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Premarket Approval (PMA) P170032 for the Woven EndoBridge (WEB) Aneurysm Embolization System

Neurological Devices Advisory Panel Meeting
September 27, 2018

Presentations By: Samuel Raben, Ph.D., Xin (Shane) Fang, Ph.D., and Patrick Noonan, Jr., M.D.

Division of Neurological and Physical Medicine Devices (DNPMD)
Office of Device Evaluation (ODE)
Center for Devices and Radiological Health (CDRH)

Review Team

Samuel Raben, PhD	– Lead/Engineering
Patrick Noonan, Jr., MD	– Clinical
Xin Fang, PhD	– Statistical
Dhanya Williams, MS	– Biocompatibility
Robert Herrmann, PhD	– Animal Study
Myra Smith, MS	– Sterility/Microbiology
Yuzhi Hu	– Epidemiology
Tamika Allen	– Bioresearch Monitoring
Arabella Pelina, MPH	– Manufacturing

Indications for Use (IFU)

Original:

The WEB Aneurysm Embolization System is indicated for the embolization of intracranial WNBAs.

The WEB Aneurysm Embolization System is further indicated to embolize intracranial wide neck bifurcation aneurysms 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.

Revised:

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.*

The Panel will be asked to discuss and make recommendations on whether the proposed indications for use is supported by the data collected in the pivotal WEB-IT study, including, but not limited to, location of target intracranial aneurysm, size, morphology, and ruptured vs. unruptured status. Also, the Panel will be asked whether there should be specific 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.

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Presentation Outline

- Brief Overview of Cerebral Aneurysms
- Regulatory History
- Device Description
- Pre-clinical Evaluations
- Trial Design and Statistical Analysis Plan
- Currently Marketed Devices for Intracranial Aneurysms
- Relevant Revisions to the FD&C Act
- Clinical Trial Results
- Summary

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Cerebral Aneurysm Overview: Diagnosis and Characteristics

Samuel Raben, Ph.D.
Lead Reviewer / Mechanical Engineer
CDRH/ODE/DNPMD

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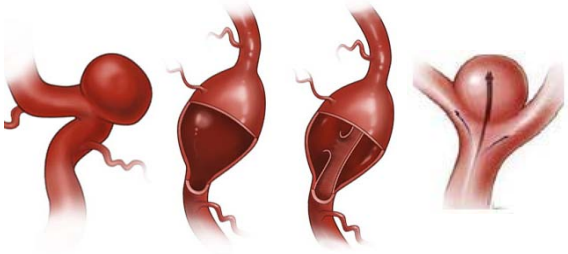
Morphology of Cerebral Aneurysms

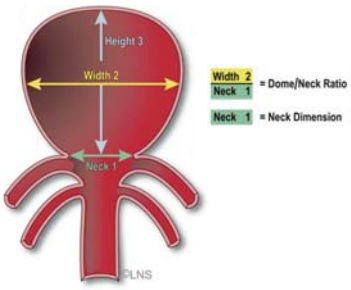
- Saccular aneurysms protrude from a side wall (most common)
  - Bifurcation aneurysms are saccular aneurysms that that form where vessels divide and form a “Y”.
- Fusiform is a dilation of the vessel
- Dissection is the result of a tear between the vessel wall layers.

- Wide Neck is defined as a neck width ≥ 4 mm or a dome to neck ratio < 2



Sidewall Saccular Fusiform Dissection Bifurcation

Hopkinsmedicine.org



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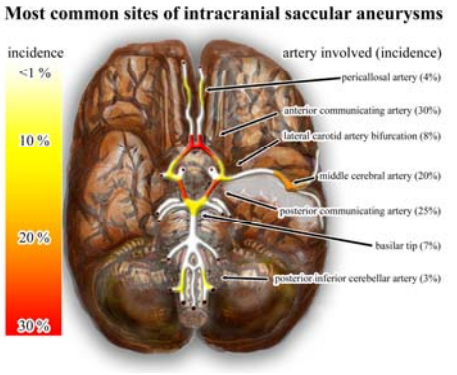
Anatomical Locations

- Typically occur at or near vessel branch points or bifurcations.
- Aneurysm occur more frequently in the anterior circulation.
  - Anterior ~85%–90%
  - Posterior ~10%–15%
- Patient outcomes can be influenced by aneurysm location for both surgical and endovascular treatment[1].



[Wikipedia]

FDA is seeking discussion and recommendations for the treatment of wide-neck bifurcation intracranial aneurysms, both ruptured and unruptured, located in the anterior (middle cerebral artery (MCA) bifurcation, internal carotid artery (ICA) terminus, anterior communicating artery (AComm) complex) and posterior (basilar apex) circulations.

[1] Wiebers, David O. 2003. The Lancet 362 (9378): 103–10

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Cerebral Aneurysm Size

- Aneurysms sizes can vary
- Small aneurysms occur most frequently

Size	Range	Occurrence (n=1449)
Small	≤ 5 mm	47%
Medium	6-10 mm	27%
Large	11-25 mm	12%
Giant	≥ 25 mm	14%

[Wiebers 1998]

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Risk Factors for Aneurysm Rupture

- Difficult to predict the risk of aneurysm rupture.
- Risk factors can include, but not limited to, family history, history of prior subarachnoid hemorrhage (SAH), gender, smoking, location of aneurysm, morphology, and overall size.

Rupture Rate over 5 years (n=4060)				
	<7mm	7-12mm	13-24mm	≥ 25mm
Anterior Circulation ICA, AComm, ACA, or MCA	0%[a]	2.6%	14.5%	40%
Posterior Circulation/Posterior Communicating Artery	2.5%	14.5%	18.4%	40%

[a] Only applicable to patients that have no risk factors as listed above.

[Wiebers, 2003]

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Woven EndoBridge (WEB) Aneurysm Embolization System

[P170032, Pg. 20]

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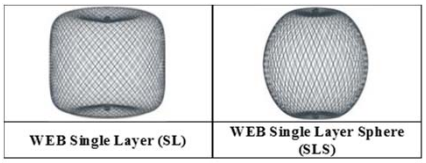
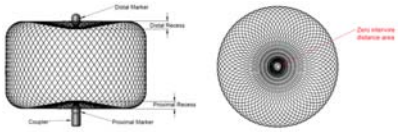
WEB Aneurysm Embolization System

- WEB is designed to treat wide-neck bifurcation aneurysms (WNBA).
- Device sizes range from 4 x 3 mm to 11 x 9 mm.
- Wires are a nitinol exterior and platinum core to provide shape memory and radiopacity.
- Delivered through microcatheters ranging from 0.021" to 0.032" depending on implant size.



[P170032, Pg. 21]



[P170032, Pg. 24]

[P170032, Pg. 20]

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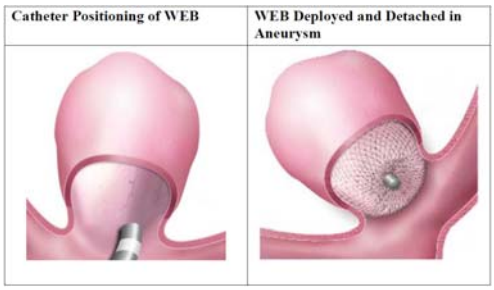
Principle of Operation

- WEB operates by restricting blood flow from entering the aneurysm.
- As the wires converge at the center of the device, the mesh density increases.



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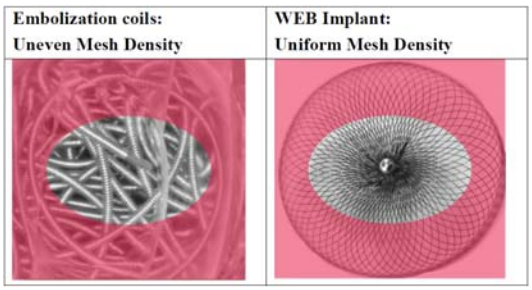

[P170032, Pg. 21]

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Regulatory History

- The WEB device was studied under an Investigational Device Exemption (IDE), G130286.
- The WEB device is CE marked and for sale outside the US in 44 countries including, but not limited to:
  - Argentina, Austria, Australia, Belgium, Bulgaria, Chile, Colombia, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Lebanon, Netherlands, New Zealand, Norway, Slovenia, Spain, Sweden, Switzerland, Turkey, United Arab Emirates, and United Kingdom

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Pre-clinical Evaluations

- Pre-clinical testing was provided to FDA as part of the IDE and PMA evaluation.
- Testing included:
  - Design Verification/Validation testing
    - Including, but not limited to: accelerated fatigue, corrosion, simulated use, particulate generation analysis, detachment reliability.
  - Animal Study (acute and chronic evaluations)
  - Biocompatibility
  - Sterilization, Shelf-life, and Packaging
  - MR Conditional Testing

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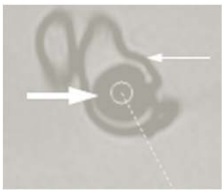
Potential Challenges with MRA for Follow-Up

- MR Conditions for Safe Scanning:
  - Static magnetic field of 1.5-Tesla or 3-Tesla
  - Maximum spatial gradient field of 4,000-Gauss/cm (40-T/m)
  - Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2.0-W/kg for 15 minutes of scanning (i.e., per pulse sequence) in the Normal Operating Mode
  - Maximum temperature rise of +1.4 °C after 15 minutes of continuous scanning (i.e., per pulse sequence) under the above conditions.
  - Image artifact caused by the WEB Implant extends approximately 5 mm from the implant when imaged with a gradient echo pulse sequence and a 3-Tesla MRI system.
- Significant signal lost is observed with MR imaging near/inside the implant, raising concerns regarding the use of MRA for follow-up.

CT Imaging



Gadolinium enhanced MRI

[Nawka et al. (2018) JNS]

The Panel will be asked to discuss the labeling recommendations regarding patient follow-up with regards to specific imaging modalities for the subject WEB device. In addition, the Panel will be asked whether additional MRA image artifact testing is needed if MRA is believed to be an acceptable imaging modality for long-term follow-up of the IA occlusion status.

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WEB Intrasaccular Therapy Study (WEB-IT): Study Design and Statistical Analysis Plan

Xin (Shane) Fang, Ph.D.
Statistical Reviewer
CDRH/OSB/DBS/TBSII

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Outline

- Study type: single-arm
- Primary and secondary endpoints
- Study hypotheses and success criterion
- Sample size determination
- Statistical analysis plan
  - Analysis populations
  - Statistical analyses

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Study Type and Primary Endpoints

- A prospective, single-arm, international multicenter, clinical study, with
  - 150 subjects at up to 25 US and 6 OUS sites
  - at least 127 evaluable subjects at the 1 year follow-up time point
- **Primary effectiveness endpoint:** The proportion of subjects with complete aneurysm occlusion without retreatment, recurrent subarachnoid hemorrhage, and significant parent artery stenosis at 1 year after treatment.
- **Primary safety endpoint:** The proportion of subjects experienced with any of the following adverse events: death of any nonaccidental cause, any major stroke within the first 30 days after treatment, major ipsilateral stroke, and death due to neurologic cause from Day 31 to 1 year after treatment.

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Secondary Endpoint and Patient Follow-Up

- **Secondary endpoint:** The proportion of subjects experienced with angiographic aneurysmal recurrence defined as aneurysm growth or recanalization at one year after treatment.

- **Follow Up:** At discharge, 30 days, 6 months, 1 year, and annually throughout 5 years.

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Primary Hypotheses

- **Primary Effectiveness Hypothesis (PG=35%, noted as a Study Design Consideration*)**

H_0: $P_E \leq 35\%$ versus H_a: $P_E > 35\%$,
P_E = proportion of subjects who met patient success criteria at 1 year

- **Primary Safety Hypothesis (PG=20%, noted as a Study Design Consideration*)**

H_0: $P_S \geq 20\%$ versus H_a: $P_S < 20\%$
P_S = Proportion of subjects who experienced Primary Safety Event through 1 year

- **The study is considered a success by the sponsor if both the primary effectiveness endpoint and the primary safety endpoint are met. But the PGs were raised as a Study Design Consideration by the FDA.**

- * **To be discussed in more detail later in the presentation.**

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Derivation of Performance Goal for the Primary Effectiveness Endpoint

Location	Treatment	# of Adjusted Events	# of Evaluated Patients	Fleiss Inverse Variance Weighted Rate (SE)
Anterior	EVT	256	617	0.5084 (0.0967)
	Surgery	87	143	
Posterior	EVT	253	542	0.4669 (0.0211)
	Surgery	8	17	

- 80% of the aneurysms to be anterior and 20% posterior bifurcated or wide neck
- Occlusion Rate (SE) Estimated by Fleiss Inverse Variance Weighting: 0.5001 (0.07746)
- 95% CI: (0.3483, 0.6519)
- Effectiveness PG: 35%

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Derivation of Performance Goal for the Primary Safety Endpoint

Location	Treatment	# of Events	# of Patients	Fleiss Inverse Variance Weighted Rate (SE)
Anterior	Coil	216	1056	0.1850 (0.0440)
	Stent/Coil	41	423	
	Surgery	336	1130	
Posterior	Coil	241	946	0.1906 (0.0506)
	Stent/Coil	59	594	
	Surgery	140	641	

- anterior aneurysms is 80%, posterior bifurcated or wide neck is 20%
- MAE Rate (SE) Estimated by Fleiss Inverse Variance Weighting: 0.1861 (0.03668)
- 95% CI: (0.1142, 0.2580)
- Safety PG: 20%

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Sample Size Determination

Planned sample size: 150 subjects at up to 25 US sites and 6 OUS sites, with at least 127 evaluable subjects at the 1 year follow-up time point

- For effectiveness endpoint
  - Assume: P_E =46%
  - one-sided alpha of 0.05, 80% power
  - 127 subjects are needed based on Binomial proportion formula
  - loss to follow-up of about 15%
- For safety endpoint
  - Assume: P_S =11.4%
  - one-sided alpha of 0.05, 80% power
  - 118 subject are needed based on Binomial proportion formula
- Final sample size: 150 after being adjusted for 15% attrition rate

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Analysis Populations

- **Primary population** (denoted as **ITT** by the sponsor, N=150): all subjects with an attempt to place the WEB device.
- **Completed cases** (**CC**, N=143): all ITT subjects who completed the 12 month visit.
- **Per-protocol (PP) population** (N=143): all CC subjects who meet all study eligibility criteria, have available study data for the study endpoint without a major protocol violation that affects primary safety or effectiveness.

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Statistical Analysis

- The point estimate and the associated 90% confidence interval (CI) for the two primary endpoints are derived using the exact binomial distribution method in ITT population.
- Missing data are imputed using multiple imputation method, which is acceptable from a statistical perspective.
- If the lower limit of the 90% CI for the primary effectiveness endpoint is > 35%, the primary effectiveness null hypothesis would be rejected in favor of the WEB device.
- If the upper limit of the 90% CI for the primary safety endpoint is < 20%, the primary safety null hypothesis would be rejected in favor of the WEB device.

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WEB Intrasaccular Therapy Study (WEB-IT): Patient Demographics and Clinical Trial Results

Patrick Noonan, Jr., M.D.
Interventional Neuroradiologist
Clinical Reviewer
CDRH/ODE/DNPMD

Samuel Raben, Ph.D.
Lead Reviewer
Mechanical Engineer
CDRH/ODE/DNPMD

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Recent PMA Approvals for Intracranial Aneurysm Devices

- Pipeline – Medtronic (P100018)
  - 106 in the mITT population (110 total Subjects) . All subjects with large and giant ICA aneurysms
  - 70.8% (75/106) with completed occlusion without clinically meaningful stenosis (i.e., <50%)
  - 5.6% (6/107) of subjects suffered a Major Stroke (NIHSS $\geq$ 4) or death at 180 days

- LVIS – MicroVention (P170013)
  - 153 in the ITT population(117 anterior, and 36 posterior)
  - 70.6% with complete occlusion without clinically meaningful stenosis (i.e., < 50%)
  - 5.9% (9/153) of subjects suffered a disabling stroke or neurological death at 1 year

- Surpass – Stryker Neurovascular (P170024)
  - 180 in the mITT population (213 total enrolled). All subjects with large and giant ICA aneurysms
  - 62.8% (113/180) with complete occlusion without clinically meaningful stenosis (i.e., < 50%)
  - 6.1% (11/180) of subjects suffered disabling stroke or neurological death at 1 year

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Prior HDE Approvals for Intracranial Aneurysm Devices

- Neuroform ATLAS – Stryker Neurovascular (H020002)
  - 30 subjects (24 anterior, 6 posterior)
  - At 12 months, 25/30 (83.3%) had Raymond-Roy 1 (complete 100%) without retreatment or parent artery stenosis
  - There was no deaths, with 1 major stroke (NIHSS$\geq$ 4) strokes (1/30, 3.3%) and 2 minor strokes (2/30, 6.7%)

- Enterprise – Cerenovus (H060001)
  - 28 subjects (22 anterior, 6 posterior)
  - Greater than 95% occlusion observed in 64% of subjects at 6 months
  - 1 Subject death (1/28, 3.6%), 2 subjects with Intracerebral Hemorrhage (2/28, 7.1%) and 2 TIA (2/28, 7.1%)

- PulseRider – Pulsar Vascular (H160002)
  - 34 subjects were enrolled (27 Basilar apex, 7 ICA terminus)
  - At 180 days, 22/33 (60.6%) had Raymond-Roy I Occlusion with 29/33 (87.9%) has Raymond-Roy I/II
  - Zero subjects with neurological death, and 1 subjects (2.9%) with a disabling stroke (mRS > 2)

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Revision to FD&C Act, July 2012

- FDA shall not disapprove an IDE because:
  - *The investigation may not support a substantial equivalence or de novo classification determination or approval of a device*
  - *The investigation may not meet a requirement, including a data requirement, relating to the approval or clearance of a device; or an additional or different investigation may be necessary to support clearance or approval of the device*
- This means that an IDE cannot be disapproved on the bases of FDA's belief that the study design is inadequate to support a future PMA, 510(k), humanitarian device exemption (HDE), or de novo classification.
  - *Disapproval is based on concerns related to subject safety and protections.*

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Most Recent Study Provided to the Sponsor

In an FDA letter dated January 6, 2017, FDA informed the sponsor of the following study design concerns :

- FDA believe that the 35% effectiveness Performance Goal may be too low given the patient population.
- FDA was concerned with a Safety Performance Goal of 20%
- FDA recommended the sponsor consider revising their Safety and Effectiveness Performance Goals to reflect the rates for the most successful treatment modality according to your literature analysis.
- This concern was provided in multiple letters throughout the trial.

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Objective Performance Criterion vs. Performance Goal

- OPC is a numerical target value
  - Developed when device technology has sufficiently matured
  - Historical patient-level data from clinical studies/registries
  - Used in a dichotomous (pass/fail) manner by FDA for the review and comparison
  - Usually not done by a single company nor FDA
  - It is important to point out that there are currently very few validated OPCs
- PG is also a numerical value
  - Developed when the device technology is not as well-developed or mature
  - Considered sufficient by FDA for use as a comparison for safety/effectiveness
  - Typically FDA works with Sponsors regarding Performance Goals

https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm373766.pdf

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WEB-IT Trial Design and Patient Population

- This trial was a prospective, multicenter, single arm study
- Include a total of 27 sites (21 US sites and 6 Outside the US)

Population	Description	# of Subjects
Consented	Subjects who signed informed consent form.	179
Screen Failures	Subject who were consented and failed initial screening of inclusion/exclusion criteria.	10
	Subject who were consented and failed procedural angiographic screening criteria.	18
Consented Not Treated	Subjects who were consented and passed initial screening but were not scheduled for procedure.	1
Intent to Treat (ITT)	All subjects in whom a WEB device was attempted to be implanted.	150
Complete Cases (CC)	ITT subjects with a 12-month evaluation for effectiveness.	143
Per Protocol (PP)	CC subjects without a serious protocol deviation.	143

Characteristic	WEB-IT Study (Mean)
Age	59
Weight (kg)	77
Height (cm)	165
Index Aneurysm - Maximum Sac Width (mm)	6.35
Index Aneurysm - Maximum Neck Width (mm)	4.75
Index Aneurysm - Max Dome-to-Neck Ratio (mm)	1.33

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Key Inclusion/Exclusion Criteria

Key Inclusion Criteria

- Single ruptured or unruptured IA requiring treatment.
  - *A ruptured IA patient was defined as a patient with CT, MRI, or LP evidence of subarachnoid hemorrhage attributed to the index aneurysm within the last 60 days.*
- The IA treated must have had the following characteristics:
  - Saccular in shape
  - Located in basilar apex (BA), MCA bifurcation, ICA terminus, AComm complex
  - Dome-to-Neck ratio ≥ 1
  - Diameter of the IA appropriate for treatment with the WEB per Instructions for Use
  - Wide-neck IA with neck size ≥ 4 mm or Dome-to-Neck ratio < 2;

Key Exclusion Criteria

- Patient had an IA with characteristics unsuitable for endovascular treatment
- Patient's index IA was previously treated
- Patient had modified Rankin Scale (mRS) ≥ 2 prior to presentation or rupture (as applicable);
- Patient had a subarachnoid hemorrhage (SAH) from a non-index aneurysm or any other intracranial hemorrhage within 90 days;
- Patient had a life expectancy of less than 5 years due to other illness or condition (in addition to an intracranial aneurysm)

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Treatment Population and Evaluation of Indication for Use

- Primarily treated incidental unruptured aneurysms.
- The Basilar Apex was the most common anatomical location
  - Only 4% of aneurysms were located at the ICA terminus.

Characteristic	%
Gender (Male)	26.67
Prior Rupture	6.00
Hunt and Hess (Ruptured Only)	
I	66.67
II	33.33
Unruptured Discovered	
Symptomatic	23.40
Incidental	76.60
Aneurysm Location	
AComm Complex	26.67
Basilar Apex	39.33
ICA Terminus	4.00
MCA Bifurcation	30.00
NIHSS Score at Baseline	
0	90.00
1	7.33
2	1.33
5	0.67
6	0.67
mRS (Unruptured)	
0	80.85
1	19.15

[N=150]

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Primary Safety Endpoint

- Primary safety endpoint was defined as the proportion of subjects with death of any non-accidental 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)) 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.

- The primary safety event rate was 0.67% (1/150) in the ITT.
  - A single primary safety endpoint event, a SAH adjudicated as a major stroke, occurred on post-procedure day 22.

Safety Results – Death and Stroke

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

The Panel will be asked to discuss and make recommendations on whether the rate of all neurological deaths or ischemic events observed within 1-year post-procedure in the WEB-IT study supports a reasonable assurance of safety. The Panel should also discuss and make recommendations on whether there are additional categories of AEs that should be included in the assessment of device safety.

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Safety – Late Death and Stroke

- While no deaths were reported during the trial, 4 Subjects died after completing 1 year of follow-up
  - ICH on day 753 related to a traumatic head injury
  - respiratory failure on day 589
  - bladder cancer day on 826
  - SAH on day 625 resulting from procedural rupture of the anterior cerebral artery after a second retreatment procedure of the index aneurysm with a Pipeline Embolization Device
- One subject suffered an ischemic stroke attributed to cerebrovascular disease unrelated to index aneurysm on day 556.

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Safety Results – modified Rankin Scale (mRS)

- As recommended by the prior Panel meeting, mRS assessments were performed at baseline and at 12 months follow-up.
- 10 subjects with unruptured aneurysms had an increased mRS at 12 months
  - One subjects with a baseline of zero had 12 month mRS of 4.

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

- For subjects with ruptured aneurysms, all subjects either maintained or improved their mRS

The Panel will be asked to discuss and make recommendations on the pre-specified primary safety endpoint definition and related analyses proposed in the WEB-IT study protocol. The Panel should be prepared to discuss the specific types, severity, and rates of serious adverse events (SAEs) that should be considered in the determination of reasonable safety of the WEB device for the proposed IFU, and whether additional ancillary safety analyses are needed to make this determination.

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Safety Results – AE's

System Organ Class	Preferred Term	AE Rate[a] %
Non-serious Adverse Events within 30 Days		
All	All	45.33
Nervous System Disorders	Ataxia	0.67
	Carotid Artery Dissection	0.67
	Dizziness	0.67
	Dizziness Postural	0.67
	Headache	13.33
	Hypoaesthesia	0.67
	Ischaemic Stroke	0.67
	Migraine	1.33
	Nystagmus	0.67
	Paraesthesia	0.67
	Subarachnoid Hemorrhage	0.67
	Transient Ischemic Attack	2.00

[N=150]

System Organ Class	Preferred Term	AE Rate[a] %
Non-serious Adverse Events within 31-365 Days		
All	All	43.33
Eye Disorders	Visual Impairment	2.67
Nervous System Disorders	Aphasia	0.67
	Carpal Tunnel Syndrome	0.67
	Cerebrovascular Disorder	0.67
	Dementia	0.67
	Dizziness	0.67
	Gait Disturbance	0.67
	Headache	13.33
	Ischaemic Stroke	1.33
	Memory Impairment	0.67
	Migraine	1.33
	Restless Leg Syndrome	0.67
	Sciatica	0.67
	Sensory loss	1.33
	Transient Ischemic Attack	1.33

[N=150]

Primary and Secondary Effectiveness Endpoints

- Primary effectiveness defined as the proportion of subjects with complete aneurysm occlusion using the WEB Occlusion Scale (WOS) without retreatment, recurrent subarachnoid hemorrhage, or significant parent artery stenosis (> 50% stenosis) at one year after treatment as assessed by the Core Laboratory.

- Secondary and other Effectiveness
  - Target Aneurysm Recurrence
  - Parent Artery Stenosis
  - Technical Success

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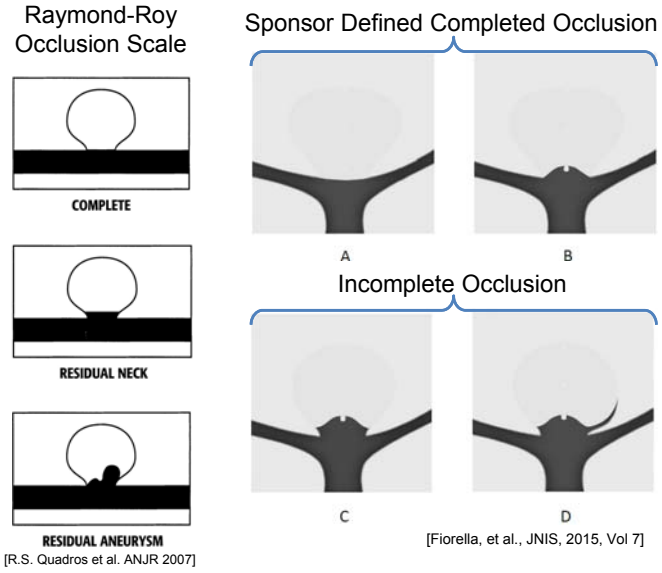
Evaluating the WEB Occlusion Scale (WOS)

- Effectiveness results were evaluated using the WOS as opposed to the more standard Raymond-Roy Occlusion Scale.
- Aneurysms with WOS-A and WOS-B were considered complete occlusions and therefore primary effectiveness successes.



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

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

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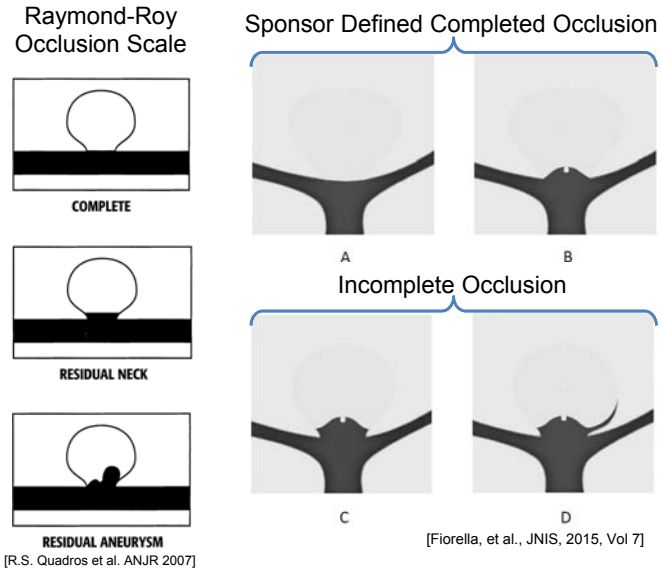
Evaluating the WEB Occlusion Scale (WOS)

The Panel will be asked to discuss and make recommendations on the appropriateness of the WEB Occlusion Scale (WOS) for effectiveness of IA occlusion using the WEB device as compared to the standard Raymond-Roy occlusion scale. FDA also requests the Panel to discuss and make recommendations on the appropriateness of defining WOS Grade B as complete intracranial aneurysm occlusion for device effectiveness success given the novel design and mechanism for cerebral blood flow disruption/diversion of the intrasaccular WEB device.



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

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

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Effectiveness Results – Occlusion Rates

Component	%
Primary Effectiveness Endpoint Success	53.85
With imaging without imputation in CC	95.10
Imputed as failure for CC	4.90
Aneurysm Occlusion	
Complete	53.85
Residual Neck	30.77
Residual Aneurysm	15.38
Imputed as Failure for Primary Effectiveness	4.90
Parent Vessel Stenosis	
None	89.51
≤ 50%	4.90
> 50%	0.70
Imputed as Failure for Primary Effectiveness	4.90
Adjunctive Device (Imputed as Failure)	1.40
Failure to Implant (Imputed as Failure)	1.40
Retreatment of Index Aneurysm (Imputed as Failure)	2.10
Recurrent Subarachnoid Hemorrhage	0.00

N=143 subjects, which is the total number of subjects with evaluable 12 month imaging data in the Completed Cases (CC) population

- Primary effectiveness was achieved in 54.77% of ITT subjects.
- 44 subjects (31%) had residual aneurysm neck at 12 months.
- More then 15% of subjects had a residual aneurysm at 12 months.

The Panel will be asked to consider the totality of the effectiveness data presented regarding whether the results support the reasonable assurance of effectiveness of the WEB device in the treatment of wide-neck bifurcation intracranial aneurysm studied in the WEB-IT study. The Panel should discuss any additional considerations in the effectiveness results compared to the performance goal of 35% for the primary effectiveness endpoint considering alternative available treatment modalities for the proposed patient population.

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N=143 subjects, which is the total number of subjects with evaluable 12 month imaging data in the Completed Cases (CC) population

- Primary effectiveness was achieved in 54.77% of ITT subjects.
- 8 subjects had vessel stenosis of less then or equal to 50%
- 3 subjects received retreatment and were imputed as failures
  - An addition 5 subjects had retreatment but remained angiographical not completely occluded.

The Panel will be asked to consider the totality of the effectiveness data presented regarding whether the results support the reasonable assurance of effectiveness of the WEB device in the treatment of wide-neck bifurcation intracranial aneurysm studied in the WEB-IT study. The Panel should discuss any additional considerations in the effectiveness results compared to the performance goal of 35% for the primary effectiveness endpoint considering alternative available treatment modalities for the proposed patient population.

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Effectiveness Results – Percent Occlusion

- The rate of complete occlusion decreased from 6 months to 12 months.
  - 87 subjects versus 81 subjects
- The number of subjects with a residual aneurysm neck Increased from 6 months to 12 months.
  - 35 subjects versus 44 subjects

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

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

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Effectiveness Results – Anatomical Location and Aneurysm Size

- Aneurysms were primarily located at the Basilar Apex (58/150).
  - Only 6 aneurysms were treated at the ICA bifurcation.
  - Trial was not powered for subgroup analysis based on aneurysms location.
- The aneurysm size was primarily smaller (< 8 mm, 79%)

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

N=143

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

N = 118 for < 8 mm
N = 25 for ≥ 8 mm

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Questions regarding retreatment options

- 5.6% of the CC population (8 subjects of the 143 CC cases) underwent or had planned retreatment during the 12 month study.
  - Additional retreatments have occurred outside of the study 12 month window for which the panel should also consider in its deliberations.
- Ability to retreatment may be a concern with this device.
  - Patient population (wide-neck bifurcation aneurysms) presents challenges for treatment with stents or flow diverters.
  - Device shape reduces the ability to retreat with embolic coils as the coils may not be stable in the aneurysm neck.
- The panel will be asked to consider retreatment as part of the benefit risk determination.

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Technical Success using the WEB Device

- Technical success was observed in 98.67% of subjects in the ITT population.
- Adjunctive Devices were used in a total of 7 cases.
  - 5 subjects were treated using an adjunctive balloon (acceptable under the protocol)
  - 2 subjects had implanted adjunctive devices (stents).
- Subjects with implantable adjunctive devices were considered failures with respect to the primary effectiveness outcome.
- Almost 30% of devices inserted were not implanted, with the most common reason being improper size.

Event	%
Technical Success[a] (N=150)	98.67
Technical Success[b] (N=150)	97.33
Adjunctive Devices Used[c] (N=148)	4.73
Balloon (Acceptable under Protocol)	3.38
Coils (Unacceptable under Protocol)	0.00
Stent (Unacceptable under Protocol)	1.35
Flow Diverter (Unacceptable under Protocol)	0.00

[a] Successful implantation of the WEB device during the index procedure.

[b] Successful implantation of the WEB device with implantable adjunctive device use during the index procedure as failures.

[c] Statistics computed for only cases where the WEB device was implanted during the index procedure (148 case)

Note: All 95% CIs presented in this table are unadjusted.

Disposition	%
Inserted	100
Not Implanted Reason	29.86
Improper Size	88.88
Other	11.11
Implanted	70.14

N = 211

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Clinical Data Summary

- The WEB-IT trial enrolled 150 intracranial bifurcation aneurysms.
- The primary effectiveness success was observed in 54.77% of subjects.
  - The lower bound 90% confidence interval resulted in primary effective rate of 46.63%
  - Occlusion was evaluated using the novel WEB Occlusion Scale (WOS).
- The primary safety analysis looked at major stroke (NIHSS $\geq$ 4 at 7 days) and death.
  - There was only 1 primary safety failure (major stroke) within 1 years.
  - 4 Subject deaths were reported greater then 1 year post treatment.
  - 12 strokes (8.0%) in 11 (7.3%) patients, where 11 were non-debilitating strokes and was 1 a debilitating stroke reported within 1 year post treatment.

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Presentation summary areas for discussion

Based on the information provided in the executive summary and today's presentation, FDA would like the panel to consider and comment on the following:

- The proposed indications for use.
- Appropriateness of MRA for longer term follow-up.
- Primary safety endpoint definition and related analyses.
- Appropriateness of the WEB Occlusion Scale (WOS).
- Rate of all neurological deaths or ischemic events observed.
- The totality of the effectiveness data presented for the intended population.

Thank You

Questions?

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