24 Hour Summary
Circulatory System Devices Panel
of the
Medical Devices Advisory Committee

GENERAL ISSUES MEETING RELATING TO
DEVICE BASED THERAPIES FOR HYPERTENSION
DECEMBER 5, 2018

Introduction:

The Circulatory System Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met on December 5, 2018 to discuss and make recommendations regarding issues relating to the emergence of medical devices, which aim to treat hypertension. Currently, clinical studies to evaluate the safety and effectiveness of these devices are progressing. FDA requested panel input regarding the potential indications and labeling for devices intended to treat hypertension and optimal study designs needed to evaluate the potential benefits and risks, while considering issues such as medication compliance, patient perspective, and appropriate study controls.

Panel Deliberations/FDA Questions:

Question 1: Indications and Labeling

The panel noted that it would be reasonable and prudent for clinical studies to evaluate a diverse set of hypertensive patients currently treated in US clinics, including those with resistant hypertension, Stage 2 hypertension, and drug naïve patients. However, many panel members expressed hesitance with including the drug naïve population and some believed that devices should be limited to those with resistant hypertension until additional evidence on safety and effectiveness is obtained. Overall, the panel agreed that only a subset of patients in future studies should be drug naïve, particularly those with more severe hypertension (i.e. Stage 2). The panel agreed that the approved indications should be based on the patient population evaluated in the clinical trial and the outcomes. As the ongoing clinical trials include medications, the future device indications can include the device therapy as an adjunct to medication. While the panel expressed less comfort with device-based therapies as a first-line indication, the panel noted that if clinical trial results demonstrate that a portion of patients achieve hypertension control with only the device, an indication as a first-line therapy may be appropriate. The panel noted that extrapolation of the relationship between reduction of blood pressure (BP) and cardiovascular (CV) outcomes, as shown with drugs, may not necessarily be exhibited for devices. To date, there is no data available to adequately evaluate the safety and effectiveness of devices as first-line or solo therapy. This was supported by data that the panel requested from the industry representatives showing that only 20-25% of patients have achieved BP control with device therapy alone. The panel suggested that the initial goal of a trial is to show that the device

can induce a reduction in BP. Thereafter, a study can assess if the reduction in BP can result in reduced CV events.

Additionally, the panel indicated that sub-analyses to evaluate differences across age, gender, ethnicity/race, and socioeconomic factors will be valuable to support clinical interpretation and treatment. These analyses should be incorporated into premarket and postmarket studies, keeping in mind the limited sample sizes available in the premarket trial(s). Additional analyses regarding the role of physician training and patients who may be responders would be valuable premarket.

The panel emphasized the need for evaluation of the effects of devices on long-term cardiovascular outcomes, especially as the panel members were uncertain whether the device effects would differ depending on the anatomical target and the device technology. The panel also emphasized the need for such analysis of cardiovascular outcomes using different population subgroups discussed above.

Question 2: Clinical Study Design

In general, the panel agreed that a sham as a trial control should be used whenever ethical and when the known risks are low. However, the panel noted that a sham may not be useful in certain situations when the trial subjects cannot be blinded. In general, the panel expressed concern with considering other control groups, such as a comparison between an experimental and approved device due to the difference in designs and treatment targets. The panel noted that a comparison with an approved device may be appropriate, but some panelists raised concerns regarding non-inferiority creep. Several panelists noted that evaluating the durability of the effectiveness (e.g., blood pressure reduction) would be valuable at one year and could be ascertained by withdrawing medication for a short period for both groups. However, the panel understood the limitations and challenges associated with a second withdrawal.

The panel agreed that both the on- and off-medication trials provided unique information to support a premarket application. In general, the panel did not support crossover before one year because of the potential challenges with interpreting data due to a lack of an adequate number of control patients. Additionally, the panel expressed concern that the crossover may limit the ability to assess the device effects on long-term CV outcomes.

Question 3: Safety Endpoints

To support a reasonable assurance of device safety, the panel indicated that both comparison between trial groups and against a performance goal would be appropriate as each provide unique information. This endpoint should be based on acute and chronic risks associated with the device and procedure. The panel discussed if it is appropriate to continue a clinical trial and let the device on the market if the number and/or severity of adverse events is high. The panel also stressed the importance of a control group in order to assess safety as well as to include close monitoring of the adverse events by the DSMB.

The nephrologists on the panel were asked to comment specifically on evaluation of the safety of renal nerve denervation therapies. Generally, they indicated that evaluation of renal artery stenosis (RAS) at 6 months in all patients, with additional imaging at a later timepoint (e.g., 12 months) for a subset of subjects, should be acceptable to support a premarket application. Acknowledging the lower sensitivity for the diagnosis of RAS with duplex ultrasound (DUS), the panel believed that DUS may be an adequate screening mechanism with an algorithm approach for subjects with suspected RAS, as this reflects current clinical practice. Moreover, the panel stated that while computed tomography or magnetic resonance angiography (CTA, MRA, respectively) may provide better visualization of the renal vasculature, there are risks associated with those modalities. However, the panel members acknowledged that as nephrologists, clinical experience is focused moreso on assessments of renal function than the radiographic detection of RAS. They explained that it remains unclear what level of RAS would be deemed clinically significant and as such, emphasized that measures of renal function are used in clinical practice and would continue to be important. The panel discussed the availability of biomarkers for RAS, but concluded that there may not be any validated markers currently in use. While the panel agreed that changes in eGFR should also be captured, they acknowledged that it is an insensitive measure of renal function. They added that following intra-patient slope of eGFR may provide additional information about the effect of the device on renal function. Regardless of the methodology, long-term data on the effect of devices on renal function is needed.

For carotid device therapies, the panel agreed that cerebrovascular imaging (MRI and/or CT) should be conducted prior to the procedure and at various timepoints after the procedure to evaluate for microembolic events. The panel noted that this subset should include both low- and high-risk patients.

Question 4: Effectiveness Endpoints

The panel unanimously agreed that reduction in BP is a clinically meaningful endpoint. While there was some disagreement about the exact degree of reduction that is considered to represent an effective treatment, the panel generally agreed that a reduction in 5-7mmHg using ambulatory blood pressure monitoring (ABPM) would be adequate to support a regulatory submission. The panel noted that this value may be similar to literature values which are typically reported based on office blood pressure (OBP), which is typically a few points higher than 24-hour ambulatory measurements. The panel suggested that a 5 mmHg reduction in BP using ABPM may correlate with a 10 mmHg reduction with OBP. Yet, the panel acknowledged that a better understanding about the relationship between BP readings obtained via ABPM and OBP would be helpful. In general, the panel expressed that they would prefer to evaluate a 12-month endpoint in BP reduction to support a premarket application, particularly since industry noted that there may be a delayed reduction in BP following renal denervation. The panel added that if a drug is approvable for a reduction of 5 mmHg, one may need to show a greater reduction for devices. However, they acknowledged that the FDA must also consider the benefit-risk profile of the device, patient perspectives, and whether the device is indicated as first line or adjunctive therapy.

The panel also noted that the following secondary endpoints would be clinically meaningful even if there is no significant reduction in 24-hour ABPM: reduction in the number, type, and dose of drugs while considering the blood pressure level; improvement in night-time ABPM; and the impact of patient demographics on BP reduction. The panel suggested that the evaluation of medication changes could provide value as a measure of quality of life in combination with patient-reported outcomes, including but not limited to the medication side effects experienced.

The panel indicated that hypothesis testing for simple superiority between the test and control groups is adequate for most devices, and super-superiority testing should be conducted if the risks are higher. Following the first approval, the panel noted that evaluation of non-inferiority against an approved device with a carefully chosen non-inferiority margin may be appropriate if the device designs and anatomical targets are similar.

The panel agreed that medication adherence should be evaluated in a least burdensome manner. Although they acknowledged that adherence rates may appear to be poor in the studies presented at the meeting by industry and in the literature, they explained that these results likely reflect real-world experience. In addition, the panel submitted that adherence rates would likely be comparable between treatment arms in a trial. However, the panel acknowledged that the interpretation of effectiveness data may be obscured if there are considerable differences in the adherence rates between the study arms. The panel added that using pill counts to assess adherence is not a reliable method; regardless of the method, the panel suggested that adherence be assessed with minimal invasiveness.

Question 5: Benefit-Risk Profile

The panel agreed that patient preference information and quality of life assessments would be valuable to further determine the potential benefits and risks for devices. Many panel members further emphasized the need for studies to capture the durability of the benefit as well as evaluate safety in the long term. The panel cautioned that as many of the critical study design evaluations have been suggested to be captured post-market, that the future design of post-market studies will be critical.

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