



**Brief Summary
of the
Neurological Devices Panel of the Medical Devices Advisory Committee Meeting
March 1, 2018**

Introduction

On March 1, 2018, the committee discussed and made recommendations to the FDA regarding the evaluation of clinical study data to support the risks and benefits of intracranial aneurysm treatment devices and factors that can affect clinical outcomes such as aneurysm morphology, size, and location in the neurovasculature. FDA also convened this committee to seek expert opinion on the scientific and clinical considerations relating to the clinical trial design that may be relevant to the determination of safety and effectiveness for these devices.

FDA Presentations

Drs. Carlos Peña, Ph.D., Xiaolin Zheng, Ph.D., Samuel Raben, Ph.D., and Patrick Noonan, M.D., presented for FDA. They provided introductory statements, a cerebral aneurysm overview, aneurysm treatment methods, and additional points to consider in evaluating the risks and benefits of aneurysm treatments.

Industry Presentations

Multiple device manufacturers presented a joint presentation to the FDA. Their presentation focused on target aneurysm treatment populations and challenges associated with understanding the natural history data, how to use current safety and effectiveness data to evaluate new device technology, and recommendations for current and future studies, including post-marketing studies. Device manufacturers also provided their recommended answers to several FDA questions.

Professional Organization Presentations

Representatives from the American Association of Neurological Surgeons (AANS), Society of Vascular Interventional Neurology (SVIN), and Society of Neurointerventional Surgery (SNIS) presented recommendations to the FDA and Panel, including responses to some FDA questions.

Open Public Hearing Testimony

Six open public speakers presented to the panel. Two patients presented who were diagnosed with an intracranial aneurysm, received an implanted device, and benefited from treatment. The Lisa Colagrossi Foundation and Brain Aneurysm Foundation presented on the importance of having timely access to safe and effective products and patient education about the disease. Practicing physicians presented to the Panel, providing their experiences with aneurysm treatment procedures and some recommendations to FDA questions, including use of pre- and post-market data to bring safe and effective therapies to patients, and inclusion of diverse populations in clinical trials.

Discussion Questions

The FDA questions to the panel were presented by Dr. Christopher M. Loftus MD, and the discussion was led by panel Chair Dr. Mary E. (Lee) Jensen. The summary of the panel discussion and recommendations are provided below with a listing of the question followed by the panel response.

Safety

Adverse Events & Endpoints

1. Typically, aneurysm device trial primary safety endpoints have focused on death and major ipsilateral stroke (defined as an increase in the National Institutes of Health Stroke Scale (NIHSS) by 4 points at the time of stroke event within 1 year after treatment). Additional safety events (adverse events or AEs) that are considered in our safety assessment of new devices include:

Adverse Events
Access Site Issues (e.g., Dissections, Hematomas)
Aneurysm Leak, Rupture, or Contrast Extravasation
Distal Embolic Phenomena
Dual Antiplatelet Therapy (DAPT) Related AEs
Mechanical Device Failures and/or Acute or Delayed Device Migration or Embolization
I Minor Ipsilateral Strokes (NIHSS Change < 4)
Transient Ischemic Attacks (TIAs)

Please address the following:

- a. Is the AE list above complete? If not, what AE(s) should be added?

Panel Recommendations-The panel recommended vessel dissection and injury, excessive radiation exposure, visual loss, cranial nerve palsy, and unplanned intervention be added to the AE list. The panel also recommended that instead of major and minor stroke, the terms disabling and nondisabling stroke be used with a disabling stroke being considered as a primary outcome measure and non-disabling stroke being considered an additional safety event.

- b. Are there specific rates of AEs that would raise serious concerns about the safety of any specific device?

Panel Recommendations-The panel believed that it was difficult to assign specific rates to individual AEs or in aggregate. Some panelists recommended reviewing the current literature to match the incidence rate to specific AEs and other panelists indicated a 3-5% rate should be the rate limit for death and disabling strokes for unruptured aneurysms and a 10% rate for ruptured aneurysms. The panel acknowledged it was important to differentiate between ruptured and unruptured aneurysm cases.

2. The modified Rankin Scale (mRS) has often been incorporated as a secondary endpoint. Can the mRS at 1 year also be a potential primary safety outcome measure for all endovascular device trials? If yes, what magnitude of decline in the mRS and for what percentage of treated subjects with a decline in the mRS at 1 year follow-up would raise serious concerns

about the safety of the device? If no, what alternative primary safety outcomes are possible and for what duration of time.

Panel Recommendations-The panel was split on the use of the mRS as a primary safety outcome measure. For unruptured intracranial aneurysms, most panel members believed that the mRS between 3 months and 1 year would be a good primary safety outcome measure. Panelists also noted that if using mRS as the primary safety endpoint for unruptured aneurysm trials, any deterioration such as by 1 point from the baseline mRS should be considered a failure with respect to device safety. Other panelists recommended to keep death and major stroke as the primary safety endpoint. The panel also noted to differentiate between ruptured and unruptured cases, and for the most part did not support the use of mRS as the primary safety outcome in cases of ruptured aneurysms.

Safety & Patient Demographics

3. Considering the AE list above and any additional AEs specified in response to question #1a., what patient characteristics (e.g., malignancy, advanced age, aneurysm size) justify foregoing treatment for an aneurysm that would otherwise be considered for treatment?

Panel Recommendations-Several panel members highlighted the difficulty of identifying specific inclusion or exclusion criteria that could be broadly applied. Some panel members recommended that aneurysm sizes between less than 3 mm up to 5 mm would be an appropriate cutoff for inclusion into a device study. Most of the panel agreed that patients with < 1 year of life expectancy should be excluded from a device study. The panel had less enthusiasm for recommending an age as a patient characteristic for study inclusion. Some panel members expressed that vessel physiology was more important than patient age in considering who should be considered for treatment. Some panelists indicated that < 85 years of age was also an appropriate age limit for inclusion in a device study. The panel also noted guidelines for the treatment of intracranial aneurysms.

Effectiveness

Effectiveness Measures

4. Typically, intracranial aneurysm device trial primary effectiveness endpoints have focused on the percentage of subjects who achieve a Raymond Classification I (complete 100% occlusion) without significant parent artery stenosis ($\geq 50\%$) or re-treatment at 1 year post-procedure. Please address the following:

- a. Do you consider the Raymond Classification Scale to be the standard to assess effectiveness for ALL endovascular intracranial aneurysm treatment devices? If you do not consider the Raymond Classification Scale to be standard, please identify an alternative well accepted assessment(s) to adequately assess effectiveness for ALL endovascular intracranial aneurysm treatment devices.

Panel Recommendations-The panel agreed that the Raymond classification is widely used to assess the degree of aneurysm occlusion and should be used in the endovascular intracranial aneurysm device trials. The panel also noted that novel technologies may require alternative validated assessment tools to evaluate a device.

- b. Many studies have used the Raymond Classification Scale. If the Raymond Classification scale is used, is Raymond II (or higher) classification a satisfactory outcome for

aneurysm patients with unruptured aneurysms? And is Raymond II (or higher)

classification a satisfactory outcome for aneurysm patients with ruptured aneurysms?

Panel Recommendations-The panel acknowledged that the interpretation of the Raymond scale can depend on the technology used for treatment. The panel agreed that Raymond I for flow diversion and either Raymond I or II for intrasaccular devices are acceptable occlusion results. If a patient has a Raymond II at 1 year, additional follow-up may be considered to categorize a Raymond II as a satisfactory outcome for an intrasaccular device. Some panel members believed that the definition of “stable” Raymond II aneurysm occlusion would be when there is no change or deterioration in the aneurysm occlusion status assessed via imaging 6 months apart and that this may be a reasonable determination of aneurysm stability.

Aneurysm Occlusion

5. For device effectiveness, what percent of morphological occlusion is acceptable and in what percent of patients should this result be achieved?

Panel Recommendations-The panel believed that the Raymond classification was appropriate to assess aneurysm occlusion status. They did not support the use of a specific percentage of morphological occlusion to assess acceptable aneurysm occlusion. The panel also reiterated their recommendations for adequate aneurysm occlusion as summarized in response to FDA question #4.b.

6. Do your aneurysm occlusion assessment recommendations using Raymond (or another system if identified in question #4.b.) differ for endosaccular devices (e.g., neurovascular embolization coils, balloon assisted coiling (BAC), stent-assisted coiling (SAC), saccular obturation devices)? intraluminal flow diversion devices? If so, how?

Panel Recommendations-The panel reiterated their response to FDA question #4.b. in which they stated that a binary assessment of whether Raymond I was achieved or not should be considered for flow diverters and that either a Raymond I or II should be considered an acceptable outcome for intrasaccular devices as long as the Raymond II classification was “stable”.

Follow Up

7. What length of follow-up is recommended to assess effectiveness for endovascular aneurysm treatment devices? Please discuss how your recommendation is impacted if the aneurysm status of the patient at 1 year is a Raymond II or III classification.

Panel Recommendations-For a premarket decision, the panel generally believed that one year assessment of treatment was appropriate provided that the aneurysm was stable (Raymond I for flow diverters and Raymond I or II for intrasaccular devices). If stability was not achieved, follow up should continue at 6 month intervals until aneurysm stability is established, even potentially up to 2 years. The panel generally recommended 5 year follow up for long-term post-market surveillance of novel intracranial aneurysm devices and potentially 2-3 years for intracranial aneurysm devices that are similar to currently marketed devices. Some panel members also believed that for large or giant aneurysms, a two year waiting period to achieve Raymond I status was more appropriate for flow diversion devices.

Retreatment

8. Some initial interventions result in a clinically unacceptable outcome and retreatment is considered. Does a worsening in the Raymond scale at follow-up imaging warrant retreatment and should FDA consider a worsening of the Raymond scale during 1 year follow-up to represent a failure of treatment?

Panel Recommendations-The panel discussed that if retreatment is involved, it may be considered a failure of the initial treatment. Beyond retreatment being a failure, decisions about treatment failures are complex and difficult to summarize. The panel discussed whether a worsening of the Raymond scale during 1 year follow up suggests a failure of treatment. The panel also discussed how the type of device utilized can impact outcomes. For flow diverters, the panel recommended a deterioration of the Raymond score as a failure since the only acceptable effectiveness outcome should be Raymond I. For intrasaccular devices, if the aneurysm occlusion status changes from a Raymond I to Raymond II, this would only be considered a failure if the aneurysm was not considered a “stable” Raymond II or if the Raymond II neck remnant was unprotected near the wall of the aneurysm. The majority of the panel believed that a Raymond III result is not acceptable with respect to demonstrating the effectiveness of a device treatment.

Alternative Imaging Assessments

9. We consider digital subtraction angiography (DSA) to be the gold standard to assess aneurysm occlusion at follow-up. Can magnetic resonance angiography (MRA) or computed tomography angiography (CTA) serve as a surrogate follow-up examination and when should this take place?

Panel Recommendations-The panel agrees that DSA is the gold standard to assess aneurysm occlusion for clinical trials. MRA or CTA may be good surrogate imaging assessment tools for longer term follow up provided the initial DSA imaging results are acceptable. Many panelists noted that there should be more studies to validate the accuracy of MRA compared to DSA with respect to assessment of aneurysm occlusion for different intracranial aneurysm devices and respective designs and uses.

Post Approval Studies

10. In some cases, a post-approval study may be warranted, for example when limited follow up exists for patients. What is a sufficient long term follow-up period for a post-approval study where the majority of patients have the following outcomes for ruptured or unruptured aneurysms?

- a. Raymond I
- b. Raymond II
- c. Raymond III

Panel Recommendations-The panel suggested differentiating between unruptured vs. ruptured aneurysms. Suggestions for follow up from panelists for ruptured aneurysms included a minimum of 2 years up to 5 year follow up. Some panelists suggested 5 year follow up for both ruptured and unruptured aneurysms. Other panel members recommended that 2 year long term follow up was reasonable for devices similar in technology to something already marketed but 5 year follow up was more appropriate for novel intracranial aneurysm treatment devices.

Labeling

11. What patient characteristics should be specified in the Indications for Use (IFU) (i.e., age, aneurysm morphology, location, size, Type 1 or Type 2 status, ruptured vs. unruptured)? For intraluminal flow diverters? And for endosaccular devices?

Panel Recommendations-The panel recommended consideration of patient characteristics including morphology, location, and differentiating between ruptured and unruptured aneurysms. The panel recommended that the indications for use should be dependent on the clinical trial design (inclusion/exclusion criteria of the study) and the patient population studied in the trial. The panel also discussed that age limits were not as important in the IFU statement for adults and limitations with device use may be further described in the labeling.

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