# SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

## I. GENERAL INFORMATION

| | |
|---|---|
| Device Generic Name: | Intrasaccular Flow Disruption Device |
| Device Trade Name: | Woven EndoBridge (WEB) Aneurysm Embolization System |
| Device Procode: | OPR |
| Applicant's Name and Address: | Sequent Medical, Inc.<br>11A Columbia Street<br>Aliso Viejo, CA 92656 |
| Date(s) of Panel Recommendation: | September 27, 2018 |
| Premarket Approval Application (PMA) Number: | P170032 |
| Date of FDA Notice of Approval: | 12/31/2018 |

## II. INDICATIONS FOR USE

The WEB Aneurysm Embolization System is indicated for use at the middle cerebral artery (MCA) bifurcation, internal carotid artery (ICA) terminus, anterior communicating artery (AComm) complex, or basilar artery apex for the endovascular treatment of adult patients with saccular, wide neck, bifurcation intracranial aneurysms with dome diameter from 3 mm to 10 mm and either neck size 4 mm or greater or the dome-to-neck ratio is greater than 1 and less than 2.

## III. CONTRAINDICATIONS

The WEB Aneurysm Embolization System is contraindicated in the following patients:

- Patients with known active bacterial infection that may interfere with or negatively affect the implantation procedure.
- Patients with known hypersensitivity to nickel.

## IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the WEB Aneurysm Embolization System labeling.

## V. DEVICE DESCRIPTION

The WEB Aneurysm Embolization System ("WEB") consists of an implantable device attached to a delivery system. The delivery system is navigated through compatible microcatheters with a specified minimum inner diameter (see Table 1) to the intracranial aneurysm (IA). An introducer sheath can be used to assist in the placement of the delivery system into the microcatheter. The WEB implant is electro-thermally detached by the physician with a hand-held, battery-powered detachment controller device designed specifically for the WEB Aneurysm Embolization System. The WEB Detachment Controller (WDC) is provided separately and is for single use only.


**Figure 1. WEB Aneurysm Embolization System**

The WEB implant is manufactured from nitinol wires and nitinol wires with a platinum core in a braided, self-expanding mesh configuration. The WEB implant is provided in a range of sizes (diameters and lengths) and two different shapes (barrel and sphere) (see Figure 2 and Table 1). During treatment, the physician selects the appropriate device size and shape based on the size, shape, and location of the IA.

**Figure 2. WEB Single Layer – Enhanced Visualization (SL EV) (left) and WEB Single Layer Sphere – Enhanced Visualization (SLS EV) (right) Implant Shapes**

**Table 1. WEB Sizes and Recommended Microcatheters**

| WEB SL/SLS EV Diameter (mm) | SL Heights Offered (mm) | SLS Height Offered (mm) | Minimum Microcatheter Inner Diameter (inches) | Recommended Microcatheter |
|---|---|---|---|---|
| 4 | 3 | 2.6 | 0.021 | VIA 21 |
| | 4 | | | |
| 5 | 3 | 3.6 | 0.021 | |
| | 4 | | | |
| | 5 | | | |
| 6 | 3 | 4.6 | 0.021 | |
| | 4 | | | |
| | 5 | | | |
| 7 | 3 | 5.6 | 0.021 | |
| | 4 | | | |
| | 5 | | | |
| | 6 | | | |
| 8 | 3 | 6.6 | 0.027 | VIA 27 |
| | 4 | | | |
| | 5 | | | |
| | 6 | | | |
| | 7 | | | |
| 9 | 4 | 7.6 | 0.027 | |
| | 5 | | | |
| | 6 | | | |
| | 7 | | | |
| | 8 | | | |
| 10 | 5 | 8.6 | 0.032 | VIA 33 |
| | 6 | | | |
| | 7 | | | |
| | 8 | | | |
| 11 | 6 | 9.6 | 0.032 | |
| | 7 | | | |
| | 8 | | | |
| | 9 | | | |

As shown in Figure 3 below, proximal and distal platinum radiopaque markers in all WEB device models allow WEB implant delivery under fluoroscopic visualization. The proximal end of all WEB implants incorporates a platinum-iridium coupler for attachment to the delivery system. There is zero (0) interwire distance at the proximal marker band adjacent to the coupler where all the wires converge (100% metal coverage and zero porosity).

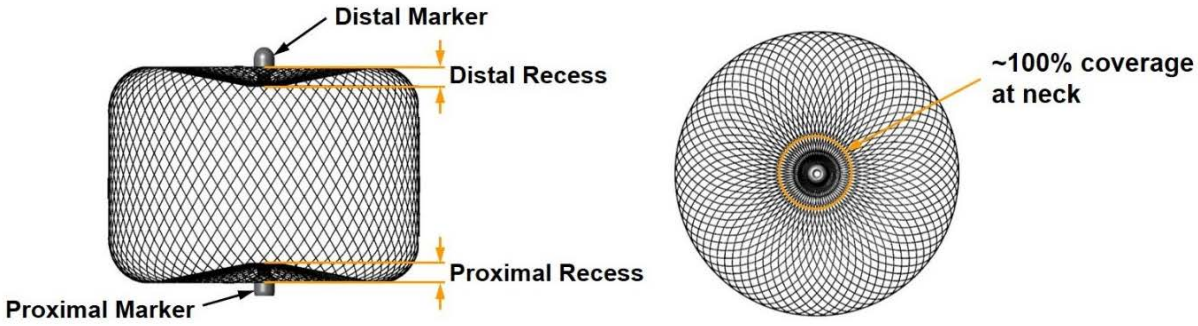



**Figure 3. WEB Implant Design Characteristics**

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of wide-neck intracranial aneurysms that are directed at the aneurysm itself. These alternatives include open surgical clipping and endovascular treatment using neurovascular embolic coil assist stents to support embolization coils in the intracranial aneurysm sac and balloon catheter assisted coiling of the intracranial aneurysm. The neurovascular embolic coil assist stents available in the United States (US) for stent-assisted coiling of wide-neck intracranial aneurysms were approved through the premarket approval (PMA) and Humanitarian Device Exemption (HDE) regulatory pathways. Specifically, these are the MicroVention, Inc. Low-Profile Visualized Intraluminal Support (LVIS) and LVIS Jr. (P170013), the Stryker Neurovascular Neuroform EZ, 3, Atlas Stent Systems (H020002), and the Codman & Shurtleff, Inc. Enterprise Vascular Reconstruction Device and Delivery System (H060001). A similar HDE approved device that is indicated to support neurovascular embolization coils specifically for the treatment of unruptured wide-necked intracranial aneurysms originating on or near a vessel bifurcation of the basilar tip or carotid terminus is the Pulsar Vascular, Inc. PulseRider Aneurysm Neck Reconstruction Device (H160002).

Neurovascular flow-diverting stents are implanted in the parent artery adjacent to an aneurysm. They are intended to be used by themselves as a stand-alone device. Flow diverters are implanted in the parent artery across the neck of the intracranial aneurysm to divert the blood flow away from the intracranial aneurysm sac. Eventually, endothelial growth around the stent may promote intracranial aneurysm occlusion. The Micro Therapeutics, Inc., Pipeline Embolization Device (PED) and Pipeline Flex Embolization Device (P100018) and Stryker Neurovascular's Surpass Streamline Flow Diverter (P170024) are approved neurovascular flow diverting stents in the US. The PED is approved with the indications for use of endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms in the internal carotid artery (ICA) from the petrous to the superior hypophyseal segments. The Pipeline Flex Embolization Device has the same indications for use as the PED and also the expanded indications for use in the ICA up to the terminus for the endovascular treatment of adults (22 years of age or older) with small and medium wide-necked (neck width $\geq$ 4 mm or dome-to-neck ratio < 2) saccular or fusiform IAs arising from a parent vessel with a diameter $\geq$ 2.0 mm and $\leq$ 5.0 mm. The Surpass Streamline Flow Diverter is approved

with the indications for use in the endovascular treatment of patients (18 years of age and older) with unruptured large or giant saccular wide-neck (neck width ≥ 4 mm or dome-to-neck ratio < 2) or fusiform IAs in the ICA from the petrous segment to the terminus arising from a parent vessel with a diameter ≥ 2.5 mm and ≤ 5.3 mm.

Instead of interventional treatments, some may choose conservative medical management or observation with brain imaging to detect any significant morphological changes in the intracranial aneurysm.

Each alternative has its own advantages and disadvantages. Also, each of these alternatives has long and short-term risks and benefits that should be understood by the patients. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

## VII. MARKETING HISTORY

The WEB Aneurysm Embolization System is approved for marketing in the following countries:

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.

The WEB Aneurysm Embolization System has not been withdrawn from marketing for any reason related to its safety or effectiveness.

## VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the probable adverse effects and complications associated with the use of the device.

- Allergic reaction, including but not limited to: contrast dye, nitinol metal, and any other medications used during the procedure
- Anesthesia related complications including airway injury, dental injury, adverse effects of anesthetics, hypoxia, corneal abrasions, and malignant hyperthermia
- Local field inhomogeneity and susceptibility artifacts during magnetic resonance angiography (MRA)
- Aphasia
- Blindness
- Cardiac arrhythmia
- Complications of arterial puncture including pain, local bleeding, local infection, pseudoaneurysm, arteriovenous fistula, injury to the artery, vein, or adjacent nerves, limb ischemia, and retroperitoneal hematoma
- Cranial neuropathy
- Death

- Device fracture, migration or misplacement including device prolapse or migration into normal vessel adjacent to intracranial aneurysm
- Embolic shower: thrombus, cholesterol, or air emboli
- Dissection or perforation of the aneurysm or vessels in the vasculature
- Headache
- Hemorrhage including intracranial hemorrhage (ICH), subarachnoid hemorrhage (SAH), retroperitoneal (or in other locations), and gastrointestinal
- Hemiplegia
- Hydrocephalus
- Infection
- Injury to normal vessel or tissue
- Ischemia
- Mass effect
- Myocardial infarction
- Neurological deficits
- Patient positioning related injuries including pressure ulcers, limb ischemia, and neuropathy
- Pseudoaneurysm formation
- Reactions to anti-platelet and anti-coagulant agents
- Reactions due to radiation exposure including alopecia, burns ranging in severity from skin reddening to ulcers, cataracts, and delayed neoplasia
- Renal failure
- Rupture of intracranial aneurysm
- Seizure
- Stroke or transient ischemic attack
- Thromboembolic event
- Urinary tract injury secondary to bladder catheterization
- Vasospasm
- Visual impairment

For the specific adverse events that occurred in the clinical study, please see Section X below.

## IX. SUMMARY OF NONCLINICAL STUDIES

The WEB Aneurysm Embolization System and the WDC underwent non-clinical mechanical, functional, biocompatibility, sterilization validation, bacterial endotoxin, and animal testing to support the proposed intended use.

## A. Laboratory Studies

Performance (Bench) Testing

The following table (Table 2) shows laboratory design verification bench testing performed on the WEB Aneurysm Embolization System. The device met all established acceptance criteria.

**Table 2. WEB Aneurysm Embolization System Bench Testing**

| Test Name | Test Method Description | Results |
|---|---|---|
| Visual and Dimensional (WEB Implant and Delivery System) | Inspect for visual WEB Implant and Delivery System criteria. Measures dimensional attributes of the WEB Implant and Delivery System. Measures the device's initial electrical resistance. | **PASS** |
| Dome Deployment Force | Measures peak force exerted on the dome of an aneurysm model as WEB Implant is deployed. | **PASS** |
| Flat Plate Crush (Radial Force) | Measures the force required to compress the WEB Implant between two plates until it reaches a defined percent of its original outer diameter. | **PASS** |
| WEB Tensile Distal End Weld | Measures ultimate tensile strength (peak force) of WEB Implant (distal to proximal marker band). | **PASS** |
| Detachment Zone Tensile | Measures ultimate tensile strength (peak force) of distal detachment zone junction (tether to WEB Implant) and ultimate tensile strength of tether anchor junction (tether to WEB Delivery System). | **PASS** |
| Hypotube to Core Wire Tensile | Measures ultimate tensile strength of proximal WEB Delivery System junctions. | **PASS** |
| Proximal Connector to Core Wire Tensile | Measures ultimate tensile strength of proximal WEB Delivery System junctions. | **PASS** |
| Overcoil Tensile: Hypotube to Segment II | Measures ultimate tensile strength of overcoil junctions. Tests that the overcoil will not kink when subjected to a worst-case diameter. | **PASS** |
| Overcoil Tensile: Segment II to Segment III | Measures ultimate tensile strength of overcoil junctions. Tests that the overcoil will not kink when subjected to a worst-case diameter. | **PASS** |
| Overcoil Kink | Measures ultimate tensile strength of overcoil junctions. Tests that the overcoil will not kink when subjected to a worst-case diameter. | **PASS** |
| Tracking Force | Measures the peak force required to track a WEB device through the smallest recommended microcatheter in a clinically relevant tortuous model. | **PASS** |

| Test Name | Test Method Description | Results |
|---|---|---|
| WEB Retraction in Microcatheter | Measures the distance that the microcatheter tip pulls back when a worst-case WEB size is recaptured inside of a clinically relevant tortuous model. | **PASS** |
| Particulate Evaluation after Simulated Use with Microcatheter | Counts the particulates generated after a worst-case WEB size is cycled through a microcatheter inside a clinically relevant tortuous model. | **PASS** |
| Cycling and Detachment | Test that the device's electrical resistance remains intact during worst case cycling through a microcatheter in a clinically relevant tortuous model. Test that the tether does not break during worst case cycling through a microcatheter in a clinically relevant tortuous model. Test that the WEB Implant successfully detaches after worst case cycling through a microcatheter in a clinically relevant tortuous model. | **PASS** |
| Magnetic Resonance Imaging (MRI) Compatibility | Magnetic field interaction heating and image artifacts at 3 Tesla (T). Detailed methods described in test report. | **PASS** |
| Corrosion Resistance | Measures the pitting/crevice corrosion of WEB Implants pre-fatigue, as well as after 3-month and 10-year simulated fatigue. Measures rate of galvanic corrosion for WEB Implant wires/marker band couples. | **PASS** |
| WEB Wire Integrity after 10-Year Equivalent Fatigue | Measures number of broken WEB Implant wires after simulated fatigue. Implants are deployed in mock vessels and are subjected to clinically relevant flow conditions for a defined number of cycles equivalent to 10-years before inspection for broken wires. | **PASS** |
| WEB Percent Metal Analysis | Characterization Only – Characterizes the relationship between number of wires, wire size, braid angle, and percent metal coverage compared to flow diverter. Mathematical calculations to establish porosity and % metal coverage of WEB Implants. | **N/A** – Characterization Only. Average WEB Implant % metal coverage at aneurysm neck is ≥ 58%. The % metal coverage of WEB Implant is greater than comparison flow diverter device. |
| WEB Fluid Penetration Characteristics (Wash-Out from an | Characterization Only – Devices deployed in in-vitro aneurysm model. Dye penetration and wash out characteristics were captured with digital imaging/video. | **N/A** – Characterization Only. Dye penetration and washout characteristics |

| Test Name | Test Method Description | Results |
|---|---|---|
| In-Vitro Aneurysm Model) | | similar to comparison flow diverter device. |
| Characterization of WEB Implant Nitinol Properties | Characterization Only – Austenite finish ($A_f$) temperature determined with ASTM F2004 thermal analysis method and ASTM F2082 bend and free recovery method. Super-elastic properties of wire demonstrated via tensile testing per ASTM F2516. | **N/A** – Characterization Only. Average $A_f$ temperature was 14 °C. Heat set nitinol wire exhibited super-elastic properties. |

Table 3 shows laboratory design verification bench testing performed on the WDC. The device met all established acceptance criteria.

**Table 3. WEB Detachment Controller Bench Testing**

| Test Name | Test Method Description | Results |
|---|---|---|
| Power Off When Not in Use | Test there is no current through device when device is not in use, tested at both the +8 volt (V) and +5 V terminals. | **PASS** All units had a current ≤ 1 mA at both terminals when device was powered off. |
| Timeout | Device shuts off automatically if detachment button is not pressed within specified length of time. Measures the time until shut off after a WEB Delivery System is inserted. | **PASS** |
| Detachment Voltage Output and Duration (Detachment Time) | Measures the voltage output and firing duration during detachment. | **PASS** |
| Pre-detachment Resistance Check - Load In Range (LIR) & Load Out of Range (LOR) | Verifies that the WDC produces the correct indicators when both in-range and out-of-range probes are inserted. | **PASS** All units displayed correct light emitting diode (LED), buzzer, and firing signals for LIR and LOR probes. |
| Shut-off Current | The WDC shuts off automatically if current limit is reached. Measures current at which WDC automatically shuts off. | **PASS** |
| Electrical Safety Testing | Ensures the WDC passes all electrical safety testing in accordance with ISO 60601-1:2006+A12:2014. | **PASS** |
| Electromagnetic Compatibility (EMC) Testing | Ensures the WDC passes all EMC testing in accordance with ISO 60601-1-2:2015. | **PASS** |

Biocompatibility

Biocompatibility testing of sterile finished WEB Aneurysm Embolization Systems were performed in accordance with ISO 10993-1, Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing within a Risk Management Process (see Table 4 and Table 5

for biocompatibility testing for the WEB implant and delivery system, respectively). The device passed all established acceptance criteria.

**Table 4. WEB Implant Biocompatibility**

| Biological Effect | Test | Applicable Standard | Result |
|---|---|---|---|
| Cytotoxicity | International Standard Organization (ISO) Minimum Essential Media (MEM) Elution Assay with L-929 Mouse Fibroblast | ISO 10993-5:2009 | Non-cytotoxic |
| Sensitization | ISO Guinea Pig Maximization Sensitization | ASTM F720-81 (2002) | No sensitization response |
| Irritation/ Intracutaneous Reactivity | ISO Intracutaneous Reactivity Test | ISO 10993-10:2010 | Non-irritant |
| Systemic Toxicity (Acute) | ISO Acute Systemic Injection Test | ISO 10993-11:2006 | Non-toxic |
| Pyrogenicity | Materials Mediated Rabbit Pyrogen Test | ISO 10993-11:2006 | Non-pyrogenic |
| Implantation | 2 Week Subcutaneous Implant Study in Rabbits | ISO 10993-6:2007 | Non-toxic, non-irritant compared to control. |
| Subchronic Toxicity/ Implantation | 13 Week Subcutaneous Implant Toxicity Study in Rabbits | ISO 10993-6:2007<br>ISO 10993-11:2006 | Non-toxic, non-irritant compared to control. |
| Genotoxicity | In Vitro Mouse Lymphoma Assay | ISO 10993-3:2003 | Non-mutagenic |
| Genotoxicity | Bacterial Mutagenicity Test – Ames Assay | ISO 10993-3:2003 | Non-mutagenic |
| Genotoxicity | In Vivo Mouse Micronucleus Assay | ISO 10993-3:2003 | Non-mutagenic |
| Hemocompatibility | Complement Activation with Comparison Article | ISO 10993-4:2002 (2006) | Results of test group comparable to control group. |
| Hemocompatibility | ASTM Hemolysis Assay Direct Contact and Extract | ISO 10993-4:2002 (2006)<br>ASTM F619-03<br>ASTM F756-08 | Non-hemolytic under direct and extract test conditions. |
| **Extractables and Leachables Testing** | | | |
| Metal Leachables Testing | 14-Day and 60-Day Metal Leachables in Saline at 37 °C | N/A | All metal leachables below tolerable intake levels. |
| Extractables Testing (Metals | Metal and Organic Chemical Extractables Testing in Worst Case | N/A | All extractables below tolerable intake levels. |

| Biological Effect | Test | Applicable Standard | Result |
|---|---|---|---|
| and Organic Chemicals) | Solvents (Isopropyl Alcohol (IPA), Hexane, Acidified Water) at 50 °C | | |

**Table 5. WEB Delivery System Biocompatibility**

| Biological Effect | Test | Applicable Standard | Result |
|---|---|---|---|
| Cytotoxicity | ISO MEM Elution Assay with L-929 Mouse Fibroblast | ISO 10993-5:2009 | Non-cytotoxic |
| Sensitization | ISO Guinea Pig Maximization Sensitization | ASTM F720-81 (2002) | No sensitization response |
| Irritation/ Intracutaneous Reactivity | ISO Intracutaneous Reactivity Test | ISO 10993-10:2010 | Non-irritant |
| Systemic Toxicity (Acute) | ISO Acute Systemic Injection Test | ISO 10993-11:2006 | Non-toxic |
| Pyrogenicity | Materials Mediated Rabbit Pyrogen Test | ISO 10993-11:2006 | Non-pyrogenic |
| Genotoxicity | In Vitro Mouse Lymphoma Assay | ISO 10993-3:2003 | Non-mutagenic |
| Genotoxicity | Bacterial Mutagenicity Test – Ames Assay | ISO 10993-3:2003 | Non-mutagenic |
| Genotoxicity | In Vivo Mouse Micronucleus Assay | ISO 10993-3:2003 | Non-mutagenic |
| Hemocompatibility | Complement Activation with Comparison Article | ISO 10993-4:2002 (2006) | Results of test group comparable to control group. |
| Hemocompatibility | 4 Hour Thromboresistance Evaluation in Dogs | ISO 10993-4:2002 (2006) | Thromboresistance characteristics of test group similar to control. |
| Hemocompatibility | ASTM Hemolysis Assay Direct Contact and Extract | ISO 10993-4:2002 (2006) ASTM F619-03 ASTM F756-08 | Non-hemolytic under direct and extract test conditions. |
| **Extractables Testing** | | | |
| Extractables Testing (Metals and Organic Chemicals) | Metal and Organic Chemical Extractables Testing in Worst Case Solvents (IPA, Hexane, Acidified Water) at 50 °C | N/A | All extractables below tolerable intake levels. |

## B. Animal Studies

Animal studies in elastase induced aneurysms in New Zealand White rabbits were performed to evaluate the acute, subchronic, and chronic performance of the WEB Aneurysm Embolization System regarding immediacy, degree, and durability of aneurysm occlusion (see Table 6). Histopathology findings were also examined and reported in some studies. Test results show that the 45-day, 90-day and 365-day specimens demonstrated high rates of progressive aneurysm occlusion. Histologic evaluation demonstrated an absent or mild inflammatory response.

**Table 6. Preclinical Animal Studies**

| Study | Animal Model | Total # of Animals | Follow-up Time Points | Major Endpoints |
|---|---|---|---|---|
| Feasibility of WEB SL and SLS | Rabbit vein-pouch arterial aneurysm model | 8 | Time of deployment, 2-months, and 3-months. | Immediacy, degree, and durability of aneurysm occlusion. |
| Feasibility of WEB SLS | Rabbit elastase aneurysm model | 6 | Time of deployment and 1.5 months. | Immediacy, degree, and durability of aneurysm occlusion. Histopathology. |
| Acute, Subchronic, and Chronic Evaluation of WEB | Rabbit elastase aneurysm model | 36 | Time of deployment, 3-months, and 12-months. | Immediacy, degree, and durability of aneurysm occlusion. Histopathology. |

## C. Additional Studies

MRI Compatibility

Non-clinical testing demonstrated that the WEB implant is magnetic resonance (MR) Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 3-Tesla or less.
- 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.

Under the scan conditions defined above, the WEB implant is expected to produce a maximum temperature rise of +1.4 °C after 15 minutes of continuous scanning (i.e., per pulse sequence).

In non-clinical testing, the 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.

The WEB device may create local field inhomogeneity and susceptibility artifacts during magnetic resonance angiography (MRA), which may degrade the diagnostic quality to assess effective intracranial aneurysm treatment. Users should only use digital subtraction angiography (DSA) or computed tomography angiography (CTA) to assess intracranial aneurysm occlusion for patient follow-up.

Sterilization Validation

The WEB Aneurysm Embolization System is sterilized using gamma irradiation with a sterility assurance level (SAL) of $10^{-6}$ validated per BS EN ISO 11137-1 (2013) and BS EN ISO 11137-2 (2015). The WEB Detachment Controller is sterilized using ethylene oxide sterilization to a SAL of $10^{-6}$ and validated per BS EN ISO 11135-1 (2014) and ISO 10993-7 (2009).

Routine Limulus Amebocyte Lysate (LAL) batch release testing is performed for every sterile load of WEB devices using the kinetic chromogenic method. Devices are held to the specification of < 0.06 endotoxin units (EU)/mL and < 2.15 EU/device in accordance with ANSI/AAMI ST72 (2011).

Shelf-Life

Real time shelf-life testing was conducted on the WEB device and packaging to support a labeled shelf-life of 36 months. Real time shelf-life testing was conducted on the WEB Detachment Controller and packaging to support a labeled shelf-life of 12 months.

## X. SUMMARY OF PRIMARY CLINICAL STUDY (WEB-IT)

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of endovascular treatment with the WEB Aneurysm Embolization System for obtaining occlusion of wide-neck aneurysms at the MCA bifurcation, ICA terminus, AComm complex, and basilar apex. The study was limited to adult patients with saccular, wide neck, bifurcation intracranial 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 greater than 1 and less than 2 mm. The study was performed in the US, Canada, Denmark, Hungary, Turkey, and Germany under IDE #G130286. Data from this clinical study are the basis for the PMA approval decision. A summary of the clinical study is presented below.

### A. Study Design

Patients were treated between August 19, 2014 and March 7, 2016. The database for this PMA reflected data collected through April 21, 2017 and included 179 patients. There were 27 investigational sites.

The study, titled "*The WEB Intrasaccular Therapy Study (WEB-IT),*" was a prospective, multi-center, single arm, open label clinical study. The pivotal study included follow-up

at discharge, 30-days, 6-months and 12-months. The pre-specified safety and effectiveness primary endpoints in the clinical study protocol were:

- Safety: 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) as of day 7 post onset) 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.

- Effectiveness: Successful aneurysm treatment with WEB as defined by 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 Lab.

The control group was based on performance goals (PGs) developed using prior published data from endovascular intracranial aneurysm treatment and open surgical clipping. The PGs for the primary safety and effectiveness endpoints are 20% and 35%, respectively. Study analyses were conducted using a standard frequentist approach to statistical analysis. The clinical study report provides descriptive statistics such as mean, standard deviation, and frequency charts for baseline participant characteristics, subject disposition, and other relevant study parameters. The primary analysis population was the 150-patient modified intent-to-treat (mITT) population of all study subjects in whom there is an attempt to place the WEB device. All planned statistical analyses were performed using a one-sided nominal significance level of 0.05.

This study included an independent Clinical Events Committee (CEC), Data Safety and Monitoring Board (DSMB), angiographic imaging Core Laboratory ("Core Lab"), and study monitors who confirmed neurological assessments, adverse events, imaging data, and study data with source documentation.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the WEB-IT study was limited to patients who met the following inclusion criteria.

   - Patient must be 18-75 years of age at the time of screening.
   - Patient must have a single ruptured or unruptured IA requiring treatment. If the patient had an additional IA requiring treatment, the additional IA must not require treatment within 60-days of the index procedure.
     *Definition: For the purposes of this study, a ruptured IA patient was defined as a patient with computed tomography (CT), magnetic resonance imaging (MRI), or lumbar puncture (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, anterior communicating artery complex (AComm);
    - Dome-to-Neck (DN) ratio ≥ 1;
    - Diameter of the IA appropriate for treatment with the WEB Aneurysm Embolization System per device Instructions for Use; and
    - Wide-neck IA with neck size ≥ 4 mm or DN < 2.
- Patient had an IA that was appropriate for treatment with WEB without the use of additional implanted devices.
- If the IA previously ruptured, patient must be neurologically stable with Hunt & Hess Score of I or II.
- Patient was able to comply with all aspects of the screening, evaluation, treatment, and the post-procedure follow-up schedule.
- Patient signed and dated an institutional review board (IRB)/Ethics Committee (EC)-approved written informed consent prior to initiation of any study procedures.

Patients were <u>not</u> permitted to enroll in the WEB-IT study if they met any of the following exclusion criteria.

- Patient had an IA with characteristics unsuitable for endovascular treatment.
- Microcatheter did not reach patient's index aneurysm to allow necessary access to treat with study device.
- Patient had vessel characteristics, tortuosity or morphology which precluded safe access and support during treatment with study device.
- Patient had vascular disease or other vascular anomaly that precluded the necessary access to the aneurysm for use of the study device.
- Patient had clinical, angiographic or CT evidence of vasospasm, vasculitis, an intracranial tumor (except small meningioma) or any other intracranial vascular malformations on presentation.
- Patient had conditions placing them at high risk for ischemic stroke or had exhibited ischemic symptoms such as transient ischemic attacks, minor strokes, or stroke-in-evolution within the prior 60-days.
- Patient had any circulatory, neurovascular, cardiovascular, or neurologic conditions that resulted in unstable neurological symptoms.
- Patient had modified Rankin Scale (mRS) score ≥ 2 prior to presentation or rupture (as applicable).
- Patient had an SAH from a non-index aneurysm or any other intracranial hemorrhage within 90-days.
- Patient had physical, neurologic or psychiatric conditions which precluded his/her ability to comply with all aspects of the screening, evaluation, treatment, and the post-procedure follow-up schedule.
- Patient's index IA was previously treated.
- Patient was taking anticoagulants or had a known blood dyscrasia, coagulopathy, or hemoglobinopathy.
- Patient was pregnant.

- Patient had known hypersensitivity, which could not be medically treated, to any component of the study device, procedural materials, or medications commonly used during the procedure.
- Patient was concurrently involved in another investigational study or a post-market study that could affect the safety and effectiveness of IA treatment with the study device or with the study's follow-up schedule.
- Patient had an acute life-threatening illness other than the neurological disease to be treated in this trial.
- Patient had a life expectancy of less than 5 years due to other illness or condition (in addition to an intracranial aneurysm).

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at discharge, 30 days (± 7 days), 6 months (± 30 days), and 12 months (± 7 weeks) postoperatively. Table 7 shows the parameters measured during the study visits, which included a review of the concomitant medications, physical, clinical, neurological, and angiographic evaluations. Adverse events and complications were recorded at all visits. The key assessment timepoints are shown below in the tables summarizing safety and effectiveness.

**Table 7. Schedule of Assessments.**

| **Parameter** | **Screening** | **Procedure** | **Discharge** | **30-Day Follow-Up** | **6-Month Follow-Up** | **1-Year Follow-Up** | **2- and 4-Year Follow-Up** | **3- and 5-Year Follow-Up** |
|---|---|---|---|---|---|---|---|---|
| Health history | X | | | | | | | |
| Physical examination | X | X | X | | X | X | | X |
| Neurological examination | X | | | | X | X | | X |
| Site and subject information | X | | | | | | | |
| Aneurysm information (size, location, etc.) | X | X | | | | | | |
| Rupture status | X | | | | | | | |
| Hunt and Hess Grade (ruptured aneurysms only) | X | | | | | | | |
| Microcatheter(s) used | | X | | | | | | |
| Ancillary devices used (e.g., stent, balloon used) | | X | | | | | | |
| Medications used | X | X | X | | X | X | | X |
| Size and lot number of WEB device(s) used | | X | | | | | | |
| WEB procedure fluoroscopy time | | X | | | | | | |
| Total procedure fluoroscopy time | | X | | | | | | |
| 3D angiographic imaging | X | X | | | X | X | **Optional** | X* |
| Additional imaging per standard of care | | | | | | | X | X |
| Occlusion assessments (Core Lab) | | X | | | X | X | **Optional** | X* |
| Modified Rankin Scale (mRS) score | X | | X | X | X | X | | |
| NIHSS score | X | **As required** | | | | | | |
| Quality of Life (QOL) Assessment (EQ-5D) | | | | | X | | | |

| Parameter | Screening | Procedure | Discharge | 30-Day Follow-Up | 6-Month Follow-Up | 1-Year Follow-Up | 2- and 4-Year Follow-Up | 3- and 5-Year Follow-Up |
|---|---|---|---|---|---|---|---|---|
| Additional scales as appropriate | | X | | | X | X | Optional | Optional |
| Technical events | | X | | | | | | |
| Adverse events | | X | X | X | X | X | X | X |
| Retreatments/Additional Procedures | | | | X | X | X | X | X |
| Re-bleed (if ruptured)/New bleed | | | X | X | X | X | X | X |
| Comments | X | X | X | X | X | X | X | X |

* Per local site standard of care.

3. Clinical Endpoints

With regards to safety, the percentage of patients who had a disabling stroke (defined as mRS score ≥ 3 assessed at a minimum of 90-days post-stroke event), major stroke (increase of 4 or more points on the NIHSS at 24 hours after symptom onset), or neurological death within 12-months post-procedure was used to analyze the clinical study results.

With regards to effectiveness, the percentage of subjects who had complete occlusion of the target intracranial aneurysm assessed using the WOS A or B without re-treatment, recurrent subarachnoid hemorrhage (SAH), or significant parent artery stenosis (> 50% stenosis) within 12-months post-procedure was used to analyze the clinical study results.

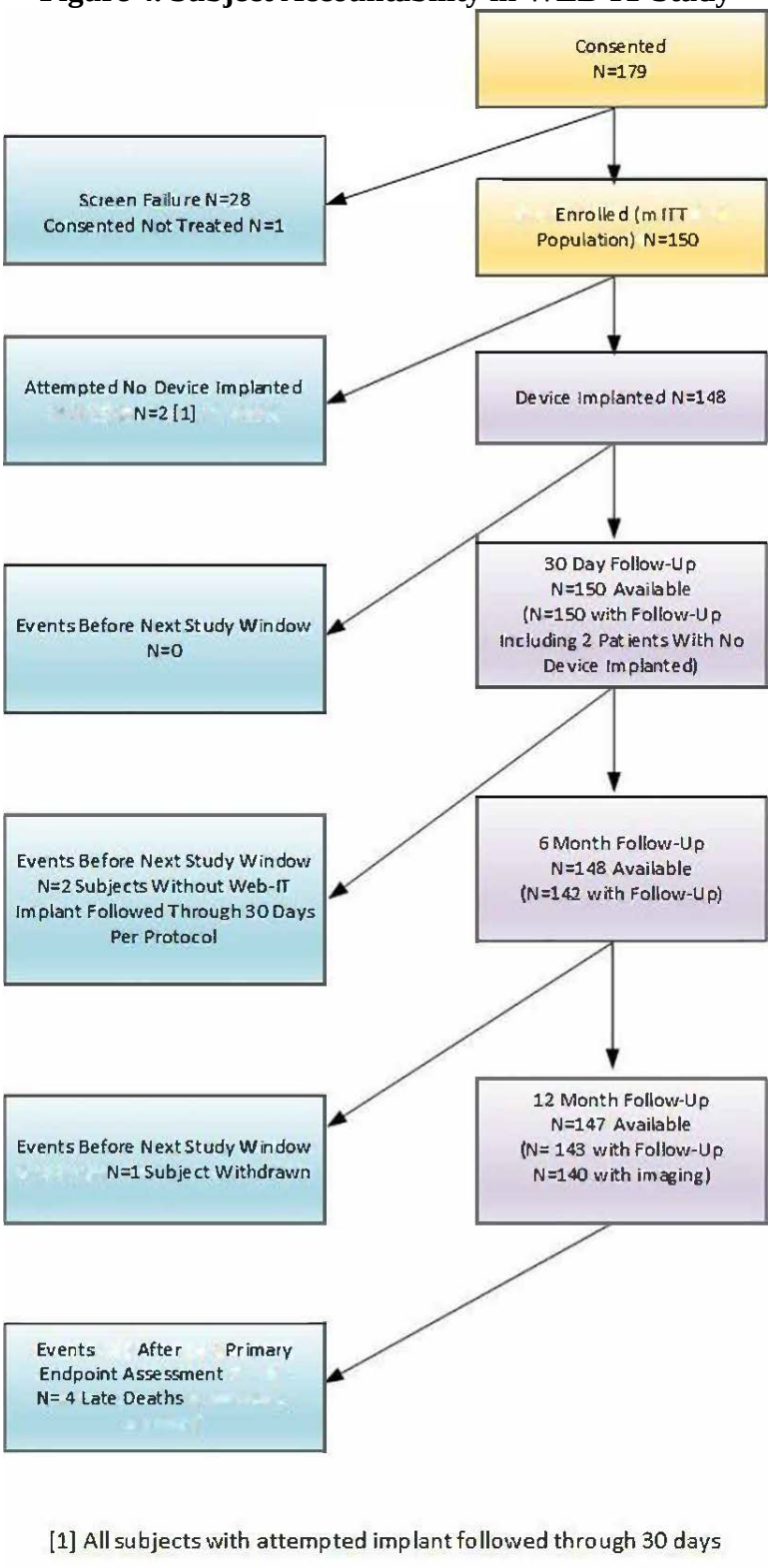
Criteria for success and failure compared the primary outcomes to pre-specified PGs developed from the published literature based on a patient population similar to those treated in the WEB-IT trial using alternative treatment modalities (endovascular treatment or open surgery). The primary endpoints were analyzed using the mITT population and Fisher's Exact Binomial test. The mITT population (N=150) was defined in the clinical protocol as all enrolled subjects for whom the investigational device entered the body, regardless of whether the device was successfully implanted. For safety, a one-sided p-value < 0.05 results in rejecting the null hypothesis that the primary safety endpoint is 20% or higher with the WEB Aneurysm Embolization System. For effectiveness, a one-sided p-value < 0.05 results in rejecting the null hypothesis that the likelihood of effective treatment with the subject device based on the primary effectiveness endpoint definition is ≤ 35%. As part of the decision-making process for the subject PMA, the FDA did not consider the effectiveness or safety PGs of 35% and 20%, respectively, to be acceptable and evaluated the safety and effectiveness profile of the WEB Aneurysm Embolization System based on the results of the WEB-IT trial.

## B. Accountability of PMA Cohort

At the time of database lock, of 179 patients enrolled in the PMA study, 83.8% (150) of patients are available for analysis at the completion of the study, the 12-month post-

operative visit. See Figure 4 below for a modified CONSORT diagram of the disposition of subjects enrolled in the study.

**Figure 4. Subject Accountability in WEB-IT Study**



## C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an intracranial aneurysm treatment study performed in the US. This disease predominantly affects more women than men and most patients are Caucasian. The WEB-IT trial population baseline characteristics aligned with these expectations. Baseline characteristics are described in Table 8 and Table 9. Table 8 presents baseline age, weight, and height and digital subtraction angiogram (DSA) measurements of the target intracranial aneurysm.

**Table 8. IA Continuous Baseline Measurements (N=150)**

| Characteristic | Mean (Standard Deviation (SD)) Median (Min, Max) |
|---|---|
| Age | 58.98 (10.16)<br>59 (29, 79) |
| Weight (kg) | 77.25 (19.47)<br>75.8 (40.8, 142.9) |
| Height (cm) | 165.33 (9.70)<br>163.5 (149.9, 193.0) |
| Index Aneurysm - Maximum Sac Width (mm) | 6.35 (1.55)<br>6.25 (3.58, 11.40) |
| Index Aneurysm - Maximum Neck Width (mm) | 4.75 (1.13)<br>4.67 (2.0, 8.2) |
| Index Aneurysm - Max Dome-to-Neck Ratio | 1.3365 (0.2474)<br>1.2898 (1.0000, 1.9968) |

**Table 9. Categorical Baseline Characteristics**

| Characteristic | Number (%) Unadjusted (Lower Confidence Limit, Upper Confidence Limit) |
|---|---|
| Gender (Male) | 40/150 (26.67) (19.78, 34.49) |
| Race[a] | |
| Asian | 4/116 (3.45) (0.95, 8.59) |
| Black or African American | 14/116 (12.07) (6.76, 19.42) |
| White | 98/116 (84.48) (76.59, 90.54) |
| Ethnicity[a] | |
| Hispanic or Latino | 2/116 (1.72) (0.20, 6.09) |
| Not Hispanic or Latino | 114/116 (98.28) (93.91, 99.79) |
| Prior Rupture | 9/150 (6.00) (2.78, 11.08) |
| Hunt and Hess (Ruptured Only) | |
| I | 6/9 (66.67) (29.93, 92.51) |
| II | 3/9 (33.33) (7.49, 70.07) |
| Unruptured | |
| Symptomatic | 33/141 (23.40) (16.69, 31.27) |

| Characteristic | Number (%) Unadjusted (Lower Confidence Limit, Upper Confidence Limit) |
|---|---|
| Incidental | 108/141 (76.60) (68.73, 83.31) |
| History of Cardiovascular/Circulatory Disease | 106/150 (70.67) (62.69, 77.81) |
| Angina | 2/150 (1.33) (0.16, 4.73) |
| Arrhythmia | 7/150 (4.67) (1.90, 9.38) |
| Cardiomyopathy | 1/150 (0.67) (0.02, 3.66) |
| Coronary Artery Disease | 21/150 (14.00) (8.88, 20.60) |
| Heart Failure | 3/150 (2.00) (0.41, 5.73) |
| Heart Block | 1/150 (0.67) (0.02, 3.66) |
| Hypertension | 98/150 (65.33) (57.14, 72.91) |
| Hypotension | 5/150 (3.33) (1.09, 7.61) |
| Myocardial Infarction | 6/150 (4.00) (1.48, 8.50) |
| Peripheral Vascular Disease | 5/150 (3.33) (1.09, 7.61) |
| Valve Disease/Dysfunction | 5/150 (3.33) (1.09, 7.61) |
| History of Dermatological Disease | 5/150 (3.33) (1.09, 7.61) |
| Acne | 1/150 (0.67) (0.02, 3.66) |
| Eczema | 2/150 (1.33) (0.16, 4.73) |
| Psoriasis | 2/150 (1.33) (0.16, 4.73) |
| History of Endocrine Disease | 30/150 (20.00) (13.92, 27.30) |
| Diabetes | 14/150 (9.33) (5.20, 15.16) |
| Hyperthyroidism | 4/150 (2.67) (0.73, 6.69) |
| Hypothyroidism | 13/150 (8.67) (4.70, 14.36) |
| History of Eye, Ear, Nose, Throat, Head or Neck Disease | 29/150 (19.33) (13.35, 26.57) |
| Cataracts | 16/150 (10.67) (6.22, 16.74) |
| Chronic Ear Infection | 2/150 (1.33) (0.16, 4.73) |
| Glaucoma | 4/150 (2.67) (0.73, 6.69) |
| Macular Degeneration | 3/150 (2.00) (0.41, 5.73) |
| Tinnitus | 11/150 (7.33) (3.72, 12.74) |
| History of Gastrointestinal Disease | 56/150 (37.33) (29.58, 45.60) |
| Colitis | 3/150 (2.00) (0.41, 5.73) |
| Crohn's Disease | 1/150 (0.67) (0.02, 3.66) |
| Diverticulitis | 7/150 (4.67) (1.90, 9.38) |
| Gallstones | 2/150 (1.33) (0.16, 4.73) |
| Gastroesophageal Reflux Disease (GERD) | 49/150 (32.67) (25.24, 40.79) |
| Hepatitis B | 1/150 (0.67) (0.02, 3.66) |
| Hepatitis C | 3/150 (2.00) (0.41, 5.73) |
| Pancreatitis | 3/150 (2.00) (0.41, 5.73) |
| Ulcers | 3/150 (2.00) (0.41, 5.73) |
| History of Genitourinary Disease | 36/150 (24.00) (17.41, 31.65) |
| Endometriosis | 4/110 (3.64) (1.00, 9.05) |
| Menopause | 18/110 (16.36) (10.00, 24.62) |
| Polycystic Ovaries | 1/110 (0.91) (0.02, 4.96) |
| Prostate Problems | 9/40 (22.50) (10.84, 38.45) |

| Characteristic | Number (%) Unadjusted (Lower Confidence Limit, Upper Confidence Limit) |
|---|---|
| Sexual Dysfunction | 1/150 (0.67) (0.02, 3.66) |
| Sexually Transmitted Diseases | 1/150 (0.67) (0.02, 3.66) |
| Testicular Disorders | 1/40 (2.50) (0.06, 12.16) |
| Urinary Incontinence | 5/150 (3.33) (1.09, 7.61) |
| Uterine Fibroids | 2/110 (1.82) (0.22, 6.41) |
| History of Hematological or Lymphatic Disease | 12/150 (8.00) (4.20, 13.56) |
| Anemia | 7/150 (4.67) (1.90, 9.38) |
| Bleeding Disorder | 1/150 (0.67) (0.02, 3.66) |
| Blood Clots/Deep Vein Thrombosis (DVT) | 1/150 (0.67) (0.02, 3.66) |
| HIV/AIDS | 1/150 (0.67) (0.02, 3.66) |
| Leukemia | 1/150 (0.67) (0.02, 3.66) |
| Lupus | 1/150 (0.67) (0.02, 3.66) |
| Rheumatoid Disease/Arthritis | 3/150 (2.00) (0.41, 5.73) |
| History of Metabolic Disorders | 64/150 (42.67) (3464, 50.99) |
| Cancer | 6/150 (4.00) (1.48, 8.50) |
| Diabetes Mellitus | 7/150 (4.67) (1.90, 9.38) |
| Hypercholesterolemia | 21/150 (14.00) (8.88, 20.60) |
| Hyperlipidemia | 42/150 (28.00) (20.98, 35.91) |
| History of Musculoskeletal Disorders | 45/150 (30.00) (22.80, 38.01) |
| Arthritis | 33/150 (22.00) (15.65, 29.49) |
| Fractures | 8/150 (5.33) (2.33, 10.24) |
| Gout | 1/150 (0.67) (0.02, 3.66) |
| Osteoporosis | 8/150 (5.33) (2.33, 10.24) |
| Scoliosis | 2/150 (1.33) (0.16, 4.73) |
| History of Neurological Disorders | 73/150 (48.67) (40.43, 56.95) |
| Headaches/Migraines | 61/150 (40.67) (32.73, 48.98) |
| Intracranial Bleeding | 8/150 (5.33) (2.33, 10.24) |
| Meningitis | 1/150 (0.67) (0.02, 3.66) |
| Multiple Sclerosis | 2/150 (1.33) (0.16, 4.73) |
| Neuropathy | 12/150 (8.00) (4.20, 13.56) |
| Seizures | 7/150 (4.67) (1.90, 9.38) |
| History of Psychological/Psychiatric Disorders | 64/150 (42.67) (34.64, 50.99) |
| Anxiety | 43/150 (28.67) (21.59, 36.61) |
| Depression | 44/150 (29.33) (22.19, 37.31) |
| Schizophrenia | 3/150 (2.00) (0.41, 5.73) |
| Addiction | 3/150 (2.00) (0.41, 5.73) |
| History of Respiratory Disorders | 35/150 (23.33) (16.82, 30.93) |
| Asthma | 13/150 (8.67) (4.70, 14.36) |
| Chronic Bronchitis | 2/150 (1.33) (0.16, 4.73) |
| Chronic Obstructive Pulmonary Disease | 15/150 (10.00) (5.71, 15.96) |
| Emphysema | 5/150 (3.33) (1.09, 7.61) |
| Pneumonia | 5/150 (3.33) (1.09, 7.61) |
| Sleep Apnea | 10/150 (6.67) (3.24, 11.92) |

| Characteristic | Number (%) Unadjusted (Lower Confidence Limit, Upper Confidence Limit) |
|---|---|
| Tuberculosis | 1/150 (0.67) (0.02, 3.66) |
| History of Renal Diseases | 6/150 (4.00) (1.48, 8.50) |
| Kidney Failure/History of Dialysis | 1/150 (0.67) (0.02, 3.66) |
| Renal Insufficiency | 1/150 (0.67) (0.02, 3.66) |
| Kidney Stones | 2/150 (1.33) (0.16, 4.73) |
| Urinary tract Infection | 2/150 (1.33) (0.16, 4.73) |
| Current or Former Smoker | |
| Current | 66/150 (44.00) (35.91, 52.33) |
| Former | 32/150 (21.33) (15.07, 28.76) |
| Non-Smoker | 52/150 (34.67) (27.09, 42.86) |
| Visual Disturbance | 26/150 (17.33) (11.65, 24.36) |
| Motor Disturbance | 13/150 (8.67) (4.70, 14.36) |
| Aneurysm Location | |
| AComm Complex | 40/150 (26.67) (19.78, 34.49) |
| Basilar Apex | 59/150 (39.33) (31.47, 47.63) |
| ICA Terminus | 6/150 (4.00) (1.48, 8.50) |
| MCA Bifurcation | 45/150 (30.00) (22.80, 38.01) |
| Previous Ischemic Stroke | 18/150 (12.00) (7.27, 18.30) |
| Previous Hemorrhagic Stroke | 10/150 (6.67) (3.24, 11.92) |
| NIHSS Score at Baseline | |
| 0 | 135/150 (90.00) (84.04, 94.29) |
| 1 | 11/150 (7.33) (3.72, 12.74) |
| 2 | 2/150 (1.33) (0.16, 4.73) |
| 5 | 1/150 (0.67) (0.02, 3.66) |
| 6 | 1/150 (0.67) (0.02, 3.66) |
| mRS (Unruptured) | |
| 0 | 114/141 (80.85) (73.38, 86.99) |
| 1 | 27/141 (19.15) (13.01, 26.62) |

[a] Race and ethnicity were not obtained for subjects from the European and Canadian sites (N=34) due to Ethics Committee regulations in these countries.

## D. Safety and Effectiveness Results

### 1. Safety Results

The analysis of safety was based on the mITT cohort of 150 patients available for the 12-month evaluation. The key safety outcomes for this study are presented below in Tables 10 to 14. Adverse effects are reported in Table 15 and Table 16. The major stroke and death rate, the primary safety outcome, at one year in WEB-IT study is less than 1%. The rate for all strokes and neurological deaths at one year is 8%.

The primary safety endpoint is the proportion of subjects with death of any non-accidental cause or any major stroke (an ischemic or hemorrhagic stroke resulting in

an increase of 4 points or more on the NIHSS as of day 7 post onset) within the first 30-days after treatment or major ipsilateral stroke or death due to neurologic cause from day 31 to 365 after treatment. A major stroke is "a stroke, which increased the NIHSS by ≥ 4 at the time of assessment and which remained present after 7 days." A stroke is any "rapidly developing clinical signs of focal (or global) disturbance of cerebral function lasting more than 24 hours with no apparent cause other than of vascular origin, including ischemic stroke and/or hemorrhagic stroke (i.e., intraparenchymal hemorrhage (IPH), subarachnoid hemorrhage (SAH), subdural hemorrhage (SDH), epidural hemorrhage (EDH)) accompanied with radiological evidence."

The primary safety endpoint analysis based on subjects with clinical information at 12-months post-procedure (N=147) is presented in Table 10. There were 3 missing subjects in the mITT cohort at 12-months postoperative in which 2 subjects did not have a WEB device implanted and 1 subject withdrew prior to the 12-month follow-up visit.

There was a single primary safety endpoint event. A major stroke caused by SAH occurred on post-procedure day 22. Adjudicators determined the SAH was likely related to antiplatelet medication and underlying cerebrovascular disease and was not related to the treated IA. The location was ipsilateral but remote from the target IA. The subject's intracranial aneurysm was unruptured, in the AComm complex, and with an IA sac width of 7.4 mm. The subject had a baseline NIHSS and mRS of 0 (zero). The subject's NIHSS was 13 on day 7 post-stroke. At 12-months, the subject had an mRS of 4 due to residual left hemiplegia. The IA was completely occluded with no stenosis of the parent artery. This subject was therefore considered a primary effectiveness endpoint success and a primary safety endpoint failure.

**Table 10. Primary Safety Composite Endpoint Analysis in Completed Cases (N=147)**

| Endpoint | n/N (%) | 90% Upper Confidence Limit[a] |
|---|---|---|
| Composite | 1/147 (0.68) | 3.19 |
| Death within 30-Days | 0/147 (0.68) | 2.02[b] |
| Major Stroke within 30-Days | 1/147(0.68) | 3.19[b] |
| Major Ipsilateral Stroke Days 31 to 365 | 0/147 (0.00) | 2.02[b] |
| Neurological Death Days 31 to 365 | 0/147 (0.00) | 2.02[b] |

[a] To be compared to a PG of 20%. The upper 90% confidence limit needs to be less than the PG rate of 0.20.

[b] Unadjusted 90% upper confidence limit.

A sensitivity tipping point analysis was performed to account for the 3 missing subjects with 12-month data as primary safety endpoint failures (Table 11) using the mITT cohort (N=150).

**Table 11. Sensitivity Analysis for Primary Safety Imputation = Tipping Point Analysis**

| Tipping Point Analysis Steps | Subject Successes n/N (%) | Upper 90% Confidence Limit[a] |
|---|---|---|
| 1-Worst Case | 4/150 (2.67) | 6.00 |
| 2 | 3/150 (2.00) | 5.09 |
| 3 | 2/150 (1.33) | 4.14 |
| 4-Best Case | 1/150 (0.67) | 3.12 |

[a] When stated as a percent, this value must be smaller than 20% to reject the null primary endpoint hypothesis. Tested sequentially.

A modified primary safety endpoint analysis that included any subject with neurological death or stroke within 12-months follow-up as a primary safety endpoint failure was also performed (see Table 12). For this modified primary safety endpoint analysis, there were an additional 11 subjects in the mITT population who had ischemic or hemorrhagic stroke events in the WEB-IT study within 12-months post-procedure that were not counted as failures based on the pre-specified primary safety endpoint definition.

**Table 12. FDA-Requested All Stroke Primary Safety Endpoint**

| Endpoint | n/N (%) | Unadjusted 95% Exact Confidence Interval (CI)* |
|---|---|---|
| Composite FDA Requested All Stroke Primary Safety Endpoint | 12[a]/150 (8.00%) | (4.20, 13.56) |
| Death within 30-Days | 0/150 (0.00%) | (0.00, 2.43) |
| Any Stroke within 30-Days | 10/150 (6.67%) | (3.24, 11.92) |
| Any Ipsilateral Stroke Days 31 to 365 | 2/147 (1.36%) | (0.17, 4.83) |
| Neurological Death Days 31 to 365 | 0/147 (0.00) | (0.00, 2.48) |

[a] One subject experienced two events: SAH and ischemic stroke.

*The CI was calculated without multiplicity adjustment. As such, the CI is provided to show the variability only and should not be used to draw any statistical conclusions.

Modified Rankin Scale (mRS) scores were evaluated for the subset of subjects with unruptured target intracranial aneurysms at 12-months post-procedure compared to their baseline pre-procedure mRS as displayed in Table 13 (N=141). There were 6 subjects with unruptured IAs that did not have 12-month mRS scores resulting in N=135 subjects. Of these 135 subjects with available mRS data at 12-months postoperative, the large majority of unruptured IA subjects had an mRS of 0 (111 subjects) or mRS of 1 (22 subjects) at 12-months. Eleven (11) out of the 135 subjects with available mRS scores at the 12-month follow-up visit had increased mRS scores (8.1%) compared with their baseline mRS, signifying a worsening in disability after device treatment. If the 6 subjects with missing mRS data at 12-months postoperative were assumed to have a worsening of their mRS scores compared to their baseline scores in a worst-case analysis, then the rate of subjects with worsening mRS after device treatment would be 12% (17/141).

**Table 13. Modified Rankin Score Change from Baseline to 12-Months in Unruptured Aneurysms (N=135)**

| mRS Score at Baseline | mRS Score at 12-Months | | | | Total |
|---|---|---|---|---|---|
| | 0<br>x/n (%)[a]<br>LCL, UCL | 1<br>x/n (%)[a]<br>LCL, UCL | 3<br>x/n (%)[a]<br>LCL, UCL | 4<br>x/n (%)[a]<br>LCL, UCL | |
| **0** | 99 (90.83)<br>83.77, 95.51 | 9 (8.26)<br>3.84, 15.10 | 0 (0.00)<br>0.00, 3.33 | 1 (0.92)<br>0.02, 5.01 | 109 |
| **1** | 12 (46.15)<br>26.59, 66.63 | 13 (50.00)<br>29.93, 70.07 | 1 (3.85)<br>0.10, 19.64 | 0 (0.00)<br>0.00, 13.23 | 26 |
| **Total** | 111 (82.22)<br>74.71, 88.26 | 22 (16.30)<br>10.50, 23.63 | 1 (0.74)<br>0.02, 4.06 | 1 (0.74)<br>0.02, 4.06 | 135[b] |

[a] Percent of the row total.

[b] Six unruptured subjects did not have an mRS score at 12-months.

Note: All 95% CIs are unadjusted. As such, the CI is provided to show the variability only and should not be used to draw any statistical conclusions.

Eight of the 9 subjects with ruptured target intracranial aneurysms at baseline had 12-month mRS scores (see Table 14). One subject had missing mRS scores at 6-months and 12-months. This subject was evaluated as mRS 1 at baseline, discharge and 30-day follow-up; therefore, the mRS at follow-up was carried forward for this subject using the worst-case approximation technique.

After treatment with the WEB device, 7 out of these 9 ruptured IA subjects (77.78%) demonstrated an unchanged mRS score at 12-months. Two subjects with baseline ruptured aneurysms had an mRS improvement of one (1) point from mRS of 1 at baseline to mRS 0 at 12-months. More than half of the treated ruptured intracranial aneurysms were located in the basilar artery apex (5/9 (56%)).

**Table 14. Modified Rankin Scale Score Change from Baseline to 12-Months in Ruptured Intracranial Aneurysms**

| mRS Score at Baseline | mRS Score at 12-Months | | Total |
|---|---|---|---|
| | 0<br>x/n (%) | 1<br>x/n (%) | |
| **0** | 5/5 (100.00) | 0/5 (0.00) | 5 |
| **1** | 2/4 (50.00) | 2/4 (50.00) | 4 |
| **Total** | 7/9 (77.78) | 2/9 (22.22) | 9 |

**Adverse effects that occurred in the PMA clinical study:**

Within the first peri-procedural 30 days, 135 non-serious adverse events (AEs) occurred in 68 subjects (45.3%). Of the 135 non-serious AEs, the most common peri-procedural non-serious AEs were headache (20 events in 20 subjects, 20/150 (13.3%)), nausea (10 events/9 subjects, 9/150 (6.0%)), and vessel puncture site related events (13 events including puncture site reaction, bruise, hematoma, hemorrhage, and pain, 13/150 (8.7%)). No other non-serious peri-procedural adverse events occurred in greater than 5% of the treated population. Adverse drug reactions within the first 30-days occurred in 4.7% of subjects (7/150) and were attributed to

antiplatelet therapy in 3 cases (bruising, general malaise) and to procedure or post-procedure medications (anesthesia, pain medications, Ativan, anti-hypertensives) in the other 4 cases.

Between day 31 and day 365, 151 non-serious AEs occurred in 65 subjects (65/150, 43.3%). The most common AE occurring between day 31 and day 365 was headache (24 events in 20 subjects, 20/150 (13.3%)). No other non-serious AE occurred in more than 5% of subjects. All the non-serious AEs observed within 12-months post-procedure coded by the Medical Dictionary for Regulatory Activities (MedDRA, Version 18.0) are presented in Table 15.

**Table 15. Non-Serious Adverse Events in 1-Year**

| System Organ Class | Preferred Term | AE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events |
|---|---|---|
| Non-serious Adverse Events within 30-days | | |
| All | All | 68/150 (45.33) (37.20, 53.66) 135 |
| Blood and Lymphatic System Disorders | Anemia | 1/150 (0.67) (0.02, 3.66) 1 |
| Cardiac Disorders | Angina Pectoris | 1/150 (0.67) (0.02, 3.66) 1 |
| | Arrhythmia | 2/150 (1.33) (0.16, 4.73) 2 |
| Ear and Labyrinth Disorders | Tinnitus | 1/150 (0.67) (0.02, 3.66) 1 |
| Eye Disorders | Diplopia | 1/150 (0.67) (0.02, 3.66) 1 |
| | Visual Impairment | 4/150 (2.67) (0.73, 6.69) 4 |
| | Vitreous Detachment | 1/150 (0.67) (0.02, 3.66) 1 |
| Gastrointestinal Disorders | Abdominal Pain | 3/150 (2.00) (0.41, 5.73) 3 |
| | Constipation | 1/150 (0.67) (0.02, 3.66) 1 |
| | Gastroesophageal Reflux Disease | 1/150 (0.67) (0.02, 3.66) 1 |
| | Nausea | 9/150 (6.00) (2.78, 11.08) 10 |
| | Vomiting | 2/150 (1.33) (0.16, 4.73) 2 |
| General Disorders and Administration Site Conditions | Adverse Drug Reaction | 7/150 (4.67) (1.90, 9.38) 8 |
| | Chest Discomfort | 2/150 (1.33) (0.16, 4.73) 2 |
| | Chest Pain | 1/150 (0.67) (0.02, 3.66) 1 |
| | Fatigue | 1/150 (0.67) (0.02, 3.66) |

| System Organ Class | Preferred Term | AE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events |
|---|---|---|
| | | 1 |
| | Influenza Like Illness | 1/150 (0.67) (0.02, 3.66) 1 |
| | Puncture Site Reaction | 1/150 (0.67) (0.02, 3.66) 1 |
| | Vessel Puncture Site Bruise | 2/150 (1.33) (0.16, 4.73) 2 |
| | Vessel Puncture Site Hematoma | 4/150 (2.67) (0.73, 6.69) 4 |
| | Vessel Puncture Site Hemorrhage | 1/150 (0.67) (0.02, 3.66) 1 |
| | Vessel Puncture Site Pain | 5/150 (3.33) (1.09, 7.61) 5 |
| Infections and Infestations | Laryngitis | 1/150 (0.67) (0.02, 3.66) 1 |
| | Respiratory Tract Infection | 1/150 (0.67) (0.02, 3.66) 1 |
| | Urinary Tract Infection | 1/150 (0.67) (0.02, 3.66) 1 |
| Injury, Poisoning and Procedural Complications | Arterial Injury | 1/150 (0.67) (0.02, 3.66) 1 |
| | Contusion | 1/150 (0.67) (0.02, 3.66) 1 |
| | Traumatic Hematoma | 1/150 (0.67) (0.02, 3.66) 1 |
| | Vascular Pseudoaneurysm | 1/150 (0.67) (0.02, 3.66) 1 |
| Investigations | Blood Pressure Increased | 2/150 (1.33) (0.16, 4.73) 2 |
| Metabolism and Nutrition Disorders | Electrolyte Imbalance | 2/150 (1.33) (0.16, 4.73) 3 |
| Musculoskeletal and Connective Tissue Disorders | Arthralgia | 2/150 (1.33) (0.16, 4.73) 2 |
| | Back Pain | 3/150 (2.00) (0.41, 5.73) 3 |
| | Muscular Weakness | 1/150 (0.67) (0.02, 3.66) 1 |
| | Neck Pain | 2/150 (1.33) (0.16, 4.73) 2 |
| | Pain in Extremity | 4/150 (2.67) (0.73, 6.69) 4 |
| Nervous System Disorders | Ataxia | 1/150 (0.67) (0.02, 3.66) 1 |
| | Carotid Artery Dissection | 1/150 (0.67) (0.02, 3.66) 1 |
| | Dizziness | 1/150 (0.67) (0.02, 3.66) 1 |

| System Organ Class | Preferred Term | AE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events |
|---|---|---|
| | Dizziness Postural | 1/150 (0.67) (0.02, 3.66) 1 |
| | Headache | 20/150 (13.33) (8.34, 19.84) 20 |
| | Hypoesthesia | 1/150 (0.67) (0.02, 3.66) 1 |
| | Ischemic Stroke | 1/150 (0.67) (0.02, 3.66) 1 |
| | Migraine | 2/150 (1.33) (0.16, 4.73) 2 |
| | Nystagmus | 1/150 (0.67) (0.02, 3.66) 1 |
| | Paresthesia | 1/150 (0.67) (0.02, 3.66) 1 |
| | Subarachnoid Hemorrhage | 1/150 (0.67) (0.02, 3.66) 1 |
| | Transient Ischemic Attack | 3/150 (2.00) (0.41, 5.73) 3 |
| Psychiatric Disorders | Alcohol Abuse | 1/150 (0.67) (0.02, 3.66) 1 |
| Renal and Urinary Disorders | Urinary Incontinence | 1/150 (0.67) (0.02, 3.66) 1 |
| | Urinary Retention | 2/150 (1.33) (0.16, 4.73) 2 |
| Reproductive System and Breast Disorders | Postmenopausal Hemorrhage | 1/150 (0.67) (0.02, 3.66) 1 |
| Respiratory, Thoracic and Mediastinal Disorders | Cough | 1/150 (0.67) (0.02, 3.66) 1 |
| | Dyspnea | 1/150 (0.67) (0.02, 3.66) 1 |
| Skin and Subcutaneous Tissue Disorders | Alopecia | 1/150 (0.67) (0.02, 3.66) 1 |
| | Dermatosis | 1/150 (0.67) (0.02, 3.66) 1 |
| Vascular Disorders | Arterial Spasm | 1/150 (0.67) (0.02, 3.66) 1 |
| | Arterial Thrombosis | 2/150 (1.33) (0.16, 4.73) 2 |
| | Femoral Artery Dissection | 1/150 (0.67) (0.02, 3.66) 1 |
| | Hypertension | 2/150 (1.33) (0.16, 4.73) 2 |
| | Hypotension | 1/150 (0.67) (0.02, 3.66) 1 |
| | Labile Blood Pressure | 1/150 (0.67) (0.02, 3.66) 1 |
| | Thrombophlebitis | 1/150 (0.67) (0.02, 3.66) |

| System Organ Class | Preferred Term | AE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events |
|---|---|---|
| | | 1 |
| | Vasospasm | 5/150 (3.33) (1.09, 7.61) 5 |
| Non-serious Adverse Events within 31-365 Days | | |
| All | All | 65/150 (43.33) (35.27, 51.66) 151 |
| Blood and Lymphatic System Disorders | Anemia | 1/150 (0.67) (0.02, 3.66) 1 |
| Cardiac Disorders | Angina Pectoris | 1/150 (0.67) (0.02, 3.66) 2 |
| | Arrhythmia | 1/150 (0.67) (0.02, 3.66) 1 |
| | Cardiac Valve Disease | 1/150 (0.67) (0.02, 3.66) 1 |
| Ear and Labyrinth Disorders | Ear Pain | 1/150 (0.67) (0.02, 3.66) 1 |
| | Vertigo | 1/150 (0.67) (0.02, 3.66) 2 |
| Eye Disorders | Visual Impairment | 4/150 (2.67) (0.73, 6.69) 4 |
| Gastrointestinal Disorders | Abdominal Pain | 1/150 (0.67) (0.02, 3.66) 2 |
| | Constipation | 1/150 (0.67) (0.02, 3.66) 1 |
| | Diarrhea | 1/150 (0.67) (0.02, 3.66) 2 |
| | Gastric Ulcer | 1/150 (0.67) (0.02, 3.66) 1 |
| | Nausea | 1/150 (0.67) (0.02, 3.66) 1 |
| | Esophageal Spasm | 1/150 (0.67) (0.02, 3.66) 1 |
| | Pancreatitis | 1/150 (0.67) (0.02, 3.66) 1 |
| General Disorders and Administration Site Conditions | Adverse Drug Reaction | 7/150 (4.67) (1.90, 9.38) 7 |
| | Application Site Hemorrhage | 1/150 (0.67) (0.02, 3.66) 1 |
| | Fatigue | 1/150 (0.67) (0.02, 3.66) 1 |
| | Edema | 1/150 (0.67) (0.02, 3.66) 1 |
| | Edema Peripheral | 1/150 (0.67) (0.02, 3.66) 1 |
| | Pyrexia | 1/150 (0.67) (0.02, 3.66) 1 |

| System Organ Class | Preferred Term | AE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events |
|---|---|---|
| | Vessel Puncture Site Hematoma | 4/150 (2.67) (0.73, 6.69) 4 |
| | Vessel Puncture Site Pain | 1/150 (0.67) (0.02, 3.66) 1 |
| Infections and Infestations | Cellulitis | 1/150 (0.67) (0.02, 3.66) 1 |
| | Laryngitis | 1/150 (0.67) (0.02, 3.66) 1 |
| | Oral Herpes | 1/150 (0.67) (0.02, 3.66) 1 |
| | Otitis Media | 1/150 (0.67) (0.02, 3.66) 1 |
| | Pneumonia | 1/150 (0.67) (0.02, 3.66) 1 |
| | Respiratory Tract Infection | 1/150 (0.67) (0.02, 3.66) 1 |
| | Sinusitis | 1/150 (0.67) (0.02, 3.66) 1 |
| | Staphylococcal Skin Infection | 1/150 (0.67) (0.02, 3.66) 1 |
| | Tooth Infection | 2/150 (1.33) (0.16, 4.73) 2 |
| | Urinary Tract Infection | 3/150 (2.00) (0.41, 5.73) 4 |
| | Viral Infection | 2/150 (1.33) (0.16, 4.73) 2 |
| Injury, Poisoning and Procedural Complications | Animal Bite | 1/150 (0.67) (0.02, 3.66) 1 |
| | Contusion | 1/150 (0.67) (0.02, 3.66) 1 |
| | Head Injury | 1/150 (0.67) (0.02, 3.66) 1 |
| | Laceration | 1/150 (0.67) (0.02, 3.66) 1 |
| | Lower Limb Fracture | 1/150 (0.67) (0.02, 3.66) 1 |
| Investigations | Blood Creatinine Increased | 1/150 (0.67) (0.02, 3.66) 1 |
| | Blood Pressure Decreased | 1/150 (0.67) (0.02, 3.66) 1 |
| | Blood Pressure Increased | 2/150 (1.33) (0.16, 4.73) 2 |
| Metabolism and nutrition disorders | Diabetes Mellitus | 1/150 (0.67) (0.02, 3.66) 1 |
| | Electrolyte Imbalance | 3/150 (2.00) (0.41, 5.73) 3 |
| | Hyperlipidemia | 1/150 (0.67) (0.02, 3.66) |

| System Organ Class | Preferred Term | AE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events |
|---|---|---|
| | | 1 |
| | Hypocalcemia | 1/150 (0.67) (0.02, 3.66) 1 |
| Musculoskeletal and Connective Tissue Disorders | Arthralgia | 1/150 (0.67) (0.02, 3.66) 1 |
| | Arthritis | 3/150 (2.00) (0.41, 5.73) 3 |
| | Back Pain | 4/150 (2.67) (0.73, 6.69) 4 |
| | Muscle Spasms | 1/150 (0.67) (0.02, 3.66) 1 |
| | Neck Pain | 3/150 (2.00) (0.41, 5.73) 3 |
| | Palmar Fasciitis | 1/150 (0.67) (0.02, 3.66) 1 |
| Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps) | Paranasal Sinus Neoplasm | 1/150 (0.67) (0.02, 3.66) 1 |
| | Uterine Leiomyoma | 1/150 (0.67) (0.02, 3.66) 1 |
| Nervous System Disorders | Aphasia | 1/150 (0.67) (0.02, 3.66) 1 |
| | Carpal Tunnel Syndrome | 1/150 (0.67) (0.02, 3.66) 1 |
| | Cerebrovascular Disorder | 1/150 (0.67) (0.02, 3.66) 1 |
| | Dementia | 1/150 (0.67) (0.02, 3.66) 1 |
| | Dizziness | 1/150 (0.67) (0.02, 3.66) 1 |
| | Gait Disturbance | 1/150 (0.67) (0.02, 3.66) 1 |
| | Headache | 20/150 (13.33) (8.34, 19.84) 24 |
| | Ischemic Stroke | 2/150 (1.33) (0.16, 4.73) 2 |
| | Memory Impairment | 1/150 (0.67) (0.02, 3.66) 1 |
| | Migraine | 2/150 (1.33) (0.16, 4.73) 2 |
| | Restless Leg Syndrome | 1/150 (0.67) (0.02, 3.66) 1 |
| | Sciatica | 1/150 (0.67) (0.02, 3.66) 1 |
| | Sensory loss | 2/150 (1.33) (0.16, 4.73) 2 |
| | Transient Ischemic Attack | 2/150 (1.33) (0.16, 4.73) 2 |

| System Organ Class | Preferred Term | AE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events |
|---|---|---|
| Psychiatric Disorders | Anxiety | 3/150 (2.00) (0.41, 5.73) 3 |
| | Depression | 4/150 (2.67) (0.73, 6.69) 4 |
| | Insomnia | 2/150 (1.33) (0.16, 4.73) 2 |
| Renal and Urinary Disorders | Calculus Ureteric | 1/150 (0.67) (0.02, 3.66) 1 |
| | Nephrolithiasis | 1/150 (0.67) (0.02, 3.66) 1 |
| Reproductive System and Breast Disorders | Benign Prostatic Hyperplasia | 1/150 (0.67) (0.02, 3.66) 1 |
| Respiratory, Thoracic and Mediastinal Disorders | Dyspnea | 1/150 (0.67) (0.02, 3.66) 1 |
| | Rhinitis Allergic | 1/150 (0.67) (0.02, 3.66) 1 |
| Skin and Subcutaneous Tissue Disorders | Dermatitis | 1/150 (0.67) (0.02, 3.66) 1 |
| Surgical and Medical Procedures | Aneurysm Repair | 1/150 (0.67) (0.02, 3.66) 1 |
| | Eye Operation | 1/150 (0.67) (0.02, 3.66) 1 |
| | Intra-cerebral Aneurysm Operation | 1/150 (0.67) (0.02, 3.66) 1 |
| Vascular Disorders | Aortic Aneurysm | 1/150 (0.67) (0.02, 3.66) 1 |
| | Hypertension | 3/150 (2.00) (0.41, 5.73) 5 |
| | Hypotension | 1/150 (0.67) (0.02, 3.66) 1 |
| | Phlebitis | 1/150 (0.67) (0.02, 3.66) 1 |

[a] Summing across preferred terms or system organ classes will not result in the same sum overall because of multiple events per subject even in the same preferred term or organ class.
Note: The CI was calculated without multiplicity adjustment. As such, the CI is provided to show the variability only and should not be used to draw any statistical conclusions.

There were no deaths in the WEB-IT study through the primary endpoint time point of 1 year. Late deaths (> 1-year) occurred in 4 subjects (4/150, 2.7%). The cause of death in these 4 subjects included intracranial hemorrhage (ICH) on day 753 related to a traumatic head injury, SAH on day 625 resulting from procedural rupture of the AComm IA after a second retreatment procedure of the index aneurysm with a different device, respiratory failure on day 589, and bladder cancer on day 826.

A total of 62 serious adverse events (SAEs) occurred in 33 subjects (33/150, 22%) through day 365. Twenty-one (21) subjects (21/150, 14.0%) experienced 27 SAEs within the first 30-days (peri-procedural). Most of these events are related to nervous

system disorders and included events of seizure, headache, stroke, SAH, transient ischemic attack (TIA), aphasia, and syncope. In only 4 cases were peri-procedural device-related SAEs identified (ischemic stroke, SAH, TIA, and arterial thrombosis).

Between day 31 and 365, 21 subjects (21/150, 14.0%) experienced 35 SAEs. Nervous system disorders accounted for 8 of the 35 SAEs and included intracranial hemorrhage, ischemic stroke, headache, TIA, seizure, and benign intracranial hypertension. The CEC determined that no SAEs after day 30 were device-related. All the SAEs observed in the WEB-IT study within 1-year post-procedure are presented in Table 16 as coded by MedDRA.

**Table 16. Serious Adverse Events within 1-Year**

| System Organ Class | Preferred Term | SAE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events |
|---|---|---|
| Serious Adverse Events within 30-days | | |
| All | Any | 21/150 (14.00) (8.88, 20.60) 27 |
| Cardiac Disorders | Angina Pectoris | 1/150 (0.67) (0.02, 3.66) 1 |
| | Coronary Artery Disease | 1/150 (0.67) (0.02, 3.66) 1 |
| Gastrointestinal Disorders | Vomiting | 1/150 (0.67) (0.02, 3.66) 1 |
| General Disorders and Administration Site Conditions | Vessel Puncture Site Hematoma | 3/150 (2.00) (0.41, 5.73) 3 |
| Investigations | Blood Pressure Increased | 1/150 (0.67) (0.02, 3.66) 1 |
| Musculoskeletal and Connective Tissue Disorders | Lumbar Spinal Stenosis | 1/150 (0.67) (0.02, 3.66) 1 |
| Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps) | Uterine Leiomyoma | 1/150 (0.67) (0.02, 3.66) 1 |
| Nervous System Disorders | Aphasia | 1/150 (0.67) (0.02, 3.66) 1 |
| | Headache | 1/150 (0.67) (0.02, 3.66) 1 |
| | Ischemic Stroke | 6/150 (4.00) (1.48, 8.50) 6 |
| | Seizure | 1/150 (0.67) (0.02, 3.66) 1 |
| | Subarachnoid Hemorrhage | 2/150 (1.33) (0.16, 4.73) 2 |
| | Syncope | 1/150 (0.67) (0.02, 3.66) 1 |
| | Transient Ischemic Attack | 2/150 (1.33) (0.16, 4.73) 2 |
| Psychiatric Disorders | Confusional State | 1/150 (0.67) (0.02, 3.66) 1 |

| System Organ Class | Preferred Term | SAE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events |
|---|---|---|
| Respiratory, Thoracic and Mediastinal Disorders | Pulmonary Embolism | 1/150 (0.67) (0.02, 3.66) 1 |
| Vascular Disorders | Arterial Thrombosis | 1/150 (0.67) (0.02, 3.66) 1 |
| | Hypertension | 1/150 (0.67) (0.02, 3.66) 1 |
| Serious Adverse Events from 31 to 365 Days | | |
| All | All | 21/150 (14.00) (8.88, 20.60) 35 |
| Cardiac Disorders | Angina Pectoris | 1/150 (0.67) (0.02, 3.66) 3 |
| | Cardiac Arrest | 1/150 (0.67) (0.02, 3.66) 1 |
| | Coronary Artery Disease | 1/150 (0.67) (0.02, 3.66) 1 |
| Endocrine Disorders | Cushing's Syndrome | 1/150 (0.67) (0.02, 3.66) 2 |
| Gastrointestinal Disorders | Crohn's Disease | 1/150 (0.67) (0.02, 3.66) 1 |
| | Enteritis | 1/150 (0.67) (0.02, 3.66) 1 |
| | Gastrointestinal Hemorrhage | 2/150 (1.33) (0.16, 4.73) 2 |
| | Impaired Gastric Emptying | 1/150 (0.67) (0.02, 3.66) 1 |
| General Disorders and Administration Site Conditions | Chest Pain | 1/150 (0.67) (0.02, 3.66) 1 |
| | Vessel Puncture Site Hematoma | 1/150 (0.67) (0.02, 3.66) 1 |
| Hepatobiliary Disorders | Cholelithiasis | 1/150 (0.67) (0.02, 3.66) 1 |
| Infections and Infestations | Cytomegalovirus Infection | 1/150 (0.67) (0.02, 3.66) 1 |
| | Diverticulitis | 1/150 (0.67) (0.02, 3.66) 1 |
| | Pneumonia | 1/150 (0.67) (0.02, 3.66) 1 |
| Injury, Poisoning and Procedural Complications | Fracture | 1/150 (0.67) (0.02, 3.66) 1 |
| Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps) | Meningioma | 1/150 (0.67) (0.02, 3.66) 1 |
| Nervous System Disorders | Benign Intracranial Hypertension | 1/150 (0.67) (0.02, 3.66) 1 |
| | Hemorrhage Intracranial | 1/150 (0.67) (0.02, 3.66) 1 |
| | Headache | 1/150 (0.67) (0.02, 3.66) |

| System Organ Class | Preferred Term | SAE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events |
|---|---|---|
| | | 1 |
| | Ischemic Stroke | 1/150 (0.67) (0.02, 3.66) 1 |
| | Seizure | 1/150 (0.67) (0.02, 3.66) 1 |
| | Transient Ischemic Attack | 2/150 (1.33) (0.16, 4.73) 3 |
| Respiratory, Thoracic and Mediastinal Disorders | Hypoxia | 1/150 (0.67) (0.02, 3.66) 1 |
| | Pulmonary Embolism | 1/150 (0.67) (0.02, 3.66) 1 |
| | Respiratory Failure | 1/150 (0.67) (0.02, 3.66) 1 |
| | Tracheal Stenosis | 1/150 (0.67) (0.02, 3.66) 1 |
| Vascular Disorders | Hypertension | 1/150 (0.67) (0.02, 3.66) 2 |
| | Vascular Occlusion | 1/150 (0.67) (0.02, 3.66) 1 |

[a] Summing across preferred terms or system organ classes may not result in the same sum overall because of multiple events per subject even in the same preferred term or organ class.
Note: The CI was calculated without multiplicity adjustment. As such, the CI is provided to show the variability only and should not be used to draw any statistical conclusions.

2. Effectiveness Results

Using imputation for 14 patients with missing outcome data, approximately 55% of the 150 patients had complete occlusion of the aneurysm with less than 50% stenosis of the parent artery after 1 year without retreatment and recurrent SAH. There were 18 subjects (12%) who showed recanalization or regrowth of the aneurysm at 1 year. For the 150 subjects, 211 device placement attempts resulted in 148 device placements (148/211 = 70%).

The analysis of effectiveness was based on the 150 evaluable patients at the 12-month time point. Key effectiveness outcomes are presented in Table 17 to Table 20. As specified in the WEB-IT study protocol, the primary effectiveness endpoint was defined as the proportion of subjects with complete target intracranial aneurysm occlusion using the WEB Occlusion Scale (WOS) (Lubicz et al. 2014) without retreatment, recurrent SAH, or significant parent artery stenosis (> 50% stenosis) at one year after treatment as assessed by the Core Lab.

For the analysis of the primary effectiveness endpoint, subjects with missing outcomes were categorized as missing at random or not missing at random. Subjects whose data are not missing at random, such as those who exit the study due to a device-related primary safety event were considered a failure. Subjects in whom the placement of the device fails (no implant placed) or in whom adjunctive devices were

medically necessary were considered failures for the primary effectiveness endpoint. Subjects who were absent at 12-months and can be assumed to be missing at random had their success or failure imputed for the primary effectiveness endpoint. If a subject withdrew for reasons other than a device-related primary safety event or died due to an unrelated cause, that subject was not imputed as a failure for the effectiveness endpoint but was imputed by the methods discussed further below. An accounting of the available and missing data is described in Table 17 below. Subjects were determined to be complete cases with valid 12-month DSA imaging assessment without the use of adjunctive devices in 136 of the 150 subjects.

**Table 17. Primary Effectiveness Endpoint Imputation Patient Groups**

| Group | Number of Subjects |
|---|---|
| Completed case subjects with valid 12-month assessment | 136[a] |
| Subjects without 12-month assessment assumed to be missing at random (MAR) | 7 |
| Completed case subjects not missing at random imputed as a failure | 7 |

[a]One subject was not included in the top row because the subject had imaging that demonstrated full occlusion but did not allow assessment of parent artery stenosis.

Seven subjects did not have adequate imaging to assess aneurysm occlusion or parent artery stenosis. These seven subjects without 12-month assessment were considered missing at random and had their primary effectiveness endpoint outcome imputed based on outcomes of similar subjects in the study. Of note, 1 subject assumed to be missing at random at 12-months refused a 12-month imaging angiogram. Computed tomography angiography (CTA) was conducted for this subject and per assessment of the Core Lab, this CTA did not allow for a complete assessment of parent artery stenosis. The subject had successful IA occlusion per the Core Lab. As no subject with complete occlusion had parent artery stenosis > 50%, subjects with adequate IA occlusion assessed via imaging without sufficient imaging of the parent artery were imputed as a success for purposes of the primary effectiveness endpoint (1 subject). An additional 7 subjects that were categorized as not missing at random were imputed as failures due to failed device placement (2), use of adjunctive device at time of procedure (2), or index IA retreatment or planned retreatment prior to 12-months (3).

Subjects with missing data who were assumed to be missing at random were grouped by IA location and rupture status. For each imputation, the subject was assigned the occlusion status and parent vessel score (assessment of stenosis) of a subject with the same IA location and rupture status. Imputation was performed 20 times each with a randomly chosen 5-digit seed used for generation of random numbers. The results of the imputations, the summary into a single inference that includes within and between imputation variability, and the completed cases and per protocol cohort results are provided in Table 18. The primary effectiveness success rate in the mITT population

was 54.77% (lower bound of 90% CI of 47.97%) based on imputation for 14 missing subjects without 12-month effectiveness imaging follow-up data.

**Table 18. Primary Effectiveness Endpoint Imputation[a] and Analysis (Assuming Poolability of Data)**

| Source | Patient Successes % (Standard Error (SE)) | Lower 90% Unadjusted Confidence Limit |
|---|---|---|
| All Imputations Combined[a] | 54.77 (4.13) | 47.97[b] |
| Completed Cases | 77/143 (53.85) | 46.63 |
| Per Protocol | 77/143 (53.85) | 46.63 |

[a] Twenty imputations are combined into a single inference by the method of Rubin (1987) that includes within and between imputation variation.

[b] When stated as a percent, this value corresponds to the one-sided 95% lower confidence limit that must be larger than 35% to reject the null primary effectiveness endpoint hypothesis. The CI is provided to show the variability only and should not be used to draw any statistical conclusions.

In the Completed Cases (CC)/Per Protocol (PP) population (N=143), the primary effectiveness endpoint rate using the WOS was similar at 53.85% (77/143, lower bound of 90% CI of 46.63%). For the primary effectiveness endpoint analysis, the CC population included all subjects for whom an angiographic assessment by Core Lab at one-year follow up was available to allow assessment of both complete aneurysm occlusion and significant parent artery stenosis (> 50%). The PP population included all subjects in the CC cohort who met all study eligibility criteria and did not have any major protocol deviations that might affect the primary endpoint. The components of the primary effectiveness endpoint in the CC/PP population is presented in Table 19. The study met the applicant's proposed primary effectiveness endpoint PG success criterion of > 35%. The PG used for the primary effectiveness endpoint success criteria was based on a published systematic analysis of the available experience related to the treatment of wide-neck bifurcation intracranial aneurysms (Fiorella et al. 2017). Using defined inclusion criteria and a Preferred Reporting Items for Systemic Review and Meta-Analysis Protocols (PrISMA-P) approach, 43 references reporting the treatment of 2794 IAs were reviewed to derive the effectiveness PG. Success criteria were defined as total IA occlusion (Raymond-Roy I) or adequate occlusion (Raymond-Roy I or II) at 12-months. The Core Lab adjusted rate of complete occlusion for endovascular treatments was 39.8% (SE of 3.6%) for endovascular therapies and 52.5% for surgical clipping. When only Level I studies were included, the Core Lab adjusted rate of complete occlusion was much lower at 28.7% for endovascular therapies, 34.9% for all modalities inclusive of surgical clipping, and 43.5% for surgical clipping alone. Additionally, the meta-analysis rates did not include subjects with parent artery stenosis, recurrent SAH, or retreatment as failures as was required for the primary effectiveness endpoint definition in the WEB-IT study and allowed for 6-month outcomes to be carried forward to 12-months for purposes of analysis.

**Table 19. Primary Effectiveness Endpoint Component Analysis in the Completed Cases**

| Component | Number of Subjects n/N (%) |
|---|---|
| Primary Effectiveness Endpoint Success | 77/143 (53.85) |
| With imaging without imputation in CC | 136/143 (95.10) |
| Imputed as failure for CC | 7/143 (4.90) |
| Aneurysm Occlusion | |
| Complete | 77[b]/143 (53.85) |
| Residual Neck | 44/143 (30.77) |
| Residual Aneurysm | 15/143 (15.38) |
| Imputed as Failure for Primary Effectiveness | 7/143 (4.90) |
| Parent Vessel Stenosis | |
| None | 128[c]/143 (89.51) |
| ≤ 50% | 7[d]/143 (4.90) |
| > 50% | 1/143 (0.70) |
| Imputed as Failure for Primary Effectiveness | 7/143 (4.90) |
| Adjunctive Device (Imputed as Failure) | 2/143 (1.40) |
| Failure to Implant (Imputed as Failure) | 2/143 (1.40) |
| Retreatment of Index IA[a] (Imputed as Failure) | 3/143 (2.10) |
| Recurrent Subarachnoid Hemorrhage | 0/143 (0.00) |

[a] There were 8 subjects who had retreatment, but 5 of those were failures on the 12-month angiogram, so these subjects were counted under their angiogram events. For the 3 subjects in this row, 1 had a 12-month result that was a complete occlusion and 2 did not have a 12 month outcome recorded.

[b] There were 81 subjects with complete occlusion at 12 months, but 4 must be deleted because of retreatment, adjunct stent use during the procedure, or missing 12 month parent vessel score.

[c] There were 130 subjects with no parent vessel incursion but 2 of them had adjunct stent use during the procedure.

[d] There were 8 subjects with parent vessel stenosis of less than or equal to 50%, but one was a subject scheduled at 12-months for retreatment.

The secondary effectiveness endpoint in the WEB-IT study protocol was the proportion of subjects with angiographic aneurysmal recurrence defined as IA growth or recanalization at 12 months after treatment assessed by the Core Lab. The analysis of this secondary effectiveness endpoint is presented for the CC population in Table 20 below. A total of 18 subjects (18/143, 12.6%) had recurrence defined as aneurysm recanalization or regrowth. Recanalization of the original IA without growth or expansion occurred in 17 subjects and regrowth (or new growth or expansion of the aneurysm after treatment) occurred in 1 subject. Of the 18 subjects with recanalization or regrowth, 10 had complete aneurysm occlusion at 6 months, 6 had less than complete occlusion, and 2 had no occlusion assessment at 6 months.

**Table 20. Secondary Effectiveness Endpoint – Percentage of Subjects with Regrowth or Recanalization 12 Months Post-Index Procedure**

| Population | Recurrence Rate n/N (%) | Unadjusted 95% Confidence Limits (LCL, UCL) |
|---|---|---|
| Completed Cases | 18/143 (12.59)* | (7.63, 19.16) |

* 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.
Note: The CI was calculated without multiplicity adjustment. As such, the CI is provided to show the variability only and should not be used to draw any statistical conclusions.

Occlusion category (complete occlusion, residual neck, residual aneurysm) at 6 and 12 months is presented in  in the CC population in all subjects with valid imaging assessments (141 subjects at 6 months and 140 subjects at 12 months). At 6 months follow-up, 62% of subjects (87/141) had complete occlusion, 25% had a residual neck (35/141), and 13% had a residual aneurysm (19/141). At 12 months, the aneurysm occlusion category was similar with 58% of subjects (81/140) exhibiting complete occlusion based on the WOS Grades A and B, 31% with a residual neck (WOS Grade C) (44/140), and 11% with a residual aneurysm (WOS Grade D) (15/140).

**Table 21. WOS Aneurysm Occlusion Category by Follow-Up Visit**

| Visit | Complete Occlusion n/N (%) (Unadjusted LCL, UCL) | Residual Neck n/N (%) (Unadjusted LCL, UCL) | Residual Aneurysm n/N (%) (Unadjusted LCL, UCL) |
|---|---|---|---|
| 6 Months | 87[a]/141 (61.70) (53.15, 69.76) | 35/141 (24.82) (17.94, 32.79) | 19/141 (13.48) (8.31, 20.24) |
| 12 Months | 81[a]/140 (57.86) (49.23, 66.15) | 44/140 (31.43) (23.85, 39.81) | 15/140 (10.71) (6.12, 17.06) |

[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.
*Note:* The CI was calculated without multiplicity adjustment. As such, the CI is provided to show the variability only and should not be used to draw any statistical conclusions.

Table 22 presents the technical success rates in the WEB-IT study defined in two ways: a) successful implantation of a WEB device in the index intracranial aneurysm during the index procedure, and b) successful implantation without the need for adjunctive implantable devices. Technical success (a) was 98.7% (148/150) in the mITT population. Two subjects were unable to be implanted due to vessel tortuosity precluding ability to maintain catheter position during delivery of the WEB device and unavailability of a smaller device size after initial attempt with a larger device size. Technical success (b) was 97.3% (146/150) and included the use of adjunctive implantable devices (stents) in 2 subjects as failures. Both subjects received stents to open a thrombosed branch vessel near the WEB implant. Adjunctive balloons, allowed under the study protocol, were also used in 5 cases to assist in positioning of the WEB device.

**Table 22. Procedural Success of WEB Implantation**

| Event | Rate<br>n/N (%) (Unadjusted LCL, UCL) |
|---|---|
| Technical Success[a] | 148/150 (98.67) (95.27, 99.84) |
| Technical Success[b] | 146/150 (97.33) (93.31, 99.27) |
| Adjunctive Devices Used[c] | 7/148 (4.73) (1.92, 9.50) |
| Balloon (Acceptable under Protocol) | 5/148 (3.38) (1.11, 7.71) |
| Coils (Unacceptable under Protocol) | 0/148 (0.00) (0.00, 2.46) |
| Stent (Unacceptable under Protocol) | 2/148 (1.35) (0.16, 4.80) |
| Flow Diverter (Unacceptable under Protocol) | 0/148 (0.00) (0.00, 2.46) |

[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 subjects). Note: All 95% CIs are unadjusted. As such, the CI is provided to show the variability only and should not be used to draw any statistical conclusions.

For the 150 subjects in whom device placement was attempted in the mITT population, a total of 211 device attempts resulted in 148 device placements. Almost 90% of the devices that were not implanted (56/63 devices) were related to the decision by the investigator that an alternative size was preferred. The initial WEB device size was chosen based on pre-insertion DSA measurements of the IA neck width, dome width, and dome height as well as the general shape of the aneurysm. After deployment but prior to detachment, repeated DSA images were reviewed for device fit within the aneurysm. If the investigator determined that an alternative size device may result in a better outcome for the subject, the WEB was retracted back into the delivery catheter and an alternate device was advanced and deployed. In all but one instance, a correctly sized device was ultimately successfully implanted. In this one case, lack of availability of the proper size precluded a successful implantation (technical failure). Exchange of devices for an alternate size did not result in any clinical sequelae.

In 7 cases (7/63 devices, 11.1%), WEB devices were removed for a reason other than sizing. In all 7 cases, the devices were able to be removed without any adverse events. In 6 of these 7 cases, another WEB device was successfully implanted in the target aneurysm. In one case, subject anatomy (vessel tortuosity) precluded a successful implantation (technical failure).

**Table 22. WEB Device Disposition**

| Disposition | Number of Devices<br>x/N (%) |
|---|---|
| Inserted | 211 (100.00) |
| Not Implanted Reason | 63/211 (29.86) |
| Improper Size | 56/63 (88.88) |
| Other | 7/63 (11.11) |
| Implanted | 148/211 (70.14) |

**Table 24. Number of Attempts to Implant a WEB Device in mITT Cohort**

| Number of Attempts | n/N (%) |
|---|---|
| 1 | 100/150 (66.67) |
| 2 | 40/150 (26.67) |
| 3 | 9/150 (6.00) |
| 4 | 1/150 (0.67) |

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with clinical outcomes for effectiveness, including but not limited to: subject age, IA size (sac width < 8 mm vs. ≥ 8 mm), location and rupture status, gender, geographical location, and physician experience (see Table 25). No covariate resulted in a logistic regression p-value less than 0.05 and only 2 (WEB size and clinician experience) were less than the screening limit of p-value of 0.20.

**Table 25. Subgroup Sensitivity Analyses of the Primary Effectiveness Endpoint in the Completed Cases Population (N=143)**

| Covariate | Unadjusted P-value[a] |
|---|---|
| Age (< 65, ≥ 65 years old) | 0.8918 |
| Weight | 0.7531 |
| Height | 0.5537 |
| Gender (Male) | 0.6801 |
| Race (White or Other) | 0.9147 |
| Aneurysm Location (Posterior vs. Anterior) | 0.3447 |
| Aneurysm Rupture Status | 0.8218 |
| mRS Score | 0.9741 |
| Geographical Location | 0.9034 |
| Pseudo-Site (≤ 10 subjects, > 10 subjects) | 0.8972 |
| Sac Width (< 8 mm, ≥ 8 mm) | 0.8382 |
| WEB Size (Width in mm < 9, ≥ 9) | 0.1710 |
| Index Aneurysm - Maximum Neck Width (mm) | 0.6819 |
| NIHSS Score | 0.9857 |
| Clinician Experience (Years) | |
| 1-3 versus Others | 0.6966 |
| 4-6 versus Others | 0.0617 |
| > 6 versus Others | 0.1642 |

[a] Since no covariate had a p-value less than 0.05, there is no need to get a final model from this analysis. The covariates do not impact the primary effectiveness endpoint results in a statistically significant way. The p-values presented are nominal and unadjusted. As such, the CI is provided to show the variability only and should not be used to draw any statistical conclusions.

4. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

## E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 71 investigators of which none were full-time or part-time employees of the sponsor and 4 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0.
- Significant payment of other sorts: 4.
- Proprietary interest in the product tested held by the investigator: 0.
- Significant equity interest held by investigator in sponsor of covered study: 0.

The applicant has adequately disclosed the financial interests and arrangements with clinical investigators. Statistical analyses were conducted by FDA to determine whether the financial interests and arrangements had any impact on the clinical study outcome. The information provided does not raise any questions about the reliability of the data.

# XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

There are three (3) completed single-arm, prospective, post-market, multicenter clinical studies conducted in accordance with Good Clinical Practice (GCP) in Europe: WEBCAST, French Observatory, and WEBCAST 2 (see Table 26).

**Table 26. Summary of Other Clinical Studies with Completed Follow-up**

| | WEBCAST | French Observatory | WEBCAST 2 |
|---|---|---|---|
| Study Type | Single-arm, prospective, post- market, multicenter, GCP | Single-arm, prospective, post-market, multicenter, GCP | Single-arm, prospective, post-market, multicenter, GCP |
| No. of Subjects Enrolled | 51 subjects with 51 aneurysms | 62 subjects with 63 aneurysms | 55 subjects with 55 aneurysms |
| Aneurysm Population Treated | Intracranial wide-neck (≥ 4 mm) aneurysms deemed appropriate for endovascular treatment in the basilar apex (BA), MCA bifurcation, ICA terminus, and the | Intracranial wide-neck (dome to neck ratio ≥ 1) aneurysms deemed appropriate for endovascular treatment in the basilar apex (BA), MCA bifurcation, ICA terminus, the anterior communicating artery | Intracranial wide-neck (dome to neck ratio ≥ 1) aneurysms deemed appropriate for endovascular treatment in the basilar apex (BA), MCA |

| | WEBCAST | French Observatory | WEBCAST 2 |
|---|---|---|---|
| | anterior communicating artery complex (AComm). | complex (AComm), and the anterior cerebral artery (ACA). | bifurcation, ICA terminus, and the anterior cerebral artery (ACA). |
| WEB Model Used | WEB Double Layer (DL) | WEB DL and WEB SL/SLS | WEB SL/SLS EV |
| Completed Follow- up Evaluations | 30-days, 3-months (optional), 6-months, 12-months, 24-months | 30-days, 12-months, 24-months | 30-days, 12-months, 24-months |
| 30-Day Morbidity and Mortality Summary | There was no mortality at 30-days. One patient (1.96%) with a ruptured aneurysm had morbidity at 30-days (mRS 3) related to initial subarachnoid hemorrhage (Hunt & Hess 3) and was mRS 1 at 6-months. One patient treated for an unruptured aneurysm was mRS 2 preoperatively due to a previous subarachnoid hemorrhage (from another aneurysm) and remained mRS 2 at 30-days. Morbidity related to the treatment was 0.0%. | There was no mortality at 30-days. Two patients (3.2%) had morbidity at 30-days: one patient had mRS 2 at baseline and mRS 3 at 30-days due to mass effect and one patient with a ruptured aneurysm at baseline had mRS 3 at 30-days. Morbidity related to the treatment was 0.0%. | There was no mortality at 30-days. Procedural morbidity was observed in 1/55 patients (1.8%) related to a thromboembolic event (mRS 3). One patient (1.8%) with a ruptured aneurysm was mRS 4 at 30-days due to the initial bleeding. |
| Effectiveness Results Summary | Adequate occlusion (complete or neck remnant) at 12-months was exhibited in 36/42 aneurysms (85.7%). Complete occlusion at 12-months was exhibited in 26/42 aneurysms (61.9%). | Adequate occlusion (complete or neck remnant) at 12-months was exhibited in 46/58 aneurysms (79.3%). Complete occlusion at 12-months was exhibited in 30/58 aneurysms (51.7%). Adequate occlusion (complete or neck remnant) at 24 months was exhibited in 38/50 aneurysms (76.0%). Complete occlusion at 24 months was exhibited in 24/50 aneurysms (48.0%). | Adequate occlusion (complete or neck remnant) at 12-months was exhibited in 40/50 aneurysms (80.0%). Complete occlusion at 12-months was exhibited in 27/50 aneurysms (54.0%). |

## XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

### A. Panel Meeting Recommendation

At an advisory meeting held on September 27, 2018, the Neurological Devices Panel (the "Panel") of the Medical Devices Advisory Committee voted 15-0-0 (yes, no, abstain) that there is reasonable assurance the device is safe, 12-2-1 (yes, no, abstain) that there is reasonable assurance that the device is effective, and 12-1-2 (yes, no, abstain) that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication. As a condition of approval of the PMA, the Panel recommended that a post-approval study (PAS) be conducted to address some of the unanswered questions from the WEB-IT study (see Section XII.B. below for specific Panel recommendations on the PAS). The background and meeting materials for the September 27, 2018 Panel meeting can be accessed at the following link: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm598450.htm.

### B. FDA's Post-Panel Action

This section presents a summary of the Panel's recommendations and discussions at the September 27, 2018 meeting. Regarding the safety profile for the WEB Aneurysm Embolization System, the Panel discussed patient risk factors, stroke rate, changes in the mRS score, adverse events and late deaths observed during the WEB-IT clinical trial. Some Panel members 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 Panel members expressed concerns about the potential for increased adverse events post-market 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 Panel members 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 Panel members also recommended additional safety endpoints for assessment of stroke outcomes in addition to the mRS for disability such as the 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 regarding patient risk factors, location, and sample size.

When considering the device effectiveness, 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 (i.e., residual aneurysm neck greater than the WEB proximal marker recess). 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.

For device sizing and use conditions, 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.

Regarding the use of dual anti-platelet therapy (DAPT), Panel members discussed the subjects on 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.

The Panel raised concerns whether sufficient data was collected on ruptured and unruptured aneurysms; however, several Panel members expressed support that the indications for use (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 magnetic resonance angiography (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.

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.

The FDA is not going against any of the Panel's recommendations from the September 27, 2018 meeting. The only modification was respect to the PAS where the applicant did not want to evaluate DSA vs. CTA imaging because they are labeling their device to be used for DSA only for IA follow-up to assess the occlusion status.

Additional Panel Meetings

During the review of this PMA, the FDA also considered the recommendations from two general issues meetings on April 17, 2015 and March 1, 2018 of the Neurological Devices Panel (the "Panel") of the Medical Devices Advisory Committee. The March 1, 2018 general issues meeting was regarding factors to consider in the evaluation of benefits and risks when reviewing clinical evidence of new endovascular medical devices intended to treat intracranial aneurysms. The background and meeting materials for the March 1, 2018 general issues meeting can be accessed at the following link: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm598450.htm.

The April 17, 2015 general issues meeting was convened to discuss the conduct and design of clinical studies to evaluate the benefits and risks of endovascular devices used to treat IAs. The Panel from the April 17, 2015 meeting discussed the importance of subgroup analyses in the clinical trial design based on patient factors such as IA location, size, and morphology and the importance of well controlled studies in the evaluation of reasonable safety and effectiveness of these devices. The background and meeting materials for the April 17, 2015 general issues meeting can be accessed at the following link: https://wayback.archive-it.org/7993/20170114022911/http:/www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm440392.htm.

## XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

### A. Effectiveness Conclusions

The primary effectiveness success rate in the mITT analysis population defined as complete aneurysm occlusion using the WOS (A and B) at 12-month follow-up without retreatment,

recurrent subarachnoid hemorrhage, or the development of a parent artery stenosis > 50% was 54.77% (lower bound 90% CI of 47.97%) based on multiple imputation for 14 missing subjects without 12-month effectiveness imaging follow-up data. This analysis result was supported by a tipping point analysis verifying that success was achieved even under the worst-case scenario of all missing observations considered to be failures. Therefore, the pivotal study met the primary effectiveness endpoint success criteria at one year. Subgroup analyses of the primary effectiveness endpoint was conducted assessing whether there are any differences in effectiveness outcomes based on factors such as age, IA location, size, and rupture status, gender, geographical location, and physician experience. The subgroup analyses did not find any statistically significant differences in any of the groups.

Secondary effectiveness endpoint analysis investigated proportion of subjects with angiographic aneurysmal recurrence defined as aneurysm growth or recanalization at 12 months after treatment assessed by the Core Lab. The analysis demonstrated a total of 18 subjects (18/143, 12.6%) had recurrence defined as aneurysm recanalization or regrowth. Recanalization of the original aneurysm without growth or expansion occurred in 17 subjects and regrowth (or new growth or expansion of the aneurysm after treatment) occurred in 1 subject. Of the 18 subjects with recanalization or regrowth, 10 had complete aneurysm occlusion at 6 months, 6 had less than complete occlusion, and 2 had no occlusion assessment at 6 months.

## B. Safety Conclusions

The risks of the device are based on non-clinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The pre-specified primary safety endpoint was defined as the rate of 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 NIHSS as of day 7 post-onset) within the first 30-days after treatment or major ipsilateral stroke or death due to neurologic cause from day 31 to 365 after treatment. In the primary safety endpoint analysis using the mITT cohort, missing data for 3 subjects without known status at 1-year follow-up were imputed by a tipping point analysis that assessed the 3 missing subjects as primary safety endpoint failures, which resulted in a worst-case primary safety endpoint rate of 2.67% (4/150) with an upper 90% CI of 6% . Only one subject (1/150, 0.67%) sustained a primary safety endpoint event. The FDA also requested that the applicant provide a post-hoc primary safety endpoint analysis for all strokes (ischemic and hemorrhagic) or neurological deaths observed within 1 year postoperative. This resulted in a post-hoc primary safety endpoint rate of 8% (12/150).

## C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The primary effectiveness endpoint results show that 51.33% (77/150) of the mITT patients in the WEB-IT study had complete (WOS A and B) IA occlusion without clinically significant parent artery

stenosis, retreatment of the target IA, or recurrent SAH. Because the WEB device is a permanent implant and the pivotal study with 1-year follow-up data was used to support the PMA, the long-term durability of treatment after 1-year postoperative is currently unknown. Retreatment was planned or performed in approximately 5% (7/148) of study subjects who had a WEB device implanted through 1-year follow up. Retreatment may carry additional procedural and/or device-related risks to the patients. One of the probable benefits of the WEB device is that it is implanted in the sac of the IA and not in the parent artery. This may minimize the risk of thromboembolic complications and the dosage of the DAPT that needs to be administered before and after the procedure. This will be investigated as part of the new PAS as a condition of approval of the PMA.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The primary safety endpoint rate observed in the WEB-IT study was 0.67% (1/150). The post-hoc primary safety endpoint analysis for all strokes (ischemic and hemorrhagic) or neurological deaths observed within 1 year postoperative resulted in a rate of 8% (12/150). Most subjects treated with an unruptured IA had an mRS of 0 (111/135) or 1 (22/135) at 1-year follow-up. A total of eleven (11) subjects (8.1%) had an increased mRS score at 1-year, signifying a worsening in disability after device treatment. Sixty-two (62) serious adverse events were observed during this study occurring in 33 subjects (33/150, 22%) through 1 year of follow-up. The most common serious adverse events were nervous system disorders and included events of seizure, headache, stroke, SAH, transient ischemic attack (TIA), aphasia, and syncope. In only 4 cases were peri-procedural device-related SAEs identified (ischemic stroke, SAH, TIA, and arterial thrombosis).

Additional factors to be considered in determining probable risks and benefits for the WEB device included: weighing the benefits and risks of device treatment with the patient's risk of intracranial aneurysm rupture. The risk of rupture of an untreated unruptured intracranial aneurysm is dependent on multiple factors including aneurysm size, shape, and morphology, and the patient co-morbidities (e.g., high blood pressure, family history, multiple aneurysms, diabetes). Based on natural history, it has been suggested that intracranial aneurysms have an average rupture rate of around 1% per year in patients with a diagnosed intracranial aneurysm, although that number can vary based on the study (Ishibashi et al. 2009; Juvela et al. 2013). Size and location of the intracranial aneurysm in the neurovasculature can also affect the risk of rupture. In the article by Wiebers (2003), intracranial aneurysms in the ICA, anterior communicating artery (AComm), anterior cerebral artery (ACA), or middle cerebral artery (MCA) that were < 7 mm, 7-12 mm, 13-24 mm, and > 25 mm had rupture rates of 0%, 2.6%, 14.5%, and 40%, respectively, at 5 years. Larger aneurysms are at a greater risk for rupture (i.e., the rupture rate for aneurysms > 25 mm have a reported 6% rupture rate in the first year (Wiebers 1998) with other studies reporting an annual rupture rate as high as 43.1% (Ishibashi et al. 2009))

One additional factor to be considered in determining probable risks and benefits for the WEB device include some uncertainty based on the single arm pivotal trial design that may introduce some bias in patient selection for treatment because there was no blinding

or randomized concurrent control group. Since there was no active control arm in the pivotal study, there are uncertainties of whether the subject device treatment may be more or less beneficial or more or less safe than alternative treatment modalities for the indicated patient population. In addition, it is unclear whether there may have been some bias in subject selection for treatment with the WEB to result in better clinical outcomes.

1. Patient Perspectives

This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that for use at the middle cerebral artery (MCA) bifurcation, internal carotid artery (ICA) terminus, anterior communicating artery (AComm) complex, or basilar artery apex for the endovascular treatment of adult patients with saccular, wide neck, bifurcation intracranial aneurysms with dome diameter from 3 mm to 10 mm and either neck size 4 mm or greater or the dome-to-neck ratio is greater than 1 and less than 2, the probable benefits outweigh the probable risks.

## D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The overall risk to benefit ratio is favorable for the intended population. While the overall effectiveness had a lower bound of 47.97% based on a multiple imputation analysis on the mITT population (N=150), the rate of primary safety events was low (0.67% (1/150)). A Panel meeting was held on September 27, 2018 for this PMA and the Panel voted [12-1-2 (yes, no, abstain)] that the benefits of the device do outweigh the risks in patients who meet the criteria specified in the proposed indication.

# XIV. CDRH DECISION

CDRH issued an approval order on 12/31/2018. The final conditions of approval cited in the approval order are described below.

PMA Post-Approval Study (PAS) #1 – "Post-Market Surveillance Study to Evaluate the Long-Term Safety and Effectiveness of the WEB Aneurysm Embolization System": This PAS will be initiated after device approval. This new enrollment cohort PAS will collect data to investigate the safety and effectiveness of the WEB Aneurysm Embolization System as recommended by the Neurological Devices Panel of the Medical Devices Advisory Committee at a September 27, 2018 meeting. This PAS will assess the proportion of subjects experiencing death by neurological cause, any stroke event sub-divided as a disabling vs. non-disabling stroke, or additional neurological deficits in both ruptured and unruptured intracranial aneurysms (IAs), rate of re-bleed for subjects with ruptured IAs, IA occlusion rate defined as the proportion of subjects with adequate IA occlusion (WEB Occlusion Scale (WOS) A + WOS B + WOS C), IA occlusion rate stability defined as the

proportion of subjects with complete IA occlusion (WOS A and B) without retreatment or recurrent subarachnoid hemorrhage that changed within the follow-up period, investigation of antiplatelet regimens for subjects with unruptured IAs, and the effect of the marker recess on IA occlusion stability (WOS A versus B). The assessments for neurological deficits will be performed using the modified Rankin Scale (mRS), National Institutes of Health Stroke Scale (NIHSS), and a patient reported outcome measure preferably by a vascular neurologist. The imaging and clinical follow-up examinations will be performed at 1, 3, and 5 years post-procedure. All new and ongoing adverse events should be collected within 1 year post-procedure and reviewed and collected at the 1-, 3-, and 5-year study visits.

PMA PAS #2 – "The WEB Intrasaccular Therapy Study (WEB-IT)": The WEB-IT study is a prospective, multi-center non-randomized pivotal study that was conducted under IDE G130286 and was initiated prior to device approval. The study subjects were consented to be followed for up to five (5) years post-procedure. The 1-year follow-up data from the WEB-IT study was used to support the approval of the subject PMA. As part of the PMA PAS, the long-term follow-up from the WEB-IT study can provide safety and effectiveness information for the WEB Aneurysm Embolization System up to 5 years post-procedure. Patients will be followed annually up to 5 years post-procedure with imaging assessment of the IA occlusion status and clinical examinations using the approved IDE G130286 clinical study protocol. In addition, all new and ongoing adverse events will be recorded and adjudicated by the Clinical Events Committee (CEC) per the approved G130286 clinical study protocol.

The applicant's manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

## XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

## XVI. REFERENCES

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