Medtronic News

Medtronic Releases Results of SYMPLICITY HTN-3

Medtronic Commits to Further Clinical Investigation and Determining Path Forward for Next U.S. IDE with FDA

MINNEAPOLIS and WASHINGTON, DC - March 29, 2014 - Medtronic, Inc. (NYSE: MDT) today announced the full results of the SYMPLICITY HTN-3 clinical trial, which were presented today in late-breaking session at the 63rd Scientific Sessions of the American College of Cardiology (ACC) and published simultaneously in *The New England Journal of Medicine*. SYMPLICITY HTN-3, the first and only blinded, randomized, sham controlled study of renal denervation for treatment-resistant hypertension, met its primary safety endpoint but did not meet its primary or secondary efficacy endpoints. In the United States, the Symplicity renal denervation system is available for investigational use only.

The primary efficacy endpoint was the comparison of in office systolic blood pressure (SBP) change (from baseline to 6 month follow-up) between the renal denervation arm (n=353) and the control arm (n=171). The result was a statistically non-significant difference of 2.39 mm Hg [95 percent confidence interval (CI): -2.12 to 6.89, *p*=0.26], with a SBP reduction of 14.1 mm Hg in the renal denervation arm vs. 11.7 mm Hg reduction in the control arm.

The secondary endpoint was the comparison of SBP change (from baseline to 6 month follow-up) in mean 24-hour ambulatory blood pressure monitor (ABPM) between the renal denervation arm and the control arm. The result was a statistically non-significant difference of 1.96 mm Hg, [95 percent CI, -1.06 to 4.97, *p*=0.98], with a SBP reduction of 6.8 mm Hg in the renal denervation arm vs. 4.8 mm Hg reduction in the control arm.

SYMPLICITY HTN-3 met the primary safety endpoint, with a rate of major adverse events of 1.4 percent (upper 95 percent confidence bound 2.9 percent) in the renal denervation arm, which was significantly ($p<0.001$) less than the pre-specified objective performance criterion of 9.8 percent. The rate of major adverse events at six months, was 4.0 percent in the renal denervation arm and 5.8 percent in the control arm ($p = 0.37$). These results are consistent with the safety profile shown in all other Symplicity system trials. The Symplicity renal denervation system is the only renal denervation technology to show a safety profile demonstrated through three years.

"Based on our analysis of the SYMPLICITY HTN-3 data, we are considering many factors that may have contributed to the observed efficacy results beyond the employment of a more rigorous trial design," said Rick Kuntz, M.D., chief scientific officer, Medtronic. "There are several differences between the SYMPLICITY studies, including the populations studied, required medication dosing, patient behaviors in terms of lifestyle and drug adherence, and potential for procedural variability. We are evaluating the contributions of these potential factors, which are hypothesis-generating and will guide us in determining the path forward with FDA."

SYMPLICITY HTN-3 screened 1,441 patients and randomized 535 (37 percent) treatment-resistant hypertension patients with office SBP >=160 mm Hg at 88 U.S. medical centers. On initial screening, patients were required to be on at least three antihypertensive medications at maximally tolerated doses, one of which had to be a diuretic. There could have been no medication changes in the two weeks prior to enrollment and then randomization and no plan for any changes in the next six months. Patients recorded their home SBP and kept a diary recording their adherence to medical therapy both prior to randomization and at their six-month follow-up. Changes to antihypertensive medication were not allowed during the 6-month follow up period unless clinically necessary. Patients with 24-hour mean ABPM less than 135 mm Hg were excluded to screen for potential "white coat" hypertension. Of the 535 patients, nearly 70 percent had been treated for an average of ten years for uncontrolled hypertension according to standard of care.

Patients were blinded as to whether they actually received the full denervation procedure (treatment arm) or only renal

angiography (sham control arm). Clinicians assessing blood pressure were also blinded to the treatment received by patients. A blinding index was calculated at discharge and at six months and proved the effectiveness of blinding.

"While the primary efficacy endpoint was not met with this study design in these patients, SYMPLICITY HTN-3 did affirm the safety of the Symplicity renal denervation system seen in previous clinical studies," said Deepak L. Bhatt, M.D., M.P.H., executive director of interventional cardiovascular programs, Brigham and Women's Hospital Heart and Vascular Center, professor of Medicine at Harvard Medical School, and co-principal investigator. "This was a rigorously conducted trial that importantly featured a sham control and blinding of the study subjects and study team members. Unfortunately, it is not possible to determine definitively whether this trial demonstrated the failure of renal denervation to significantly reduce blood pressure or if there was a failure to achieve adequate renal denervation in these patients. Further investigation of renal denervation seems warranted."

Despite the existence of safe and effective pharmacologic therapies, uncontrolled hypertension remains highly prevalent and extremely difficult to manage with up to two-thirds of hypertensive patients remaining at higher risk for myocardial infarction, stroke and death. Because of widespread non-adherence or intolerance to complex pharmacologic regimens, the clinical need for alternative therapeutic options remains unmet.

"SYMPLICITY HTN-3 is a rigorously conducted and well-designed renal denervation clinical trial. Moving forward, it will be important to reconcile the results of SYMPLICITY HTN-3, a tightly controlled trial, with findings from the real-world Global SYMPLICITY Registry, due to differences between the two trials, including requirement for maximum tolerated medications, population differences, close supervision of patients, and multiple touch points of patients in a tertiary care setting," said Michael Böhm, M.D., Ph.D., chairman, Department of Internal Medicine, University of Saarland, Homburg/Saar, Germany and Global SYMPLICITY Registry co-chair. Six-month analysis from the first 1,000 patients enrolled in the Global SYMPLICITY Registry will be presented in a late-breaking clinical trial session during ACC.14 on Sunday, March 30, 2014.

While SYMPLICITY HTN-3 patient follow-up will continue as planned out to five years, Medtronic recently asked an independent panel of expert physicians and researchers to review the findings and make a recommendation about the future of the company's global renal denervation hypertension program.

"Based on the unique nature of these findings and support from the independent panel that additional research be considered to better understand the effects of the Symplicity technology for renal denervation, we remain convinced that resistant hypertension is a large unmet medical need and renal denervation remains a promising opportunity," said Nina Goodheart, vice president, general manager, Renal Denervation, Medtronic.

In the short-term, Medtronic has made the following decisions, which have been affirmed by the independent panel of experts:

- Medtronic will continue to provide access to the Symplicity system in countries where it has regulatory approval and will continue to support a global hypertension clinical program
- Based on our detailed analysis of SYMPLICITY HTN-3, we believe further clinical investigation is warranted; Medtronic will determine the optimal path forward, along with FDA, for the next U.S. IDE
- Medtronic will continue to enroll patients in the Global SYMPLICITY Registry
- In light of the results of the SYMPLICITY HTN-3 trial, Medtronic will discontinue the already suspended SYMPLICITY HTN-4 trial
- Medtronic will consult with local regulatory bodies to determine the future of the HTN-Japan and HTN-India clinical studies
- Medtronic will continue to pursue its studies in other disease states, including atrial fibrillation, chronic kidney disease, heart failure, etc.

About the Symplicity Renal Denervation System

The Symplicity renal denervation system consists of a flexible catheter and proprietary generator. In an endovascular procedure, the physician inserts the small, flexible Symplicity catheter into the femoral artery in the upper thigh and threads it

into both renal arteries in turn. Once the catheter tip is in place within the renal artery, the Symplicity generator is activated to deliver a controlled, low-power radio-frequency (RF) energy routine according to a proprietary algorithm aiming to deactivate the surrounding renal nerves. This, in turn, is intended to reduce hyper-activation of the sympathetic nervous system, which is an established contributor to chronic hypertension.

In collaboration with leading clinicians, researchers and scientists, Medtronic offers the broadest range of innovative medical technology for the interventional and surgical treatment of cardiovascular diseases and cardiac arrhythmias. The company strives to offer products and services that deliver clinical and economic value to healthcare consumers and providers worldwide.

ABOUT MEDTRONIC
Medtronic, Inc. (www.medtronic.com), headquartered in Minneapolis, is the global leader in medical technology -- alleviating pain, restoring health and extending life for millions of people around the world.

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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Symplicity is a trademark of Medtronic Inc. and is registered in one or more countries of the world.

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