Medtronic News

SPYRAL HTN-ON MED study demonstrates meaningful clinical benefits consistent with other SPYRAL HTN renal denervation trials

DUBLIN and CHICAGO, Nov. 7, 2022 /PRNewswire/ -- Medtronic plc (NYSE:MDT), a global leader in healthcare technology, today announced the six-month results from the full cohort of the SPYRAL HTN-ON MED clinical trial. The data were presented today as Late-Breaking Clinical Science at the American Heart Association (AHA) Scientific Sessions 2022. With this news, Medtronic has submitted the final module of the Symplicity Spyral™ Premarket Approval (PMA) package to the U.S. Food and Drug Administration (FDA) for review and approval.

Subjects who were prescribed antihypertensive medications and were treated with the Medtronic Symplicity Spyral Renal Denervation (RDN) System had a statistically significant and clinically meaningful reduction in office-based systolic blood pressure (OSBP), a key secondary endpoint, compared to subjects in the sham control group. However, in the primary endpoint, RDN did not demonstrate a statistically significant reduction in 24-hour ambulatory systolic blood pressure (ABPM) due to increased medications in the sham control group and the potential impacts of the Covid-19 pandemic on the clinical trial environment. The study also included Win Ratio, a pre-specified secondary endpoint that combines reduction in blood pressure with reduction in medication burden, which enables assessment of the overall beneficial effect of RDN. The Win Ratio demonstrated significance in favor of RDN versus a sham procedure. Finally, the study met its primary safety endpoint, with a low incidence of procedure-related and clinical adverse events.

"The ON MED study demonstrated significant reductions in office-based blood pressure, the most commonly used measure in clinical practice. Additionally, we saw reductions in absolute blood pressure that were consistent with earlier RDN studies," said David Kandzari, M.D., chief, Piedmont Heart Institute and Cardiovascular Services and SPYRAL HTN-ON MED lead principal investigator. "Surprisingly, 24-hour ABPM declined with RDN but did not differ from the sham group, and the primary endpoint was not met. More than 80% of patients in the ON MED expansion group experienced follow up during the Covid-19 pandemic. Compared with patients enrolled before the pandemic, significant differences in baseline 24-hour ABPM were observed that may reflect changes in patient behavior and lifestyle during the pandemic.[1,2,3] Additionally, patients treated with the sham procedure increased the amount of medication they were taking compared to those treated with RDN. These factors likely contributed to the smaller than expected differences in ABPM."

SPYRAL HTN-ON MED is a global, randomized, sham-controlled trial investigating the blood pressure lowering effect and safety of RDN with the radiofrequency (RF)-based Symplicity Spyral RDN system in hypertensive patients who have been prescribed up to three anti-hypertensive medications, including diuretics, calcium channel blockers, ACE/ARB inhibitors or beta blockers. A total of 337 patients with uncontrolled hypertension were enrolled at 42 sites across the United States, Europe, Japan, Australia, and Canada, and were randomized 2:1 to RDN (n=205) versus sham control (n=132). Results were as follows:

- The primary Bayesian efficacy endpoint of 24-hr systolic ABPM reduction was not met, with a 51% probability of superiority for the RDN group versus those who received a sham control procedure. However, nighttime systolic ABPM reduction was statistically significant.
    - 6.5 mmHg 24-hr systolic ABPM reduction in the RDN group versus 4.5 mmHg in the control group (treatment difference of -1.9 mmHg, p=0.119)
    - 6.7 mmHg nighttime systolic ABPM reduction in the RDN group versus 3.0 mmHg in the control group (treatment difference of -3.7 mmHg, p=0.01)
- The study met the prespecified secondary endpoint, which was the change in OSBP from baseline to six-

month follow-up between the RDN group (n=199) and the sham control group (n=126).

  - Statistically significant 9.9 mmHg OSBP reductions in the RDN group versus a 4.9 mmHg reduction in the sham control group (treatment difference of -4.9 mmHg, p=0.001)

- The study met the primary safety endpoint, evaluating major adverse events at one-month post-procedure, and renal artery stenosis at six-months, pooled across the SPYRAL HTN-ON and OFF MED studies (p<0.001)
  - RDN demonstrated a low incidence of procedure-related and clinical adverse events at six-months in the SPYRAL HTN-ON MED study specifically.
- The Win Ratio demonstrated significance in favor of RDN versus a sham procedure (p=0.005).
- Overall burden of medications was higher in the sham control group at six-months (p=0.04).

"Renal denervation lowers blood pressure and requires less medication for patients with hypertension," said Laura Mauri, M.D., chief scientific, medical, and regulatory officer at Medtronic. "It is also a safe procedure. In this study specifically, RDN met both the safety endpoint for this trial, as well as the overall safety endpoint across the SPYRAL HTN ON and OFF MED studies."

The SPYRAL HTN-ON MED Trial[4] is a part of the Medtronic SPYRAL HTN Global Clinical Program – the most comprehensive clinical program studying RDN - including the SPYRAL HTN-OFF MED Pivotal Trial[5] and the currently-enrolling SPYRAL AFFIRM Study. Along with the real-world data from the Global SYMPLICITY Registry (GSR)[6], the Medtronic RDN program is backed by experience in more than 20,000 patients treated globally, studied in the presence and absence of medication, and in patients with high baseline cardiovascular risk.

"In addition to the consistent absolute blood pressure drops that we have demonstrated across trials, long-term data from key Medtronic studies— which were highlighted in two important publications this year in *The Lancet*[7,8]— have also demonstrated the durability and 'always on' effect of RDN," said Jason Weidman, senior vice president and president of the Coronary and Renal Denervation business, which is part of the Cardiovascular Portfolio at Medtronic. "The ON MED results presented today serve as an additional piece of our extensive compendium of safety and efficacy evidence on this procedure. With these results in hand, we submitted our PMA package to the FDA, which includes the totality of available evidence from the SPYRAL HTN clinical program. We are excited about the potential to bring this important procedure to millions of U.S. patients in need."

Approved for commercial use in more than 60 countries around the world, the Symplicity Spyral RDN system is limited to investigational use in the United States, Japan, and Canada.

Investor and Analyst Briefing

Medtronic will host a webcast of its Renal Denervation Investors and Analyst Briefing on Monday, November 7, 2022 from 5:00 p.m. to 6:00 p.m. CST. The webcast will feature remarks from Medtronic Coronary and Renal Denervation management, including comments on Medtronic's clinical data for the six-month primary results from the SPYRAL HTN-ON MED Randomized Trial. The live audio webcast can be accessed by clicking on the Investor Events link at investorrelations.medtronic.com on November 7. Within 24 hours of the webcast, a replay will be available on the same webpage. This event is not part of the official AHA 2022 program.

About Medtronic

Bold thinking. Bolder actions. We are Medtronic. Medtronic plc, headquartered in Dublin, Ireland, is the leading global healthcare technology company that boldly attacks the most challenging health problems facing humanity by searching out and finding solutions. Our Mission — to alleviate pain, restore health, and extend life

— unites a global team of 95,000+ passionate people across 150 countries. Our technologies and therapies treat 70 health conditions and include cardiac devices, surgical robotics, insulin pumps, surgical tools, patient monitoring systems, and more. Powered by our diverse knowledge, insatiable curiosity, and desire to help all those who need it, we deliver innovative technologies that transform the lives of two people every second, every hour, every day. Expect more from us as we empower insight-driven care, experiences that put people first, and better outcomes for our world. In everything we do, we are engineering the extraordinary. For more information on Medtronic (NYSE:MDT), visit www.Medtronic.com and follow @Medtronic on Twitter and LinkedIn.

Any forward-looking statements are subject to risks and uncertainties such as those described in Medtronic's periodic reports on file with the Securities and Exchange Commission. Actual results may differ materially from anticipated results.

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[1] Kreutz et al. *Journal of Hypertension* 2021

[2] Azzouzzi et al. *Int. J. Environ. Res. Public Health* 2022

[3] Laffin et al. *Circulation* 2021

[4] Kandzari D, Böhm M, Mahfoud F, et al. Effect of renal denervation on blood pressure in the presence of antihypertensive drugs: 6-month efficacy and safety results from the SPYRAL HTN-ON MED proof-of-concept randomised trial. *Lancet* 2018; 391: 2346-55.

[5] Böhm M, Kario K, Kandzari D et al. Efficacy of catheter-based renal denervation in the absence of antihypertensive medications (SPYRAL HTN-OFF MED Pivotal): a multicentre, randomised, sham-controlled trial. *Lancet* 2020; 395:1444–51.

[6] Mahfoud F, Mancia G, Schmieder R, et al. Renal denervation in high-risk patients with hypertension. *J Am Coll Cardiol* 2020; 75: 2879-88.

[7] Mahfoud, F, Kandzari, D, Weber, M et al. Long-term efficacy and safety of renal denervation in the presence of antihypertensive drugs (SPYRAL HTN-ON MED): a randomised, sham-controlled trial. *Lancet.* 2022; 399: 1401-1410.

[8] Bhatt DL, Vaduganathan M, Kandzari DE, Long-term outcomes after catheter-based renal artery denervation for resistant hypertension: final follow-up of the randomised SYMPLICITY HTN-3 Trial. *Lancet.* 2022; (published online Sept 18.).

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