Circulatory System Devices Panel
General Issues Meeting:

Panel Questions

Division of Cardiovascular Devices
Office of Device Evaluation
Food and Drug Administration

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1A: Indications and Labeling

There is variability in the clinical etiology, hypertension definitions, and proposed patient demographics included in clinical studies of anti-hypertension devices. Please comment on the following:

i.   The patient population that should be evaluated in these studies (e.g., resistant hypertension, drug naïve).

1A: Indications and Labeling (cont.)

ii. Whether the indications for use and labeling for approved devices should only reflect the studied population or include a broader population that may potentially benefit. For example, potential strategies for stratification could include specification of blood pressure goals or degree of medical hypertension control.

iii. The potential for post-market evaluation, including new enrollment trials and registries, to study clinically meaningful sub-populations that are not well-represented in the pivotal study.

1B: Indications and Labeling

Antihypertensive drugs are currently indicated for management of hypertension as sole therapeutic agents and/or in combination with other antihypertensive drugs for more severe forms of hypertension. Please discuss the role for device-based therapies (e.g., first-line or adjunctive therapy) for patients with hypertension and how this should be reflected in the indications for use.

2A: Clinical Study Design

Please discuss the necessity of including a sham group, with specific attention to balancing the type of information gained versus the potential risks of a sham procedure. Additionally, please comment on whether other control groups should be considered, particularly after the initial marketing approval for an anti-hypertensive device.

2B: Clinical Study Design

Please discuss the value of the "ON" and "OFF" medication studies to support an approval determination. Please comment on whether both study designs are needed after the proof-of-concept for that technology has been established and the first such device is approved.

2C: Clinical Study Design

To support enrollment, one option is to allow crossover of control patients to be treated with the device. However, crossover may reduce the ability to evaluate longer-term safety and durability of effectiveness of the device in comparison to the control. Please discuss the potential consequences of patient crossover, including the appropriate crossover time point and any effects on data interpretability.

3A: Safety Endpoints

Although each device and treatment modality has its own specific risks, please identify the important adverse events that should be included as part of the primary and secondary safety endpoint(s), including the time of follow-up that balances capturing important safety information while maintaining a least burdensome approach. Please also consider any additional long-term safety endpoints that should be collected postmarket.

3A: Safety Endpoints (cont.)

As part of your response, please also discuss the timing and modality for imaging studies to detect new-onset RAS for renal-directed therapies, and for major cardiovascular or neurovascular events for devices that target the carotid anatomy. Currently, FDA is recommending imaging at 12 months to evaluate RAS for renal therapies and at least 12 months to evaluate ipsilateral carotid stenosis and cerebral ischemia for therapies that target the carotid anatomy.

3B: Safety Endpoints

Please discuss the appropriate statistical methodology to evaluate the frequency and severity of adverse events, such as non-inferiority between trial arms or establishing a performance goal for the safety endpoint.

4A: Effectiveness Endpoints

Currently, CDRH accepts a primary effectiveness endpoint of a reduction in ambulatory blood pressure for trials evaluating anti-HTN devices. Please discuss the acceptability of this surrogate endpoint and if the results from the series of prospective analyses discussed are applicable to device-based treatments such that a reduction in blood pressure may be sufficiently correlated to long-term cardiovascular measures. Please also identify any additional clinically important endpoints that should be collected premarket and/or during the post-market period.

4B: Effectiveness Endpoints

For trials in which reduction in blood pressure is the primary effectiveness endpoint, please address the following:

i. Please discuss what constitutes a clinically meaningful magnitude of blood pressure reduction and time period necessary to support the durability of the device performance to establish a reasonable assurance of effectiveness to support a marketing application, while considering the ability to discern the device effect from concurrent antihypertensive medication use (e.g., after washout at 2-3 months post-treatment, at 12 months).

4B: Effectiveness Endpoints (cont.)

ii. Given the clinically meaningful magnitude specified, please discuss the appropriate statistical comparison for effectiveness (e.g., super or simple superiority margin) as well as comment on how the recommendation comparisons would change after approval of the first anti-hypertension device (e.g., superiority or non-inferiority to a comparator device).

iii. If no significant blood pressure drop is determined, please comment on the value of decreased drug number, type, and dose, and indicate potential statistical analysis methods to consider the impact of medication usage.

4C: Effectiveness Endpoints

Considering observed issues with patient adherence to medication regimens, please discuss how adherence can be practically monitored during a device therapy trial. Please also discuss how to consider the impact of adherence in the final assessment of effectiveness.

5A: Benefit Risk Profile

Please identify additional factors important to patients (i.e., patient preference information (PPI), tolerable risks) and how these should be incorporated into the evaluation and review of anti-hypertension devices. As part of the discussion, please consider the burden of drug adherence and the impact of side effects associated with current antihypertensive medications. Please also identify important surveys or endpoints that may be used to capture PPI.

5B: Benefit Risk Profile

Please discuss any other issues that you think should be considered when designing and interpreting clinical studies involving evaluation of device-based hypertension treatment, particularly given the unique benefit-risk profile for each device type.