Brief Summary of the Neurological Devices Panel Meeting – September 27, 2018

Woven EndoBridge (WEB) Aneurysm Embolization System

Introduction:

The Neurological Devices Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met on September 27, 2018, to discuss, make recommendations, and vote on information related to the Premarket Approval (PMA) application for the Woven EndoBridge (WEB) Aneurysm Embolization System.

The sponsor has proposed the following Indications for Use:

The WEB Aneurysm Embolization System is indicated for the embolization of intracranial wide neck bifurcation aneurysms. The WEB Aneurysm Embolization System is further indicated to embolize saccular intracranial wide neck bifurcation aneurysms located in the anterior (middle cerebral artery (MCA) bifurcation, internal carotid artery (ICA) terminus, anterior communicating artery (AComm) complex) and posterior (basilar apex) circulations, ranging in size from 3 mm to 10 mm in dome diameter, where the neck size is 4 mm or greater or the dome-to-neck ratio is less than 2.

Panel Deliberations/FDA Questions:

Question 1: Safety

1A-Please comment on the 8% stroke rate observed (Table 2) and the change (improvement, worsening) in mRS at 1 year compared to their baseline mRS score pre-procedure (Table 3) in the assessment of device safety.

1B-Please comment on whether there are additional categories of adverse events (AEs) that should be included in the assessment of device safety.

1C-Please comment on the significance of 5 late deaths and stroke events observed after 1 year follow-up and how these events should be incorporated into the assessment of device safety.

The Panel discussed patient risk factors, stroke rate, changes in the modified Rankin Scale (mRS) score, adverse events and late deaths observed during the clinical trial. Some Panelists commented the 8% stroke rate observed in the clinical trial to be consistent with the scientific literature for endovascular treatment of the target patient population. Other Panelists expressed concerns about the potential for increased adverse events postmarket if used off label or based on different levels of physician experience. In addition to the rate of stroke events and neurological deaths in the determination of safety, some Panelists recommended that the rate of visual disturbances also be reviewed and incorporated into the determination of safety. The utilization of the mRS score change at 1 year compared to the baseline mRS score was also discussed and concerns raised on the adequacy of assessments and potential

for bias if not adequately assessed by an independent vascular neurologist. Some Panelists also recommended additional safety endpoints for assessment of stroke outcomes in addition to the mRS for disability such as the National Institutes of Health Stroke Scale (NIHSS) for stroke severity and the Barthel Index for function, and a quality of life patient reported outcome measure. The Panel summarized the stroke rate may be acceptable, but there may be other factors that raise concerns in interpreting safety with regard to patient risk factors, location, and sample size.

Question 2: Effectiveness

2A-Please comment on the acceptability of defining complete (100%) intracranial aneurysm occlusion for the WEB device based on the WOS Grades A and B in comparison to Raymond-Roy Class 1 occlusion.

2B-Please comment on the overall effectiveness rate for the WEB device in the ITT population. Also, please comment on the subgroups identified as well as poolability of the effectiveness results based on the bifurcation intracranial aneurysm location and sac width size.

2C-Please comment on the rate of recanalization observed in the WEB-IT study between 6 months to 1 year follow-up. In addition, please comment on whether the 1 year occlusion data is sufficient for the assessment of long term effectiveness and durability of treatment based on the rate of recanalization observed.

The Panel discussed the importance of understanding individual breakdown of the combined group of Web Occlusion Scale (WOS) A and B that is defined as complete occlusion. The Panel commented on whether aneurysms graded WOS-B are stable over the long term or may progress to WOS-C. Most Panel members agreed that the WOS A and B patients should be evaluated as separate groups for long-term outcomes data. Regarding the overall effectiveness rate for the WEB device, several Panel members, including the consumer representative, expressed some uncertainty on effectiveness, taking into consideration the variability in the results, missing data, subgroup analyses, and how to compare these results to currently available treatments or control populations. The Panel also noted the rate of recanalization in the WEB-IT study between 6 months to 12 months follow-up and discussed whether additional study and follow-up was needed regarding subjects that both showed a decrease of complete occlusion and an increase in neck remnant. Some Panel members noted that in some subjects with remnants, follow-up after 1 year may be needed, including year 3 and 5.

Question 3: Device Sizing and Use Conditions

3A-Please comment on the concern of device compression and the ability to retreat subjects.

3B-Please comment on oversizing the device in the case of ruptured aneurysms where the sac may already be compromised.

3C-Please comment on the ability to choose the right size device given the device's 1 mm size increments.

The Panel commented on the concern of device compression over time within the aneurysm and noted similar compaction seen clinically with neurovascular embolization coils. The Panel noted that the risk of device compression may depend on ensuring the device is sized

appropriately to the target aneurysm. The Panel also raised concerns about the ability to retreat subjects, in part dependent on the anatomical location. The Panel also discussed sizing of the device and whether the device needed to be sized for the entire aneurysm volume or only positioned securely at the neck. The Panel noted uncertainty in treating ruptured aneurysms due to so few subjects with ruptured aneurysms studied. The Panel members expressed agreement in the importance of sizing the device so that is appropriately abuts the aneurysm wall while simultaneously covering the neck, and the importance of sizing when treating both ruptured and unruptured aneurysms.

Question 4: Use of Anti-Platelet Medications

4-Please comment on the use of DAPT for subjects receiving the WEB Device. Specifically, please comment on subjects that may have a neck remnant or residual aneurysms.

Panel members discussed the subjects on dual anti-platelet therapy (DAPT) prior to the implantation procedure with the WEB device in published outside the United States (OUS) clinical studies. The Panel commented that there was insufficient information on the DAPT usage and that additional data should be collected to have more standardized guidelines for the prescribed DAPT regimen.

Question 5: Indication for Use (IFU) and Labeling

5A-Please comment on the inclusion of both ruptured and unruptured aneurysms in the IFU statement, given that the majority (94%, 141/150) of aneurysms enrolled were unruptured. Of the 9 subjects in the WEB-IT study with a prior ruptured aneurysm, these subjects were considered eligible for enrollment and inclusion in the WEB-IT study if their rupture resulted in subarachnoid hemorrhage (SAH) evidenced with CT, MRI, or lumbar puncture and attributed to the index aneurysm within the last 60 days of study entry.

5B-Please comment on any additional labeling considerations, such as contraindications, warnings, precautions, instructions for use that should be conveyed in the Directions for Use (DFU) to ensure the safe and effective use of the subject device.

5C-Please comment on labeling recommendations regarding patient follow-up with regards to specific imaging modalities for the subject WEB device.

5D-If MRA is believed to be an appropriate imaging modality for aneurysm occlusion follow-up, please comment on whether additional MRA image artifact testing is needed using MRA pulse sequences, and how this information should be communicated to the clinical users in the labeling.

The Panel raised concerns whether sufficient data was collected on ruptured and unruptured aneurysms; however, several Panel members expressed support that the IFU should reflect the design of the clinical trial including the patient population selected based on the inclusion/exclusion criteria. Panel members also further commented on revising the IFU to limit ruptured aneurysms to only those with low-grade rupture (Hunt & Hess I and II), based on the inclusion criterion for the trial. Some Panel members also recommended a restriction in the labeling that the device should only be used in previously untreated intracranial

aneurysms. Several Panel members agreed that more information is needed to determine if MRA is an appropriate imaging modality for aneurysm occlusion follow-up with the WEB device, and that MRA should not be recommended as an imaging modality for follow-up at this time. Currently, digital subtraction angiography (DSA) is considered the gold standard and was recommended for use in imaging by the Panel. The Panel agreed that after 3 years of follow up with DSA, it may be reasonable to consider following subjects with computed tomography angiography (CTA), as this will provide reasonable results and is less invasive.

Question 6: Post Approval Study (PAS) Considerations

6-If a PAS is warranted, please identify the outstanding questions that a PAS should be designed to answer, including duration of follow-up of the PAS.

The Panel agreed that a PAS is warranted for the WEB device if approved for marketing in the United States (US). The Panel recommended that the PAS should answer questions such as the collection of additional data on use of the device in ruptured aneurysms, DAPT regimen, long-term stability of treatment with the WEB device, validation of the WOS for complete aneurysm occlusion by assessing WOS Grade A and WOS Grade B separately, evaluating the adequacy of using DSA vs. CTA imaging for long-term follow-up, and evaluation of neurological deficits including stroke events by a vascular neurologist in the clinic. The Panel summarized that patient follow up is important, a PAS should include specific imaging protocols, and clinical examinations should be performed up to 1-2 years post-procedure, while imaging follow-up examinations may be evaluated up to 5 years post-procedure.

Vote:

On Question 1, the Panel voted 15-0-0 (yes, no, abstain) regarding whether there is reasonable assurance that the Woven EndoBridge (WEB) Aneurysm Embolization System is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the Panel voted 12-2-1 (yes, no, abstain) regarding whether there is reasonable assurance that the Woven EndoBridge (WEB) Aneurysm Embolization System is effective for use in patients who meet the criteria specified in the proposed indication.

On Question 3, the Panel voted 12-1-2- (yes, no, abstain) regarding whether the benefits of the Woven EndoBridge (WEB) Aneurysm Embolization System outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

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