Neurological Devices Advisory Committee Meeting
Panel Questions

September 27, 2018

Question 1: Safety

The primary safety endpoint in the WEB-IT pivotal study was defined as:

> *The proportion of subjects with death of any nonaccidental cause or any major stroke (defined as an ischemic or hemorrhagic stroke resulting in an increase of 4 points or more on the National Institutes of Health Stroke Scale (NIHSS) at the time of assessment and which remained present after 7 days) within the first 30 days after treatment or major ipsilateral stroke or death due to neurologic cause from day 31 to 365 days after treatment.*

Based on this pre-specified primary safety endpoint definition, the primary safety analysis results for the WEB-IT study are presented in Tables 1 for subjects with available 12 month safety data.

Table 1. Primary Safety Composite Endpoint Analysis

Endpoint	%
Primary Safety Rate (ITT)[a]	0.67%
Composite[b]	0.68%
Death within 30 Days[b]	0.68%
Major Stroke within 30 Days[b]	0.68%
Major Ipsilateral Stroke Days 31 to 365[b]	0.00%
Neurological Death Days 31 to 365[b]	0.00%

[a] N=150
[b] N=147

Table 2. All Stroke Safety Endpoint

Endpoint	%
Composite FDA Requested All Stroke Primary Safety Endpoint	8.00%
Death within 30 Days	0.00%
Any Stroke within 30 Days	6.67%
Any Ipsilateral Stroke Days 31 to 365	1.36%
Neurological Death Days 31 to 365	0.00%

[a] One subject experienced two events, SAH and ischemic stroke. N=150

Table 3. Modified Rankin Score Change from Baseline to 12 Months in Unruptured Aneurysms

mRS Score at Baseline	mRS Score at 12 Months				Total
	0 %[a]	1 %[a]	3 %[a]	4 %[a]	
0	90.83	8.26	0.00	0.92	109
1	46.15	50.00	3.85	0.00	26
Total	82.22	16.30	0.74	0.74	135

Question 1: Safety – Overall Evaluation Cont.

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.

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Question 2: Effectiveness

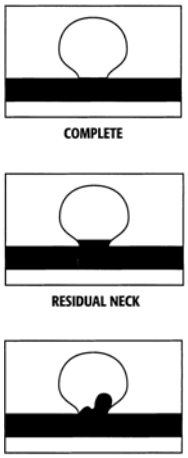
The primary effectiveness endpoint for the WEB-IT trial was defined as:

The proportion of subjects with complete intracranial aneurysm occlusion using the WEB Occlusion Scale (WOS) without retreatment, recurrent subarachnoid hemorrhage, or significant parent artery stenosis (> 50% stenosis) at 1 year post-procedure as assessed by the Core Laboratory.

Question 2a: Effectiveness – Occlusion Scale

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.

Raymond-Roy Occlusion Scale



[R.S. Quadros et al. ANJR 2007]

Sponsor Defined Completed Occlusion

Incomplete Occlusion

[Fiorella, et al., JNIS, 2015, Vol 7]

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Question 2b: Effectiveness – Subgroups

The WEB-IT pivotal study demonstrated complete intracranial aneurysm occlusion (WOS Grades A & B) as defined in the primary effectiveness endpoint in 54.77% of the Intent-to-Treat (ITT) population with a lower 90% confidence interval (CI) of 47.97%.

In the Completed Cases (CC) population for subjects with available imaging data at the 1 year follow-up visit, the primary effectiveness endpoint success rate was 53.85% (77/143) with a lower 90% CI of 46.63%.

Table 4. Subgroup Analysis of Primary Effectiveness Endpoint by Aneurysm Location (CC Population) (N=143)

Aneurysm Location	Primary Effectiveness Success (%)
Basilar Apex	58.62
ICA Terminus	66.67
MCA Bifurcation	43.90
AComm Complex	55.26
Total	53.85

Table 5. Subgroup Analysis of the Primary Effectiveness Endpoint by Intracranial Aneurysm Sac Width Size (CC Population)

Characteristic	Primary Effective Success (%)
Sac Width	
< 8 mm	54.24
≥ 8 mm	52.00

N = 118 for < 8 mm
N = 25 for ≥ 8 mm

Question 2b: Effectiveness – Subgroups cont.

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.

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Question 2c: Effectiveness – Treatment Durability

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.

Table 6. Intracranial Aneurysm Occlusion at 6 and 12 Month Visits

Visit	Complete Occlusion %	Residual Neck %	Residual Aneurysm %
6 Months	61.70	24.82	13.48
12 Months	57.86	31.43	10.71

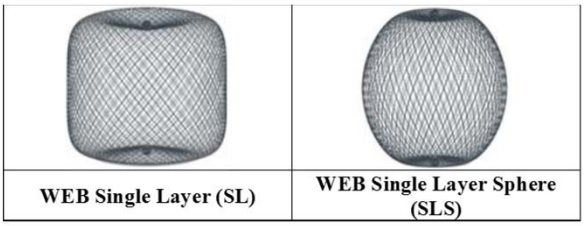
[a] Includes 3 subjects with occlusion at six months and 12 months who had additional treatments or adjunct devices besides balloons during the procedure or afterwards that disqualify them from being counted as a success.
N=141 at 6 months and N=140 at 12 months

Table 7. Subjects with Regrowth or Recanalization of the Target Intracranial Aneurysm 12 Months Post-Index Procedure (CC Population)

Population	Rate of Regrowth or Recanalization at 12 months %
Completed Cases	12.59

* There were 17 subjects with recanalization and 1 subject with regrowth. None of these 18 subjects achieved a primary effectiveness endpoint success at 12 months.
N=143

Question 3: Device Sizing and Use Conditions



WEB Single Layer (SL)	WEB Single Layer Sphere (SLS)

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.

Cognard, Christophe, and Anne Christine Januel. 2015. "Remnants and Recurrences After the Use of the WEB Intrasaccular Device in Large-Neck Bifurcation Aneurysms." Neurosurgery 76 (5):522–30
Pierot, Laurent. 2015. "WEB Aneurysm TreatmentOcclusion Stability and 'Compression.'" Neurosurgery 77 (4):E666–67

Question 4: Use of Anti-Platelet Medications

Published OUS clinical studies indicated a high number of subjects taking dual anti-platelet (DAPT) medications in the periprocedural period (52%, 29/55) with 24% (13/55) remaining on DAPT one month post-procedure. (Pierot et al., AJNR 2017)

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.

Question 5: Indications for Use (IFU) and Labeling

The sponsor has proposed the following Indications for Use (IFU):

The WEB Aneurysm Embolization System is indicated for the embolization of intracranial WNBAs. The WEB Aneurysm Embolization System is further indicated to embolize saccular intracranial WNBAs 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.

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.

Question 5: Indications for Use (IFU) and Labeling Cont.

The inclusion criteria in the WEB-IT study specified that subjects must have a target intracranial aneurysm with all the following characteristics to be eligible for enrollment:

- Saccular in shape;
- Located in the basilar apex, MCA bifurcation, ICA terminus, or AComm complex
- Dome-to-neck ratio ≥ 1
- Diameter of the intracranial aneurysm appropriate for treatment with the WEB device per the Instructions for Use
- Wide-neck intracranial aneurysm with neck size ≥ 4 mm or dome-to-neck ratio < 2.

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.

Question 5: Indications for Use (IFU) and Labeling Cont.

The sponsor is reporting a 5 mm magnetic resonance imaging (MRI) image artifact observed with the WEB Implant based on testing under standard MRI pulse sequences as part of MRI safety and compatibility testing of a permanent passive implant. There has been an increase in routine clinical follow-up for intracranial aneurysm occlusion after treatment using magnetic resonance angiography (MRA) as opposed to digital subtraction angiography (DSA). There were recent reports of the difficulty in successfully obtaining MRA images in subjects implanted with the WEB device (Nawka et al. 2018).

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.

Question 6: Post-Approval Study Considerations

If the WEB device is approved for marketing in the United States (US), please discuss whether a post-approval study (PAS) is warranted.

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.