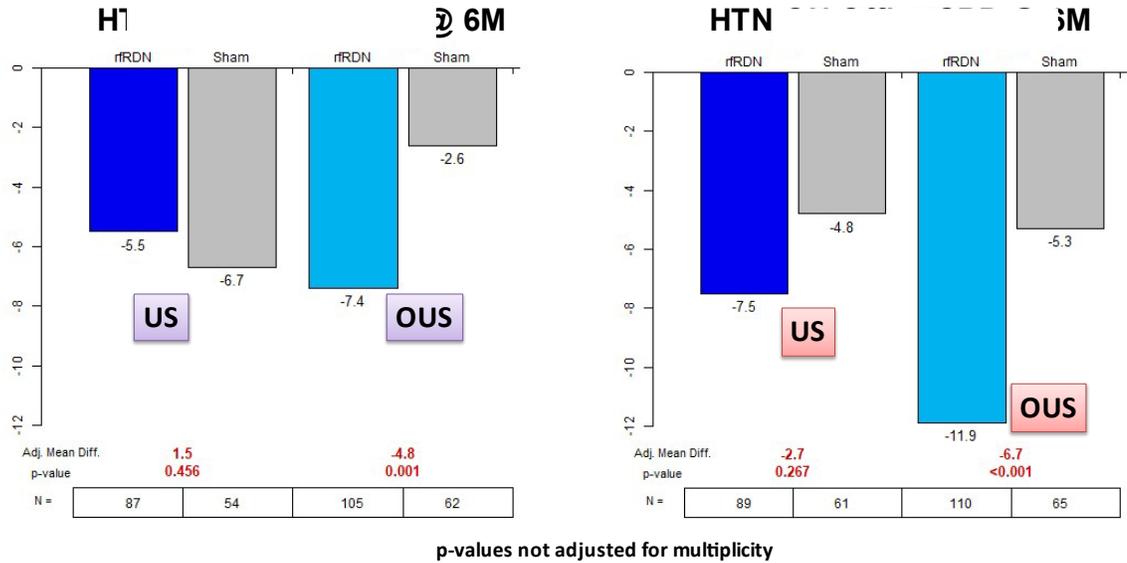
In HTN-ON, Pilot Cohort ASBP results were discordant with the Expansion Cohort ASBP results (as shown in Figure 1). Consequently, very little Pilot Cohort data were used in the Bayesian analysis, which demonstrated a between-group difference of only 0.03 mmHg; the primary effectiveness endpoint was not met. Medtronic noted potential confounders for the different outcomes between the HTN-ON Pilot and Expansion cohorts.

Please discuss:

- a. The clinical significance of the observed difference (effect size) in reducing 24-hour ASBP between the rfRDN and Sham groups in:
 - HTN-OFF
 - HTN-ON
 - The totality of the HTN-OFF and HTN-ON data
 - b. The pre-specified primary analyses used the Bayesian power prior approach. In HTN-ON, the Pilot Cohort data were heavily discounted in the Bayesian analysis, which showed a negligible ASBP reduction difference between the rfRDN and Sham groups. A frequentist analysis of the Full Cohort (pooled Pilot and Expansion Cohorts without discounting of the Pilot Cohort data) showed a between-group difference of 1.9 mmHg favoring rfRDN vs. Sham. Please discuss the clinical significance of the treatment effect in the Bayesian analysis compared to the Full Cohort frequentist analysis.
 - c. Please discuss the clinical significance of the absolute reduction of SBP from baseline in rfRDN subjects vs. the difference in reduction between rfRDN and Sham groups in evaluating the treatment effect for HTN-OFF and HTN-ON.
4. *Subgroup Analyses.* In HTN-ON, there were numerical differences in 24-hour SBP in US vs OUS subjects and in African Americans vs. US non-African Americans.

Geography. In HTN-ON at 6 months, US subjects (N=141) had a 1.5 mmHg reduction in 24-hour SBP in favor of the Sham group, and OUS subjects (N=167) had a 4.8 mmHg reduction in 24-hour SBP in favor of rfRDN (Figure 2).

Figure 2



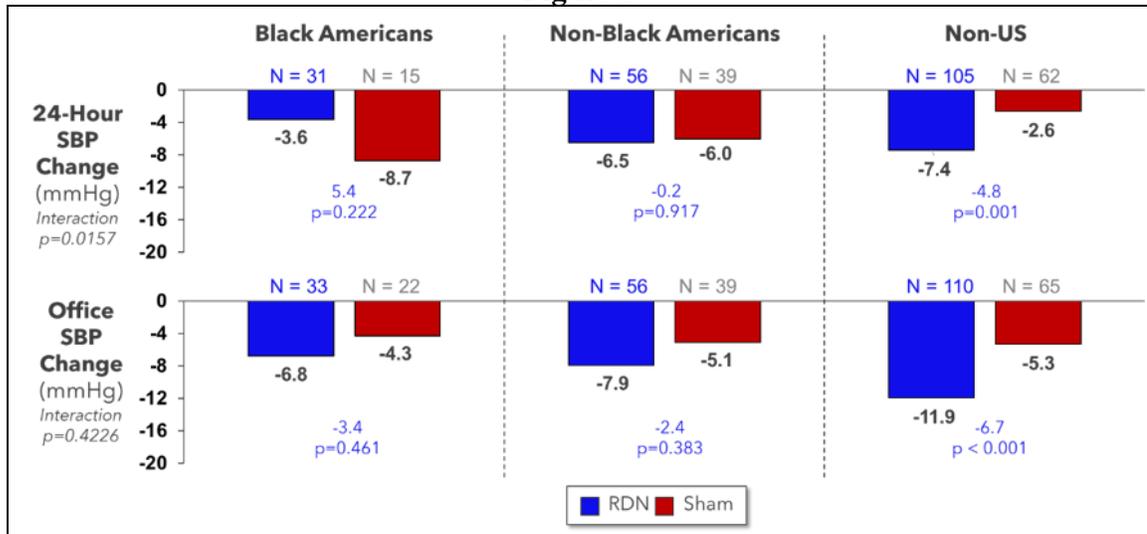
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The US Sham group had a significantly higher percentage of subjects who increased BP medication burden (37% vs 22% for rfRDN) as measured by Medication Index 1 (MI1). On average, Sham subjects increased BP medications by about 1/4 of 1 full medication dose vs. rfRDN subjects. The proportion of subjects who increased BP medications was generally similar in OUS rfRDN and Sham groups (15% and 18%, respectively). The BP medication use difference in the US may have led to a larger reduction in 24-hour SBP in the US Sham group.

Race. In HTN-ON at 6 months, Black Americans (N=46) in the Sham group had an 8.7 mmHg reduction in 24-hour SBP vs. a 3.6 mm Hg reduction in the rfRDN group (Figure 3). In contrast, for OSBP in Black Americans, the treatment difference was reversed; the rfRDN group had a 6.8 mmHg OSBP reduction vs. a 4.3 mm Hg reduction in the Sham. Group. In Black Americans in the Sham group, MI1 increased by 0.3 (corresponding to an average BP medication increase of 0.3 of 1 full medication dose), and MI1 was unchanged in rfRDN group Black Americans. Please note the small sample size of the Black American subgroup.

The directionality of the 24-hour SBP and OSBP reduction numerical trends for US non-Black Americans and non-US subjects were concordant (Figure 3).

Figure 3

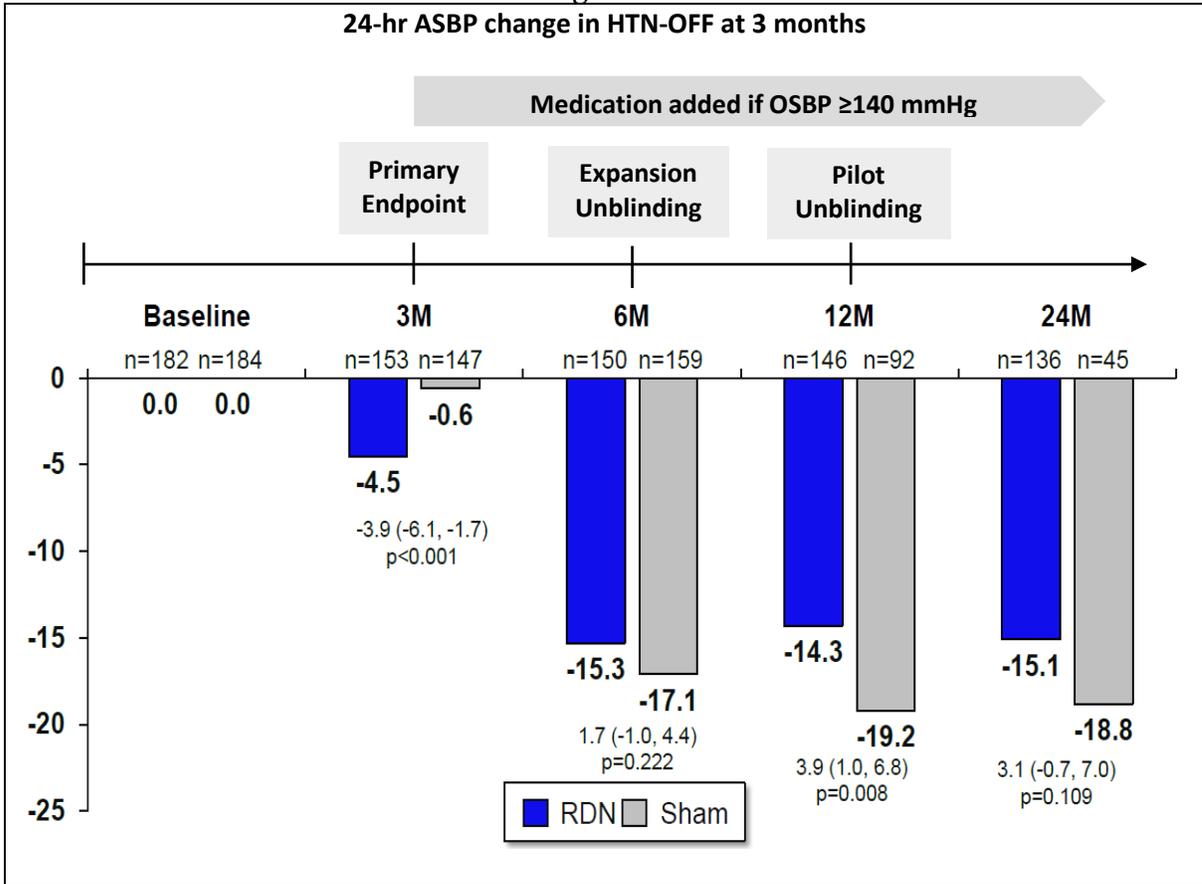


Please discuss the clinical significance of the HTN-ON discordant results between 24-hour SBP and OSBP results for rRDN vs. Sham treatment in the following groups and the generalizability of these results to the target US population:

- US and OUS patients; and
- US Black Americans

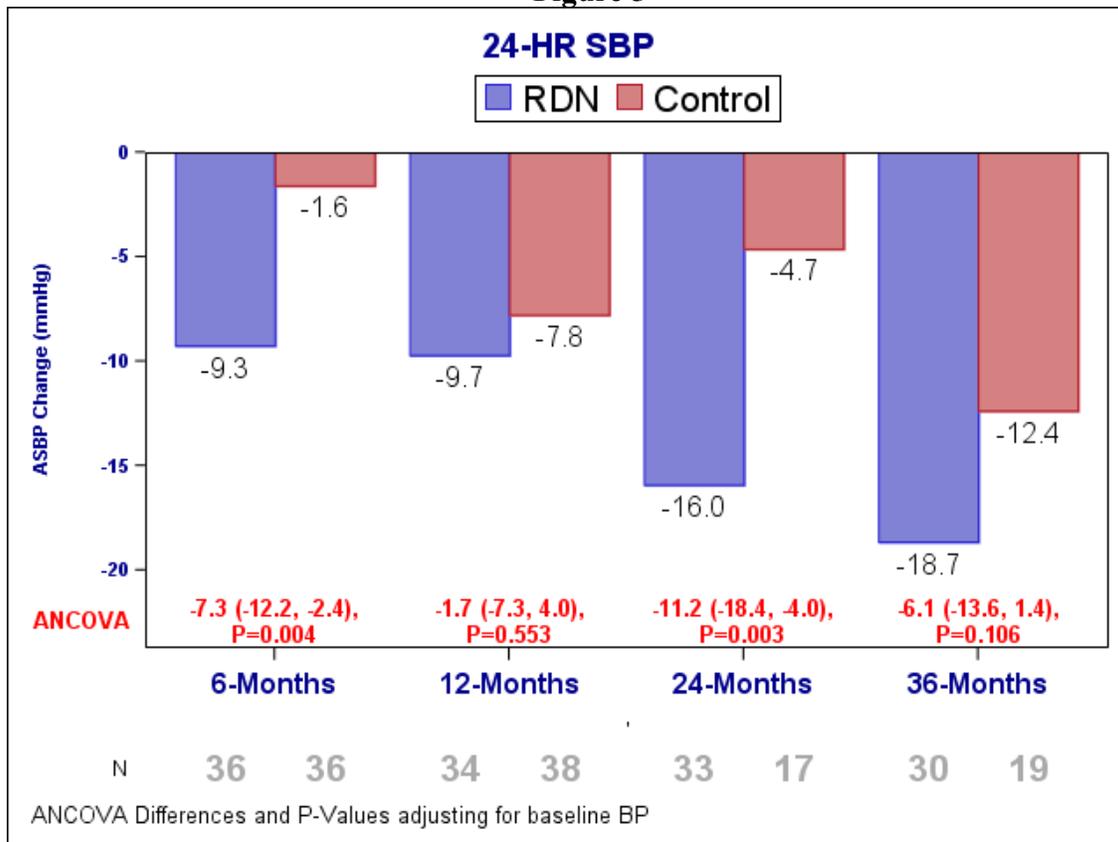
5. *Durability of effectiveness.* In HTN-OFF, in the rRDN group alone (Figure 4), the 24 hour ASBP reduction vs. baseline increased from 4.5 mmHg at 3 months to 15.3 mm Hg at 6 months, and the BP reduction was sustained through 24 months. However, when considering BP changes over time in RDN subjects vs. Sham subjects, the statistically significant 3.9 mmHg ASBP reduction difference at 3 months favoring rRDN was not seen at 6 or 12 months, although rRDN subjects had a lower medication burden as measured by Medication Index 1 and 2, which on average corresponds to 1/4 of 1 full BP medication dose.

Figure 4



Data beyond 6 months are not available for the HTN-ON Full Cohort. In the HTN-ON Pilot Cohort, sustained decreases in 24-hour SBP are noted at 12, 24, and 36 months (Figure 5). The number of medications was similar between Pilot Cohort rRDN and Sham groups during longer-term follow-up.

Figure 5



Limitations with interpreting longer-term data include the addition of BP medications, unblinding of subjects to their treatment assignment, small sample sizes (particularly for HTN-ON that was limited to the Pilot cohort with imputed data), and crossover of Sham subjects to rfRDN (which further reduced the control group sample size).

Please discuss the strengths and limitations of longer-term BP data in patients treated with rfRDN including:

- Whether rfRDN provides a durable reduction in BP;
- The clinical significance of longer-term BP changes in rfRDN subjects vs. Sham subjects; and
- The clinical significance of BP medication differences between rfRDN subjects and Sham subjects

Patient Preference Study

6. Medtronic conducted a patient preference study using a discrete choice experiment with 400 patients to ascertain preferences for rfRDN procedure compared to pills only. The study aligned with the CDRH PPI guidance document “Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and De Novo Requests, and Inclusion in Decision Summaries and Device Labeling.” The results suggest that between 15.1% - 30.9% of patients would select a RDN system intervention. Please discuss the degree of importance that the patient preference study results should be given when considering supplemental benefit-risk assessment information.

Labeling

7. *Indications for Use Statement.* In the clinical trial, the sponsor evaluated subjects with mild to moderate uncontrolled HTN in HTN-OFF and more severe uncontrolled HTN in HTN-ON, as defined in the table below.

	HTN-OFF	HTN-ON
Sample Size	Pilot: 38 rfRDN: 42 Sham Expansion: 144 rfRDN: 142 Sham	Pilot: 38 rfRDN: 42 Sham Expansion: 168 rfRDN: 89 Sham
OBP	SBP \geq 150 mmHg and $<$ 180 mmHg DBP \geq 90 mmHg	
ABMP ¹	24-hour SBP \geq 140 mmHg and $<$ 170 mmHg	
Medication	Willing to discontinue current antihypertensive medications at Screening Visit 1 through the three-month post-procedure visit	On 1-3 meds of at least 50% max dose; stable for \geq 6 weeks

Proposed indications for use statement:

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.

- a. Please discuss whether the available clinical data support the proposed indications for use.
 - b. Please discuss whether the phrase “despite the use of anti-hypertensive medications or in patients in whom blood pressure lowering therapy is poorly tolerated” should be modified or further defined. If modifications are needed, please discuss alternate language.
8. Please discuss whether labeling should contain recommendations for post-rfRDN renal artery imaging, and if recommended, please discuss labeling language to be included. Please identify any other labeling recommendations.

Benefit/Risk

9. 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.

Post-market Study

10. MDT has proposed a postmarket registry study that will continue to follow subjects in HTN-OFF and HTN-ON through 5 years and the AFFIRM continued access study with enrollment of up to 1200 subjects. This study will collect ambulatory and office BP, procedural results, medication burden, TTR, and proportion of subjects requiring repeat RDN. Medtronic plans pre-specified analyses for subjects with isolated systolic HTN, chronic kidney disease, and diabetes mellitus type 2.

- a. Please comment on the sample size and proposed endpoints.
- b. Please discuss whether sample sizes for additional subgroups or diverse patient cohorts subgroups should be prespecified and evaluated in the post-approval study.
- c. Please discuss the strengths and limitations of a single arm study design for the post-approval study.
- d. Please discuss the adequacy of 12-month imaging performed by either DUS, CTA, or MRA in the post-approval study to confirm long-term rFRDN safety.