

Brief Summary of the Circulatory System Devices Panel Meeting – May 24, 2016

Introduction:

The Circulatory System Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met on May 24, 2016 to make recommendations and vote on information related to the premarket approval application regarding St. Jude Medical's AMPLATZER Patent Foramen Ovale (PFO) Occluder System.

The sponsor has proposed the following Indications for Use:

The AMPLATZER PFO Occluder is intended for percutaneous, transcatheter closure of a patent foramen ovale (PFO) to prevent recurrent ischemic stroke in patients who have had a cryptogenic stroke due to a presumed paradoxical embolism.

Panel Deliberations/FDA Questions:

Panel Question 1: Evaluation of the RESPECT Trial Primary Effectiveness Endpoint Analysis of the Intention-to-Treat (ITT) Population

The Panel recognized that the rate of recurrent strokes was numerically lower in patients treated with the PFO Occluder compared Medical Management but that statistical significance for the primary endpoint was not met. The Panel expressed concerns regarding the large amount of missing data due to subject withdrawals from the study (with disproportionately more patient dropouts in the Medical Management group versus the PFO Occluder group). There was also uncertainty about whether the numerically lower stroke rate observed in the PFO Occluder group was mostly due to the prevention of paradoxical embolism. The Panel noted that the lower observed stroke rate in the PFO Occluder group diminished with longer-term follow-up. Overall, the Panel believed that the AMPLATZER PFO Occluder may be effective in some patients with a cryptogenic stroke and PFO. However, the RESPECT trial results did not identify specific clinical or anatomic characteristics to help select patients most likely to benefit from implantation of the PFO Occluder.

Panel Question 2: RESPECT Primary Effectiveness Endpoint Supplementary Analyses

The Panel believed that the supplementary analyses did not provide important additional insights beyond the primary endpoint analysis of the ITT population due to missing data, potential selection bias, and other confounding factors.

Panel Question 3: Safety Events

The Panel acknowledged the rate of serious adverse events was low in the RESPECT trial. However, the Panel believed that the higher rates of deep venous thrombosis (DVT) and pulmonary embolism (PE) observed in the PFO Occluder group were concerning, and rates of these events should be included as safety endpoints in a post-approval study. There was a general

consensus that patients with a history of DVT or PE who are treated with the PFO Occluder should be maintained on anticoagulant therapy.

Panel Question 4: PFO Closure by the Device

The Panel believed that the rate of PFO closure by the Device was satisfactory in the RESPECT trial, but they acknowledged that it was unknown whether complete closure of the PFO was needed to reduce the risk of paradoxical embolism.

Panel Question 5: Proposed Indications for Use

The general consensus of the Panel was that the proposed Indications for Use statement was appropriate. However, the Panel recommended that the labeling include language describing the clinical evaluation of a cryptogenic stroke in patients who might be candidates for the PFO Occluder.

Panel Question 6: Labeling

The Panel agreed that modifications to the labeling are needed, particularly a statement regarding the need for adjunctive anti-thrombotic therapy in patients treated with the device. Additionally, the panel recommended that patient selection be carefully considered and defined within the labeling.

Panel Question 7: Benefit-Risk Assessment

The Panel agreed that the results of the RESPECT trial support a role of a PFO in the pathophysiology of some cases of cryptogenic ischemic stroke. However, implantation of the PFO Occluder provided only a modest reduction in the risk of recurrent stroke compared with medical therapy with the strength of the evidence limited by the primary effectiveness endpoint results and issues related to the execution of the trial. A majority of the Panel expressed that patients with cryptogenic stroke due to paradoxical embolism likely would benefit from this device, but that identifying these patients is challenging. The Panel agreed with FDA's recommendation that potential candidates for implantation with the PFO Occluder should undergo a careful evaluation by a neurologist and a cardiologist with expertise in the evaluation of cryptogenic stroke.

Panel Question 8: Proposed Post-Approval Study (PAS)

The Panel believed the proposed post-approval study objectives were acceptable and agreed with FDA's recommendation to include additional endpoints for atrial arrhythmias, DVT, PE and complete PFO closure. Additionally, the Panel recommended carefully monitoring of anti-thrombotic therapy during the post-approval study as well as quality of life assessments and participation by a neurologist and cardiologist in selecting patients for enrollment.

Vote:

The panel voted on the safety, effectiveness, and risk benefit ratio of the AMPLATZER™ PFO Occluder.

On Question 1, the panel voted 15-1 that the data show a reasonable assurance that the AMPLATZER™ PFO Occluder is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the panel voted 9-7 that there is reasonable assurance that the AMPLATZER™ PFO Occluder is effective for use in patients who meet the criteria specified in the proposed indication.

On Question 3, the panel voted 11-5 that the benefits of the AMPLATZER™ PFO Occluder outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

Several panelists noted that their positive vote reflected their belief that the PFO Occluder should be available for selected patients with a PFO and cryptogenic stroke with a recommendation that the final labeling help identify patients who could potentially benefit from the device.

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