Brief Summary of the Neurological Devices Panel
Meeting – April 17, 2015

Introduction:

The Neurological Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met on April 17, 2015 to discuss the current knowledge regarding the conduct of clinical studies and evaluation of clinical study data for endovascular devices for the treatment of aneurysms, including flow diverter technology. FDA convened this committee to seek expert opinion on scientific and clinical considerations relating to the study design and existing clinical studies for endovascular devices.

FDA Presentation

Drs. Jeffery Toy, Ph.D., Samuel Raben, Ph.D., Mohamad Bydon, M.D., and Laura Thompson, Ph.D., presented for FDA. They provided current knowledge on the scientific, clinical, and regulatory information on aneurysm treatment devices and considerations relating to their study design and existing clinical studies.

Open Public Hearing

The professional societies listed below registered for the Open Public Hearing segment of the meeting. Each agency listed below was given between 10 and 20 minutes to present before the Panel.

1. American Association of Neurological Surgeons, Congress of Neurological Surgeons, AANS/CNS Joint Section on Cerebrovascular Surgery
2. Covidien
3. Society of NeuroInterventional Surgery

Panel Deliberations/FDA Questions:

The deliberation of the Panel discussion included imaging modalities, different aneurysm subgroups (e.g. characteristics, location, size, morphology etc.), clinical trial designs, safety and effectiveness endpoints, and durability of treatment.

Panel Question 1:

*Please discuss what aspects of these aneurysm subgroups and any additional grouping of the characteristics should be considered when designing clinical trials of aneurysm treatment.*

The consensus of the Panel recommended that the following subgroups are important to consider when designing a clinical trial for aneurysm treatment: Anatomical location, morphology (wide-neck versus non-wide-neck, saccular versus fusiform versus dissecting), size, perforator vessel density, parent vessel characteristics, and patient characteristics (e.g. age, hypertension, smoking).
Panel Question 2:

*From a safety perspective does the panel believe that the adverse event rates for the follow groups are similar?*

The consensus of the Panel believed that the anterior circulation aneurysms are dissimilar to posterior circulation aneurysms. They believed that aneurysm sizes may be grouped as either Small and Medium or Large and Giant. The Panel also believed that aneurysms located in perforator rich regions of the vasculature are different than those located in perforator poor locations and patient characteristics play a further role in distinguishing aneurysms.

Panel Question 3:

*From an effectiveness perspective does the panel believe that the occlusion rates for the following groups are similar?*

The consensus of the Panel believed that aneurysm sizes may be grouped as either Small and Medium or Large and Giant. They believed that wide neck aneurysms should not be separate from non-wide neck aneurysms. The Panel also believed that saccular aneurysms will have a different occlusion rate from fusiform/dissecting and they believed parent characteristics could lead to a dissimilarity in occlusion rates between treated aneurysms.

Panel Question 4:

a. *Please describe under what circumstances a single arm trial with a performance goal would be an appropriate trial design?*

The Panel expressed concerns with performance goal trial designs. The Panel also believed the use of performance goal trial designs should be well justified, and that these trial designs should be reserved for situations where randomized control studies and/or cohort (comparator can be current or historical) studies are not feasible.

b. *Under what circumstances should a performance goal be chosen for a study*

If a performance goal trial design is warranted, the Panel believed that performance goals should be updated as new information becomes available and the Panel expressed concern with the following trial designs: A single performance goal for effectiveness for patients treated in the intracranial anterior circulation independent of other aneurysm characteristics (e.g., aneurysm size), A single performance goal for effectiveness for patients treated in the intracranial posterior circulation independent of other aneurysm characteristics (e.g., aneurysm size), A single performance goal for effectiveness that pertains to the complete neurovasculature independent of other aneurysm characteristics (e.g., aneurysm size).

Panel Question 5:

*Please describe under what circumstances a randomized controlled trial would be an appropriate trial?


The consensus of the Panel believed that randomized controlled trial should always be considered, however, when randomized control trials or cohort studies are not feasible, a performance goal study may also be considered. When designing a study the Panel recommended that the following be considered: Well defined questions, target populations, and focused studies upon specific aneurysm types, and multiple treatment arms.

Panel Question 6:
Please discuss the strengths and limitations of each scale below. In your response, please discuss the utility of using each scale as a primary study endpoint: Raymond Scale, Meyers Scale, Kamran Scale, Szikora Scale, Target Aneurysm Retreatment Rate

The consensus of the Panel supported the Raymond Scale and Target Aneurysm Retreatment Rate as appropriate effectiveness endpoints while they were less in favor with the Meyers, Kamran and Szikora Scales.

Panel Question 7:
Clinical outcome measures provide another method for assessing the safety and effectiveness of a device. FDA has identified the following:
Secondary Effectiveness Endpoints: Retreatment Rate, Recanalization, Change in modified Rankin Scale, Change in Raymond Scale, < 50% Stenosis, Aneurysm occlusions of 90% or 95%, Improvement in symptoms.
FDA also identified the following:
Secondary Safety Endpoints: Death, Neurological death, Stroke, Neurological deficit, Transient ischemic attack, Aneurysm rupture, Neuropsychological effects (dementia), Complications of cerebral angiography, Complications of anti-platelet therapy, Silent brain imaging changes.

a. Please discuss the relevance of the secondary safety and effectiveness endpoints above.

The Panel recommended that in general, several of the safety and effectiveness endpoints were relevant when designing a clinical trial.

b. Are there any additional endpoints to consider in evaluating endoluminal aneurysm treatment safety and effectiveness?

The Panel recommended the following additional factors be considered during a clinical trial: Functional outcome score (modified Rankin Scale or Barthel Index), residual filling of aneurysms, vessel occlusion, periprocedural complications, and other safety related events, as appropriate.

c. For a performance goal based study, how should a composite safety endpoint be determined given each safety component has a different severity?

The Panel agreed that different safety endpoints have different severities but did not provide direct feedback on a composite endpoint.

Panel Question 8:
Given that the endoluminal occlusion of aneurysm by flow diverters is delayed (which could lead to delayed aneurysm rupture), is one year follow-up premarket sufficient to capture the major adverse events (safety) and demonstrate that the majority of the aneurysm healing has reached steady state (effectiveness)? In your response, please discuss what long term delayed adverse events should be considered when designing a post market study and how long should subjects be followed in order to capture the bulk of these delayed adverse events?

The Panel recommended that one year follow-up premarket is sufficient to capture major adverse events. The Panel also commented that 5 years post-market may be necessary to capture other adverse events during follow-up and that primary care physicians may also be following patients for their lifetime.

Contact: Jamie Waterhouse, Designated Federal Officer
(301) 796- 3063 Jamie.Waterhouse@fda.hhs.gov
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Food and Drug Administration
Freedom of Information Staff (FOI)
5600 Fishers Lane, HFI-35
Rockville, MD 20851
(301) 827-6500 (voice), (301) 443-1726