FDA Executive Summary

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Neurological Devices Panel
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Premarket Approval (PMA) P170032
Sequent Medical, Inc.
Woven EndoBridge (WEB) Aneurysm Embolization System

Division of Neurological and Physical Medicine Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration

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1 Introduction

This is FDA's Executive Summary of the premarket approval (PMA) P170032 application from Sequent Medical, Inc. (wholly owned subsidiary of MicroVention, Inc.) for the Woven EndoBridge (WEB) Aneurysm Embolization System (hereafter referred to as "WEB") for the treatment of wide-neck bifurcation intracranial aneurysms (IAs), both ruptured and unruptured, located in the anterior [middle cerebral artery (MCA) bifurcation, internal carotid artery (ICA) terminus, anterior communicating artery (Acomm) complex] and posterior (basilar apex) circulations. This document includes a brief review of the treatment of wide-neck bifurcation IAs, a description of the device, a review of pre-clinical studies, and the presentation of clinical data from the pivotal study titled "The WEB Intrasaccular Therapy Study (WEB-IT)" used to support the PMA P170032. The data presented in this document also incorporates information provided by Sequent Medical, Inc. in response to deficiencies in the FDA letter dated December 27, 2017.

1.1 Clinical and Regulatory Background

Intracranial aneurysms (IAs) are weak or thin spots on a blood vessel in the brain that balloon out and fill with blood. A bulging IA can put pressure on nerves, meninges, and/or surrounding brain tissue. It may also leak or rupture, spilling blood into the surrounding tissue (referred to as an intracranial hemorrhage). Some IAs, particularly those that are very small, may never bleed or cause clinical sequelae. IAs have been reported in the literature for several decades (Housepian and Pool 1958; Chason and Hindman 1958; Jellinger 1976) and it is estimated that on average five percent of the population is afflicted with this disease (Jellinger 1976).

Originally, open direct surgery was the most common method to treat IAs by placing a clip across the neck of the aneurysm to eliminate flow from the parent artery into the aneurysm sac. In recent years, there have been several advancements in the treatment of aneurysms through endovascular means (Johnston et al. 1999; Roy, Milot, and Raymond 2001; Starke et al. 2012) such as using neurovascular embolization coils alone or, with neurovascular stent assisted coiling (SAC), and flow diversion technology (Berge et al. 2012; Byrne and Szikora 2012; Wakhloo et al. 2015; D'Urso et al. 2011). Neurovascular embolization coils have been used since the 1970s and were the first type of medical device to be used via an endovascular approach to treat IAs. For traditional neurovascular embolization coiling, a catheter is inserted through entry in the femoral artery and tracked through the vasculature to the IA. Coils are delivered through this catheter to fill the sac of the aneurysm and promote occlusion. From a regulatory perspective, neurovascular embolization coils were "pre-amendment devices" meaning that they were legally marketed in the United States (US) prior to May 28, 1976. These devices were initially regulated as Class III (highest risk) devices requiring a PMA application. In 2004, FDA reclassified these devices to Class II with special controls, meaning these devices could now be cleared for market under the 510(k) regulatory pathway (21 CFR 882.5950, Neurovascular Embolization Device, product code HCG)[1].

[1] Premarket Notification [510(k)] regulatory process information can be found on the FDA website at: https://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/PremarketNotification510k/default htm. The special controls guidance document for embolization coils can be found on FDA's website at https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm072055.

1.1.1 Humanitarian Use Medical Devices and Review Standards

The first neurovascular stent for SAC approved in the US was the Stryker Neurovascular Neuroform Microdelivery Stent System (HDE H020002, 2002) under the Humanitarian Device Exemption (HDE) regulatory pathway, followed by the Codman & Shurtleff, Inc. Enterprise Vascular Reconstruction Device (H060001, 2007), MicroVention, Inc. Low-Profile Visualized Intraluminal Support (LVIS) Device (H130005, 2014), and the Pulsar Vascular, Inc. PulseRider Aneurysm Neck Reconstruction Device (H160002, 2017)[2]. For a medical device to be eligible for the HDE pathway, the manufacturer must first obtain a Humanitarian Use Device (HUD) designation noting that the medical device is intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the US per year. HDE marketing applications are supported by performance data (e.g., in vitro, in vivo, human clinical) that demonstrates that the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from the use of the device outweighs the risk of injury or illness from its use of the medical device for the proposed patient population for treatment and is exempt from the effectiveness requirement of the Federal Food, Drug, and Cosmetic (FD&C) Act[3].

1.1.1.1 Types of Regulatory Submissions and Levels of Evidence

Neurointerventional HDE applications typically are supported by smaller clinical studies of at least 30 subjects or more. These smaller studies are often not statistically powered with appropriate sample size calculations or have pre-specified success criteria for the primary endpoints. PMA applications, which are supported by more robust clinical studies, are further designed with pre-specified success criteria with defined primary and secondary endpoints, and statistically powered with sufficient sample sizes to derive meaningful clinical and statistical conclusions (see Section 1.1.2 for further discussion regarding PMA approvals). The first three approved neurovascular stents were indicated under the HDE generally for the treatment of wide-neck IAs with neurovascular embolization coils, with no consistent specification of the type, size, rupture status, or location of IA, or patient characteristics (e.g., age), that should be treated. The PulseRider Aneurysm Reconstruction Device was approved with an indication for use (IFU) to be used with neurovascular embolization coils in patients ≥ 18 years of age with an unruptured wide-neck intracranial aneurysm originating on or near a vessel bifurcation of the basilar tip or carotid terminus. The IFU for the PulseRider Aneurysm Neck Reconstruction Device identified more specific anatomical and aneurysm characteristics because the device design (T- or Y-shaped) was specifically designed to be implanted at a vessel bifurcation location and these aneurysms were what was studied in the clinical trial supporting the HDE application. Recently on May 30, 2018, FDA approved the MicroVention, Inc. LVIS

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[2] The approval information for the Neuroform Microdelivery Stent from Stryker Neurovascular can be found on FDA's website at https://www.accessdata fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H020002. The approval information for the Enterprise Vascular Reconstruction Device from Codman & Shurtleff, Inc. can be found on FDA's website at https://www.accessdata fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H060001. The approval information for the LVIS Device from MicroVention, Inc. can be found on FDA's website at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfhde/hde.cfm?id=H130005. The approval information for the PulseRider Aneurysm Neck Reconstruction Device from Pulsar Vascular, Inc. can be found on FDA's website at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/hde.cfm?id=388322.

[3] Information regarding the Humanitarian Device Exemption regulatory pathway can be found on FDA's website at https://www fda.gov/medicaldevices/deviceregulationandguidance/howtomarketyourdevice/premarketsubmissions/humanitariandeviceexemption/default htm.

and LVIS Jr. under PMA P170013, that was previously on the market in the US as an HDE approved device, with safety and effectiveness data in a pivotal study to support the IFU of the device being used with neurovascular embolization coils in patients ≥ 18 years of age for the treatment of wide-neck (neck width ≥ 4 mm or dome to neck ratio < 2) saccular intracranial aneurysms arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 4.5 mm.[4] While a device approved under an HDE may be exempt from the effectiveness requirements of a PMA, PMA medical devices must demonstrate a reasonable assurance that the device is safe and effective for its conditions of use to obtain marketing approval.[5]

1.1.2 Premarket Approval (PMA) of Medical Devices and Review Standards

The data for which CDRH considers for review is identified as valid scientific evidence. Per 21CFR860.7(c)(2), "valid scientific evidence is evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its conditions of use." PMA applications must adhere to this standard.

For flow diversion technology, the mechanism of action of the device is to divert the blood flow from entering into an aneurysm sac from the parent artery. This reduction in blood flow into the aneurysm sac is designed to promote blood stasis, endothelial growth across the neck, and occlusion of the aneurysm. There are two (2) flow diverters that are available in the US and have received FDA approval through the PMA regulatory pathway, which are the Micro Therapeutics, Inc. d/b/a ev3 Neurovascular Pipeline and Pipeline Flex Embolization Devices (PED, PFED) (P100018, 2011 and P100018/S011, 2015) and Stryker Neurovascular Surpass Streamline Flow Diverter (P170024, 2018).[6][7] The PED and PFED were approved with the IFU for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms in the ICA from the petrous to the superior hypophyseal segments. The Surpass Streamline Flow Diverter was approved with an IFU 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.

One of the newest developments reported in the literature for the treatment of wide-neck bifurcation IAs has been endosaccular flow disruption devices, sometimes referred to as "mesh balls" (Klisch et al. 2011; Kwon et al. 2011). These endosaccular devices are typically constructed from a tightly woven wire mesh that has been wrapped to form a semi-spherical shape. These devices are implanted within the aneurysm

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[4] The approval information for the LVIS from MicroVention, Inc. can be found on FDA's website at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P170013.

[5] For additional information regarding the differences between PMA approval and HDE approval, please see *FDA Guidance Document for Staff and Industry Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors: Frequently Asked Questions About Medical Devices* located at https://www.fda.gov/downloads/regulatoryinformation/guidances/ucm127067.pdf.

[6] The approval information for the Pipeline Embolization Device from Micro Therapeutics, Inc. d/b/a ev3 Neurovascular can be found on FDA's website at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpma/pma.cfm?ID=P100018.

[7] The approval information for the Surpass Streamline Flow Diverter from Stryker Neurovascular can be found on FDA's website at https://www.accessdata fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm?id=P170024.

sac and the mechanism of action is that the mesh design covers the aneurysm neck and obstructs blood flow from entering the sac of the aneurysm, creating blood stasis in the sac, and promoting endothelial growth across the neck of the aneurysm. Currently, there are no endosaccular flow disruption devices approved for use in the US. The subject WEB device will be the first endosaccular flow disruption device in the US, if approved under PMA P170032. While endosaccular flow disruption devices provide an alternative treatment approach for difficult to treat IAs (i.e., wide-neck bifurcation), the Panel will be asked to help determine if sufficient clinical evidence has been provided for the WEB device to support a determination of reasonable safety and effectiveness for the proposed indications for use based on the prospectively collected single arm trial conducted in the US, as discussed in the following sections of this Executive Summary.

2 Device Description

The WEB Aneurysm Embolization System consists of an implantable embolization device ("WEB Implant") attached to a delivery system ("WEB Delivery System") (Figure 1). The WEB Delivery System is navigated through compatible microcatheters with an introducer sheath to the target aneurysm and is electro-thermally detached 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 with a platinum core in a braided, self-expanding mesh configuration. The WEB Implant is provided in a broad range of sizes (diameters and lengths) and two different shapes (barrel and sphere) to satisfy the needs of the physician (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 intracranial aneurysm to be occluded. As shown in Figure 3 below, proximal and distal platinum radiopaque markers facilitate WEB Implant delivery under fluoroscopic visualization. Proximal and distal marker recesses are present in all WEB models.

Figure 2. WEB SL (Left) and SLS (Right) Implant Shapes

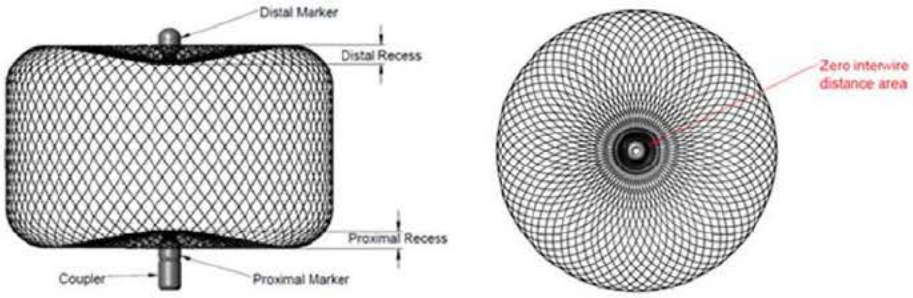

Figure 3. WEB Implant Design Characteristics

Table 1. WEB Sizes and Recommended Microcatheters

WEB SL/SLS 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			

3 Proposed Indications for Use

The proposed indications for use (IFU) for the WEB device is:

> The WEB Aneurysm Embolization System is indicated for the embolization of intracranial wide neck bifurcation aneurysms. The WEB Aneurysm Embolization System is further indicated to embolize intracranial wide neck bifurcation aneurysms ranging in size from 3 mm to 10 mm in dome diameter, where the neck size is 4 mm or greater or the dome-to-neck ratio is less than 2.

Panel Question: The Panel will be asked to discuss and make recommendations on whether the proposed indications for use is supported by the data collected in the pivotal WEB-IT study, including, but not limited to, location of target intracranial aneurysm, size, morphology, and ruptured vs. unruptured status. Also, the Panel will be asked whether there should be specific contraindications, warnings, precautions, instructions for use that should be conveyed in the Directions for Use (DFU) to ensure the safe and effective use of the subject device.

4 Regulatory History

The pivotal clinical study submitted in the PMA, WEB-IT, was conducted under Investigational Device Exemption (IDE) G130286. The WEB device is marketed outside the US in 44 countries, including, but not limited to the following countries: Argentina, Austria, Australia, Belgium, Bulgaria, Chile, Columbia, 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.

Because the WEB device has received the CE mark in the European Union (EU), there have been some small feasibility studies conducted outside the US. In an early prospective multicenter trial conducted in France, 77 patients with 79 intracranial aneurysms, 73 of which had a neck width > 4 mm, were treated using the WEB device (Papagiannaki et al. 2014). With an average follow up of 5.3 months, it was shown that 37 patients (37/77, 56.9%) had complete occlusion, 23 patients (23/77, 35.4%) had a neck remnant, and 5 patients (5/77, 7.7%) had a residual aneurysm. This study also indicated a low occurrence of safety events with 71 patients (71/77, 94.7%) having a modified Rankin Scale (mRS) score of 0 at one month post-procedure. This study did note that there can be difficulty in navigating the device in more tortuous anatomy due to the use with a larger delivery microcatheter in comparison to those used with traditional neurovascular embolization coils (Papagiannaki et al. 2014). More recently, 51 patients were treated as part of a prospective multicenter European clinical trial, investigating the use of the WEB device in the treatment of wide-neck bifurcation aneurysms (Pierot et al. 2016). In this study, 94.1% (48/51) of the aneurysms treated were unruptured occurring at bifurcations at the basilar apex, middle cerebral artery (MCA), anterior communicating artery (AComm), and internal carotid artery (ICA) terminus. The authors noted that at 6 months, 23 out of 51 patients (56.1%) had complete aneurysm occlusion while 12 out of 51 (29.3%) patients and 6 out of 51 patients (14.6%) had a neck remnant and aneurysm remnant, respectively. Regarding safety events within the follow up duration of 6 months, the authors reported only one patient suffered a safety event (thromboembolic event), that resulted in a change in the mRS score (i.e., from 0 to 1). However, this study did document technical problems in 8 out of 51 patients (15.7%) that included prolonged detachment (n=3) and device protrusion (n=5) (Pierot et al. 2016).

5 Pre-clinical Studies

5.1 Design Verification and Validation Testing

Table 2 shows the design verification bench testing performed on the WEB Aneurysm Embolization System. Table 3 shows the design verification bench testing performed on the WEB Detachment Controller. 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)	(b) (4)	**PASS**
Dome Deployment Force		**PASS**
Flat Plate Crush (Radial Force)		**PASS**
WEB Tensile Distal End Weld		**PASS**
Detachment Zone Tensile		**PASS**
Hypotube to Core Wire Tensile		**PASS**
Proximal Connector to Core Wire Tensile		**PASS**
Overcoil Tensile: Hypotube to Segment II		**PASS**
Overcoil Tensile: Segment II to Segment III		**PASS**
Overcoil Kink		**PASS**
Tracking Force		**PASS**
WEB Retraction in Microcatheter		**PASS**
Particulate after Simulated Use with Microcatheter		**PASS**

Test Name	Test Method Description	Results
Cycling and Detachment	(b) (4)	**PASS**
Magnetic Resonance Imaging (MRI) Compatibility		**PASS**
Corrosion Resistance		**PASS**
WEB Wire Integrity after 10 Year Equivalent Fatigue		**PASS**
WEB Percent Metal Analysis		**N/A –** (b) (4)
WEB Fluid Penetration Characteristics (Wash-Out from an In-Vitro Aneurysm Model)		**N/A –** (b) (4)
Characterization of WEB Implant Nitinol Properties		**N/A –** (b) (4)

Table 3. WEB Detachment Controller (WDC) Bench Testing

Test Name	Test Method Description	Results
Power Off When Not in Use	(b) (4)	PASS
Timeout		PASS
Detachment Voltage Output and Duration (Detachment Time)		PASS
Pre-detachment Resistance Check - Load In Range (LIR) & Load Out of Range (LOR)		PASS
Shut-off Current		PASS
Electrical Safety Testing		PASS
Electromagnetic Compatibility (EMC) Testing		PASS

(b) (4)

(b) (4)

5.2 Biocompatibility

Biocompatibility testing of sterile finished WEB Aneurysm Embolization Systems were performed in accordance with BS EN ISO 10993-1, Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing (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

Biological Effect	Test	Applicable Standard	Result
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 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) ASTM F619-03 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 and Organic Chemicals)	Metal and Organic Chemical Extractables Testing in Worst Case Solvents (Isopropyl Alcohol (IPA), Hexane, Acidified Water) at 50 °C	N/A	All extractables below tolerable intake levels

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

Biological Effect	Test	Applicable Standard	Result
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	Four 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

5.3 MRI Compatibility

Non-clinical testing demonstrated that the WEB device is MR Conditional. It can be scanned safely under the following conditions:

- Static magnetic field of 1.5-Tesla or 3-Tesla
- Maximum spatial gradient field of 4,000-Gauss/cm (40-T/m)
- Maximum MR system reported, whole body averaged specific absorption rate (SAR) of 2.0-W/kg for 15 minutes of scanning (i.e., per pulse sequence) in the Normal Operating Mode

Under the scan conditions defined above, the WEB device 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.

Panel Question: The 5 mm image artifact observed with the WEB Implant is based on testing under standard MRI pulse sequences as part of MRI safety and compatibility testing of a permanent passive implant. There has been an increase in routine clinical follow-up for intracranial aneurysm occlusion after treatment using magnetic resonance angiography (MRA) as opposed to digital subtraction angiography (DSA). There were recent reports of the difficulty in successfully obtaining MRA images in subjects implanted with the WEB device (Nawka et al. 2018). The Panel will be asked to discuss and make recommendations on the labeling recommendations regarding patient follow-up with regards to specific imaging modalities for the subject WEB device. In addition, the Panel will be asked whether additional MRA image artifact testing is needed if MRA is believed to be an acceptable imaging modality for long-term follow-up of the IA occlusion status.

5.4 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).

5.5 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.

5.6 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 for summary of animal studies). 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. 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.

6 The WEB Intrasaccular Therapy Study (WEB-IT)

The WEB-IT study was a prospective, multicenter, single arm, pivotal study conducted at 21 study sites in the US and 6 sites outside the US (OUS) [3 sites in the European Union (EU), 2 sites in Turkey, 1 site in Canada]. The following sections presents more detailed information on the pivotal study design and results.

A total of 34 subjects out of a total of 150 subjects in the Intent-to-Treat (ITT) population (defined as those in which a WEB device was attempted to be implanted) were treated at OUS clinical sites. A test of

homogeneity across geographic regions (US vs. OUS sites) was performed by the applicant based on the primary effectiveness endpoint and the results for this analysis are presented in Table 7. The results appear to indicate that the data may be poolable between OUS and US sites; although, there is a limited samples size for subjects treated OUS to make any definitive statistical conclusions.

Table 7. Data Pooling Analysis for the Primary Effectiveness Endpoint by Geographic Region

Region	Subject Successes[a] n/N[c] (%)	95% Unadjusted Confidence Limits (LCL, UCL)[b]
United States	59/109 (54.13)	(44.32, 63.71)
Outside of US	18/34 (52.94)	(35.13, 70.22)

[a] Subject success is defined as 100% occlusion of the target intracranial aneurysm without supplementary treatment or re-treatment.

[b] Two-sided Fisher's Exact Test. Must be less than 0.10 for heterogeneity.

[c] N=143 subjects, which is the total number of subjects with evaluable 12 month imaging data in the Completed Cases (CC) population. All 34 subjects treated OUS in the ITT population had 12 month imaging data, and there was no missing data in the OUS cohort.

6.1 Eligibility Criteria

6.1.1 Inclusion Criteria

Patients could be included in the study only if they met all the following inclusion criteria.

1) Patient must be 18-75 years of age at the time of screening.
2) 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.

3) The IA treated must have had the following characteristics:
   a. Saccular in shape
   b. Located in basilar apex (BA), MCA bifurcation, ICA terminus, AComm complex
   c. Dome-to-Neck ratio ≥ 1
   d. Diameter of the IA appropriate for treatment with the WEB per Instructions for Use
   e. Wide-neck IA with neck size ≥ 4 mm or Dome-to-Neck ratio < 2;
4) Patient had an IA that was appropriate for treatment with WEB without the use of additional implanted devices;
5) If the IA previously ruptured, patient must be neurologically stable with Hunt & Hess Score of I or II.
6) Patient was able to comply with all aspects of the screening, evaluation, treatment, and the post-procedure follow-up schedule.
7) Patient signed and dated an IRB/EC-approved written informed consent prior to initiation of any study procedures.

Panel Question: The inclusion criteria enrolled subjects with a ruptured intracranial aneurysm defined as one with evidence of subarachnoid hemorrhage (SAH) attributed to the index IA

within the past 60 days. The Panel will be asked to discuss and make recommendations on whether the proposed indications for use (IFU) statement that is currently silent on the rupture status of the IA is appropriate because ruptured IA subjects treated with the WEB device may not be acutely ruptured patients (e.g., patients requiring treatment within 14 days of their target IA rupture). There were only 9 ruptured IA subjects in the WEB-IT study. Also, the Panel will be asked to discuss and make recommendations whether additional contraindications, warnings, and/or precautions are needed in the Directions for Use (DFU) to address the benefits and risks of using the WEB device in acutely ruptured IA patients based on the WEB-IT study data.

6.1.2 Exclusion Criteria

Patients were excluded from the study for any of the following reasons:

1) Patient had an IA with characteristics unsuitable for endovascular treatment;
2) Microcatheter did not reach patient's index aneurysm to allow necessary access to treat with study device.
3) Patient had vessel characteristics, tortuosity or morphology which precluded safe access and support during treatment with study device;
4) Patient had vascular disease or other vascular anomaly that precluded the necessary access to the aneurysm for use of the study device;
5) Patient had clinical, angiographic or computed tomography (CT) evidence of vasospasm, vasculitis, an intracranial tumor (except small meningioma) or any other intracranial vascular malformations on presentation;
6) 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;
7) Patient had any circulatory, neurovascular, cardiovascular, or neurologic conditions that resulted in unstable neurological symptoms;
8) Patient had modified Rankin Scale (mRS) ≥ 2 prior to presentation or rupture (as applicable);
9) Patient had a subarachnoid hemorrhage (SAH) from a non-index aneurysm or any other intracranial hemorrhage within 90 days;
10) 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;
11) Patient's index IA was previously treated;
12) Patient was taking anticoagulants or had a known blood dyscrasia, coagulopathy, or hemoglobinopathy;
13) Patient was pregnant;
14) 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;
15) 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;
16) Patient had an acute life-threatening illness other than the neurological disease to be treated in this trial;
17) Patient had a life expectancy of less than 5 years due to other illness or condition (in addition to an intracranial aneurysm).

6.2 WEB-IT Study Design

6.2.1 Primary Safety Endpoint

The primary safety endpoint in the WEB-IT study was defined as the proportion of subjects with death of any nonaccidental cause or any major stroke (defined as an ischemic or hemorrhagic stroke resulting in an increase of 4 points or more on the National Institutes of Health Stroke Scale (NIHSS)) 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. A subject was considered a safety failure upon meeting any of the criteria in the primary safety endpoint definition. All safety events were adjudicated by an independent Clinical Events Committee (CEC).

Major and minor stroke was defined in the WEB-IT protocol as the following for the analysis of the primary safety endpoint:

- Major Stroke: A stroke, which increased the NIHSS by ≥ 4 at the time of assessment and which remained present after 7 days.
- Minor Stroke: A stroke, which increased the NIHSS ≤ 3 or had resolved completely within 7 days.

Panel Question: On March 1, 2018, FDA convened an Advisory Committee meeting to discuss the evaluation of benefits and risks of new IA treatment devices and how to interpret the clinical study results. During this meeting, the Panel recommended that stroke should be defined as debilitating/disabling (i.e., mRS ≥ 3) vs. non-debilitating/non-disabling (i.e., mRS ≤ 2) using the mRS score assessed at a minimum of 90 days post-stroke event. The Panel will be asked to discuss and make recommendations on the pre-specified primary safety endpoint definition and related analyses proposed in the WEB-IT study protocol. The Panel should be prepared to discuss the specific types, severity, and rates of serious adverse events (SAEs) that should be considered in the determination of reasonable safety of the WEB device for the proposed IFU, and whether additional ancillary safety analyses are needed to make this determination.

6.2.2 Primary Effectiveness Endpoint

The primary effectiveness endpoint for the WEB-IT study was defined as the proportion of subjects with complete aneurysm occlusion using the WEB Occlusion Scale (WOS) without retreatment, recurrent subarachnoid hemorrhage, or significant parent artery stenosis (> 50% stenosis) at one year after treatment as assessed by the Core Laboratory (Core Lab). A subject was considered an effectiveness success upon meeting all the above criteria in the primary effectiveness endpoint.

The WOS intracranial aneurysm occlusion scale was developed by the Core Lab at the Oxford University Neurovascular & Neuroradiology Research Unit lead by Prof. James V. Byrne, who proposed visual standards for angiographic assessment of complete occlusion, residual neck, and residual aneurysm for WEB device treated patients (see Figure 4). To accommodate the unique angiographic signature of the WEB marker recess, the modified Raymond-Roy Scale (Roy 2001) was adapted as the WEB Occlusion Scale (WOS, Lubicz et al. 2014).

6.2.2.1 Effectiveness Analyses of the WOS and Degrees of Occlusion

In Figure 4, images are shown to help summarize the WOS.

Grade A represents complete occlusion with no flow into the neck of the IA or the IA sac.

Grade B in Figure 4 also illustrates complete occlusion. There is a clear line of contrast extending from the edges of the IA ostium across the inflow zone. Flow of contrast agent into the proximal marker recess is excluded from the IA neck and sac and is therefore not considered to represent a residual neck or a residual aneurysm.

Grade C in Figure 4 represents a residual IA neck or neck remnant. The WEB (and associated marker recess) is located above the neck and within the IA. Persistence of a portion of the original vessel wall defect is clearly seen.

Grade D in Figure 4 illustrates residual aneurysm or incomplete occlusion. Contrast agent (flow) can be seen in the neck and within the IA sac. Flow of contrast into the WEB device also constitutes residual aneurysm.

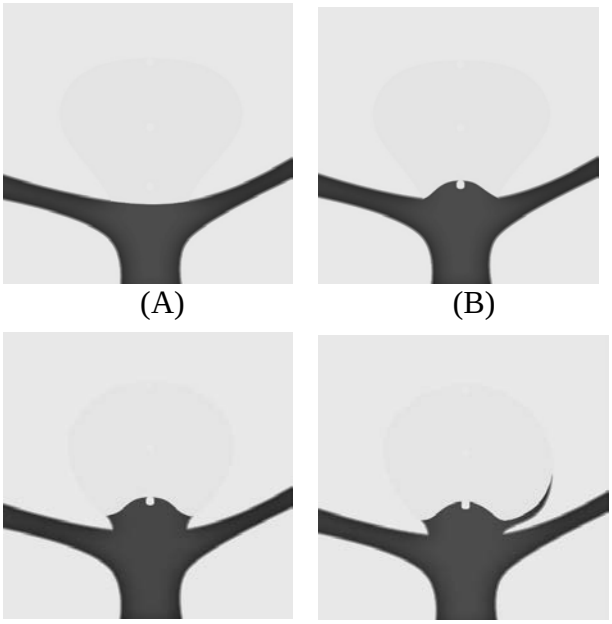

Figure 4. WEB Occlusion Scale with Grades A, B, C, and D

The WOS has been evaluated in an inter-observer agreement study led by Dr. Fiorella et al., an investigator also involved with the WEB-IT IDE pivotal study, where a group of independent reviewers assessed outcomes following WEB procedures to determine relative occlusion. Overall, inter-observer agreement was determined by a κ statistic of 0.779 with a 95% confidence interval (CI) of 0.700-0.857 (Fiorella et al. 2015). In addition, in an in vivo study with aneurysms created in 80 rabbits led by Dr. Rouchaud et al. (2016), the authors intended to compare the angiographic outcomes using Digital Subtraction Angiography (DSA) as measured by the WOS with histologic evaluation of the treated aneurysms, and to assess inter-observer and intra-observer agreement of the WOS with 4 clinical investigators. The rabbits were sacrificed for histological evaluation at day 30 (n=27), day 50 (n=5), day 90 (n=30), day 180 (n=12), or day 365 (n=6). The results showed that inter- and intra-observer weighted κ for the angiographic WOS were both 0.76. The sensitivity and specificity of the WOS for complete occlusion at follow-up compared with the histologic reference standard were 75% and 83.3%, respectively, with an overall accuracy of 80%. For adequate occlusion at follow up, the sensitivity and specificity of the WOS were 97.7% and 64.9%, respectively, with an overall accuracy of 82.5% (Rouchaud et al. 2016).

For effectiveness success in the WEB-IT study, complete intracranial aneurysm occlusion can be a WOS Grade A or B.

Panel Question: The WEB Occlusion Scale (WOS) has not been previously used to support the safety or effectiveness of any intracranial aneurysm treatment devices for marketing approval in the US. Investigational devices used for IA treatment have traditionally used the Raymond-Roy classification scale to assess effectiveness IA occlusion. The Panel will be asked to discuss and make recommendations on the appropriateness of the WEB Occlusion Scale (WOS) for effectiveness of IA occlusion using the WEB device as compared to the standard Raymond-Roy occlusion scale. FDA also requests the Panel to discuss and make recommendations on the appropriateness of defining WOS Grade B as complete intracranial aneurysm occlusion for device effectiveness success given the novel design and mechanism for cerebral blood flow disruption/diversion of the intrasaccular WEB device.

6.2.3 Statistical Methodology

The WEB-IT pivotal study was designed as a single arm study with pre-specified performance goals (PGs) for study success. The PGs for the primary safety and effectiveness endpoints were based on a meta-analysis of the clinical literature for the treatment of wide-neck bifurcation IAs. The WEB-IT study uses a standard frequentist approach to statistical analysis. A routine evaluation of the characteristics of the study variables was conducted to validate assumptions needed for the statistical test procedures. Descriptive statistics, mean, standard deviation, number evaluated, median, minimum and maximum are presented for baseline participant continuous characteristics. The number with a characteristic, number evaluated, percentage, and the exact 95% confidence limits on the percentage are presented for categorical characteristics. The primary endpoint analyses were performed using a one-sided nominal significance level of 0.05. All other categorical outcomes are presented with the number of subjects with the characteristic, the total number evaluated, the percent, and the 95% confidence interval (CI) on the percent. Continuous endpoints are presented descriptively with the mean, standard deviation, number evaluated, median, minimum and maximum.

For the statistical hypotheses of the primary effectiveness endpoint, the null and alternative hypotheses are:

$$H_0: P_{WEB} \leq 0.35 \text{ versus } Ha: P_{WEB} > 0.35$$

where P_{WEB} is the percentage of WEB subjects who have primary endpoint success at the 12-month follow-up in the treated population. The null and alternative hypotheses for the primary safety endpoint are:

$$H_0: P_{WEB} \geq 0.20 \text{ versus } Ha: P_{WEB} < 0.20$$

where P_{WEB} is the rate of primary safety endpoint events at one year in the treated population.

Panel Question: The Panel will be asked to discuss and make recommendations on the performance goals (PGs) provided to support conclusions of safety and effectiveness success of the WEB-IT trial.

6.2.4 Sample Size

The sample size for the primary effectiveness endpoint for this single arm study was computed for a single binomial proportion. The point estimate rate of complete occlusion in the WEB treatment group

was expected to be 0.46 with Core Lab adjudication and the PG is 0.35. Eighty percent (80%) power was achieved with a one-sided alpha of 0.05 with 127 evaluable subjects. Assuming a loss to follow-up of 15% in this critically ill population, the recruited sample size was 127/0.85 = 149.4 or 150 subjects.

For the sample size for the primary safety endpoint, to have 80% power to detect a difference between an expected observed primary safety event rate of 0.114 and the PG of 0.20, the sample size was 118 subjects with an alpha of 0.05. Accounting for a possible 15% loss-to-follow-up rate, the recruited sample size should have been 118/0.85 = 138.8 or 139. Since the sample size for effectiveness was larger, 150 subjects were established as the sample size for the study.

6.2.5 Follow Up Schedule

Subjects in the WEB-IT study were consented to participate and be followed up to 5 years post-procedure. The assessment visits included at screening, procedure, discharge, and 30 days, 6 months, 1 year, 2 years, 3 years, 4 years, and 5 years post-procedure. Follow-up visits consisted of a review of medical history, including adverse events, focused physical examination, functional assessments, and angiogram (i.e., DSA) at selected visits.

6.3 Subject Characteristics

6.3.1 Subject Accountability

There was a total of 179 subjects consented for the WEB-IT study. Of the 179 consented, 28 subjects were determined to be screening failures or excluded based on the pre-procedure angiographic assessment and were not enrolled in the study. One subject who passed the initial screening assessment was unable to schedule the WEB-IT procedure before the study became fully enrolled and closed to additional cases. This subject is considered consented, but not treated.

6.3.1.1 Analysis Populations

A total of 150 subjects passed the pre-procedure angiographic screening and are considered enrolled into the study. All 150 subjects had a WEB-IT device inserted with the intention to implant and are included in the Intent-to-Treat (ITT) analysis population. The ITT population is used for the primary analyses of the primary safety and effectiveness endpoints to establish study success. At the end of the 12-month follow-up period, 143 subjects had sufficient information to be evaluated for the primary effectiveness analysis. These 143 subjects comprise the Completed Cases population (CC). No subject among the CC subjects had protocol deviations that affected the primary endpoints per the review of a physician adjudicator, so the Per-Protocol population (PP) is identical to the CC population with 143 subjects. The subject accountability and definitions of patient populations in the WEB-IT study is also described in Table 8.

Table 8. Summary of Analysis Populations

Population	Description	Analysis	Number of Subjects
Consented	Subjects who signed informed consent form.	NA	179
Screen Failures	Subject who were consented and failed initial screening of inclusion/exclusion criteria.	NA	10
	Subject who were consented and failed procedural angiographic screening criteria.	NA	18

Population	Description	Analysis	Number of Subjects
Consented Not Treated	Subjects who were consented and passed initial screening but were not scheduled for procedure.	NA	1[a]
Intent to Treat (ITT)	All subjects in whom a WEB device was attempted to be implanted.	Primary Safety and Effectiveness Endpoint Analyses; Secondary Safety Endpoint Analyses	150
Complete Cases (CC)	ITT subjects with a 12-month evaluation for effectiveness.	Primary and Secondary Effectiveness Endpoint Analyses	143
Per Protocol (PP)	CC subjects without a serious protocol deviation.	Primary and Secondary Effectiveness Endpoint Analyses	143

[a] One subject passed the initial screening, but a procedure could not be scheduled prior to the completion of the study so they were not fully enrolled.

6.3.2 Demographics

The IA and baseline characteristics for the 150 subjects in the ITT population in the WEB-IT study used for the primary endpoint analyses are summarized below in Table 9 and Table 10.

Table 9. IA Continuous Baseline Measurements (N=150)

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

Table 10. Categorical Baseline Characteristics

Characteristic	x/n (%) (Unadjusted LCL, UCL)
Gender (Male)	40/150 (26.67) (19.78, 34.49)
Race[a] Asian Black or African American White	 4/116 (3.45) (0.95, 8.59) 14/116 (12.07) (6.76, 19.42) 98/116 (84.48) (76.59, 90.54)
Ethnicity[a]	2/116 (1.72) (0.20, 6.09)

Characteristic	x/n (%) (Unadjusted LCL, UCL)
Hispanic or Latino	
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 Discovered	
Symptomatic	33/141 (23.40) (16.69, 31.27)
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)
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)

Characteristic	x/n (%) (Unadjusted LCL, UCL)
Prostate Problems	9/40 (22.50) (10.84, 38.45)
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)
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)

Characteristic	x/n (%) (Unadjusted LCL, UCL)
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 due to Ethics Committee regulations in these countries.

7 WEB-IT Study Results and Analyses

7.1 Safety Results and Analyses

7.1.1 Primary Safety Endpoint

As stated above, the primary safety endpoint was defined in the WEB-IT study protocol as the proportion of subjects with death of any nonaccidental cause or any major stroke (an ischemic or hemorrhagic stroke resulting in an increase of 4 points or more on the NIHSS) 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 defined as, "A stroke, which increased the NIHSS by ≥ 4 at the time of assessment and which remained present after 7 days."

In the original PMA submission, the applicant (Sequent Medical, Inc.) presented the primary safety endpoint analysis based on subjects with clinical information at 12 months post-procedure (N=147, see Table 11) instead of the ITT population (N=150). Complete follow-up through 12 months (or 30 days for the 2 subjects in whom a WEB device was not implanted but attempted) was obtained in 145 of the 150 subjects. Two additional subjects were confirmed to be alive and stroke free at 12 months, resulting in the 147 total subjects presented for the primary safety endpoint analysis in Table 11. The 12-month visit plus this information resulted in only 3 subjects without a survival and/or stroke assessment at 12 months.

A single primary safety endpoint event, a SAH adjudicated as a major stroke, occurred on post-procedure day 22. The SAH was adjudicated as likely related to antiplatelet medication and underlying cerebrovascular disease and not related to the treated aneurysm. The location was ipsilateral but remote from the target aneurysm. This subject was a 54-year-old, non-Hispanic, Caucasian woman with gastroesophageal reflux disease (GERD), multiple sclerosis, urinary incontinence, depression, a current smoker and no history of a previous stroke. Her intracranial aneurysm was unruptured, in the anterior communicating artery and with a sac width of 7.4 mm. The subject had a baseline NIHSS and mRS of 0 (zero). Her NIHSS was 13 on day 7 post-stroke. At 12 months, the subject had an mRS of 4 due to residual left hemiplegia. Her aneurysm was completely occluded with no stenosis of the parent artery. She was therefore considered a primary effectiveness endpoint success and a primary safety endpoint failure.

Table 11. Primary Safety Composite Endpoint Analysis in Completed Cases

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 0.20. The upper 90% confidence limit needs to be less than the PG rate of 0.20.

[b] Unadjusted 90% upper confidence limit.

The primary safety endpoint analysis using subjects with available data ta 12 months (N=147) is not the most rigorous analysis, and the ITT population should have been used. In the original PMA P170032 submission, the applicant also conducted a sensitivity tipping point analysis to account for the 3 missing subjects with 12 month data as primary safety endpoint failures (see Table 12).

Table 12. 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. The upper 90% CI is unadjusted for multiplicity.

In the December 27, 2017 FDA letter, FDA requested a modified safety endpoint analysis to include any subject with neurological death or stroke within 12 months follow-up as a major safety event. This modified safety endpoint analysis is presented in Table 13. For this modified safety endpoint analysis, there were an additional 11 subjects in the ITT 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 applicant's pre-specified primary safety endpoint definition.

Table 13. FDA-Requested All Stroke Safety Endpoint

Endpoint	n/N (%)	Unadjusted 95% Exact CI
Composite FDA Requested All Stroke Safety Endpoint	12[a]/150 (8.00%)	(4.20, 13.56)

Endpoint	n/N (%)	Unadjusted 95% Exact CI
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.

7.1.2 Change in Modified Rankin Scale (mRS) Score

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 14. The large majority of unruptured aneurysm subjects had an mRS of 0 (111 subjects out of 135 unruptured aneurysm subjects) or mRS of 1 (22 out of 135 unruptured aneurysm 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. There were 6 subjects with unruptured IAs that did not have 12 month mRS scores. If these subjects 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).

Of the 9 mRS scores that increased by 1 point; 4 were due to minor ischemic strokes, 2 were due to a visual field impairment, 1 was due to dizziness, 1 was due to ongoing muscle spasms, and 1 was due to arthralgia. One subject's score increased by 2 points associated with worsening baseline cerebrovascular disease and one subject's score increased by 4 points due to her major primary safety endpoint stroke event.

Table 14. 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 n (%)[a] LCL, UCL	1 n (%)[a] LCL, UCL	3 n (%)[a] LCL, UCL	4 n (%)[a] LCL, UCL	
0	99 (90.83) 83.77, 95.51	9 (8.26) 3.84, 15.10	0 (0.00) 0.00, 3.33	1 (0.92) 0.02, 5.01	109
1	12 (46.15) 26.59, 66.63	13 (50.00) 29.93, 70.07	1 (3.85) 0.10, 19.64	0 (0.00) 0.00, 13.23	26
Total	111 (82.22) 74.71, 88.26	22 (16.30) 10.50, 23.63	1(0.74) 0.02, 4.06	1(0.74) 0.02, 4.06	135[b]

[a] Percent of the row total.

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

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

Eight of the 9 subjects with ruptured target intracranial aneurysms at baseline had 12 month mRS scores (see Table 15). 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, 7 out of these 9 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 aneurysms were located in the posterior cerebral circulation (5/9 (56%), basilar apex).

Table 15. Modified Rankin Scale Score Change from Baseline to 12 Months in Ruptured Aneurysms

mRS Score at Baseline	mRS Score at 12-Months		Total
	0 n/N (%)	1 n/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

7.1.3 All Adverse Events

7.1.3.1 Non-Serious Adverse Events

In the WEB-IT study, within the first 30 days (peri-procedural), 135 non-serious adverse events (AEs) occurred in 68 subject (68/150, 45.3% of subjects). 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% of subjects), nausea (10 events/9 subjects, 9/150, 6.0% of subjects), and vessel puncture site related events (13 events including puncture site reaction, bruise, hematoma, hemorrhage, and pain, 13/150, 8.7% of subjects). 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 again was headache (24 events in 20 subjects, 20/150, 13.3% of subjects). No other non-serious AE occurred in more than 5% of subjects. Adverse drug reactions during follow up occurred in 7 subjects (7/150, 4.7%). These were related to antiplatelet agents in 3 cases, pain and antianxiety medications in 2 cases, and other concurrent medications in 2 cases. All of 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 16.

Table 16. 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	Anaemia	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

System Organ Class	Preferred Term	AE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events
	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) 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)

System Organ Class	Preferred Term	AE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events
		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
	Dizziness Postural	1/150 (0.67) (0.02, 3.66) 1
	Headache	20/150 (13.33) (8.34, 19.84) 20
	Hypoaesthesia	1/150 (0.67) (0.02, 3.66) 1
	Ischaemic 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
	Paraesthesia	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

System Organ Class	Preferred Term	AE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events
Respiratory, Thoracic and Mediastinal Disorders	Cough	1/150 (0.67) (0.02, 3.66) 1
	Dyspnoea	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) 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	Anaemia	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

System Organ Class	Preferred Term	AE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events
	Gastric Ulcer	1/150 (0.67) (0.02, 3.66) 1
	Nausea	1/150 (0.67) (0.02, 3.66) 1
	Oesophageal 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
	Oedema	1/150 (0.67) (0.02, 3.66) 1
	Oedema Peripheral	1/150 (0.67) (0.02, 3.66) 1
	Pyrexia	1/150 (0.67) (0.02, 3.66) 1
	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
	Animal Bite	1/150 (0.67) (0.02, 3.66)

System Organ Class	Preferred Term	AE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events
Injury, Poisoning and Procedural Complications		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) 1
	Hypocalcaemia	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

System Organ Class	Preferred Term	AE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events
	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
	Ischaemic 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
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	Dyspnoea	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)

System Organ Class	Preferred Term	AE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events
		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.

7.1.3.2 Serious Adverse Events

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 re-treatment procedure of the index aneurysm with a Pipeline Embolization 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). These events primarily fell into the category of 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. No SAEs after day 30 were adjudicated to be device-related by the CEC. All of the SAEs observed in the WEB-IT study within 1 year post-procedure are presented in Table 17 as coded by MedDRA.

Table 17. 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

System Organ Class	Preferred Term	SAE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events
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
	Ischaemic 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
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 Haemorrhage	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

System Organ Class	Preferred Term	SAE Rate[a] n/N (%) (Unadjusted LCL, UCL) Events
	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
	Haemorrhage Intracranial	1/150 (0.67) (0.02, 3.66) 1
	Headache	1/150 (0.67) (0.02, 3.66) 1
	Ischaemic Stroke	1/150 (0.67) (0.02, 3.66) 1
	Seizure	1/150 (0.67) (0.02, 3.66) 1
	Transient Ischaemic 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.

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

7.2 Effectiveness Results and Analyses

7.2.1 Primary Effectiveness Endpoint

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) without retreatment, recurrent SAH, or significant parent artery stenosis (> 50% stenosis) at one year after treatment as assessed by the Core Laboratory ("Core Lab").

7.2.1.1 Approach to Missing Data

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. For example, 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 18 below. Subjects were determined to be complete cases with valid 12-month assessment in 136 of the 150 subjects.

Table 18. Primary Effectiveness Endpoint Imputation Patient Groups

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

[a] One subject was not included 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. A computed tomography angiography (CTA) was conducted and per assessment of Core Lab, this CTA did not allow for a complete assessment of parent artery stenosis. The subject had successful aneurysm occlusion per the Core Lab. As no subject with complete occlusion had parent artery stenosis > 50%, this subject was imputed as a success for purposes of the primary effectiveness endpoint assessment. 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 aneurysm retreatment or planned retreatment prior to 12 months (3).

Subjects with missing data who were assumed to be missing at random were grouped by aneurysm 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 aneurysm 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 results are provided in Table 19. The primary effectiveness success rate in the ITT population was 54.77% (lower bound of 90% CI of 47.97%) based on imputation for 14 missing subjects without 12 month effectiveness follow-up data.

Table 19. Primary Effectiveness Endpoint Imputation[a] and Analysis (Assuming Poolability of Data)

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

[a] Includes one subject who had total occlusion and a missing parent vessel stenosis score. No subject with total occlusion failed on parent vessel stenosis, so subject is imputed to be a success.

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

[c] 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. Please note that the lower 90% confidence limit presented is not adjusted for multiplicity; therefore, it may be difficult to draw any statistical conclusions.

7.2.1.2 Per Protocol Analyses

In the Completed Cases (CC)/Per Protocol (PP) population, the primary effectiveness endpoint rate using the WOS was similar at 53.85% (77/143, lower bound of 90% CI of 46.63%). The components of the primary effectiveness endpoint in the CC/PP population is presented in Table 20. The study met the applicant proposed primary effectiveness 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 aneurysms were included in the effectiveness PG analysis. Success criteria were defined as total aneurysm occlusion (Raymond-Roy I) or adequate occlusion (Raymond-Roy I or II) at 12 months. The Core Lab adjusted rate of complete occlusion was 46.3% (standard error (SE) of 3.6%) for all therapies, 39.8% (SE of 3.6%) for endovascular therapies, and 52.5% (SE of 9.6%) for surgical clipping alone. When only Level I studies were included, the Core Lab adjusted rate of complete occlusion was much lower at 34.9% (SE of 5.7%) for all therapies, 28.7% (SE of 7.7%) for endovascular therapies, and 43.5% (SE of 3.4%) for surgical clipping alone. Additionally, the meta-analysis rates did not include subjects with parent artery stenosis, recurrent SAH, or re-treatment as failures as was required for the WEB-IT study, and allowed for 6-month outcomes to be carried forward to 12 months for purposes of analysis.

Table 20. 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)

Component	Number of Subjects n/N (%)
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 Aneurysm[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.

Subgroup analyses of the primary effectiveness endpoint were conducted using the CC/PP population (see Table 21). 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 21. Subgroup Sensitivity Analyses of the Primary Effectiveness Endpoint in the Completed Cases Population

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	
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.

7.2.2 Secondary and Additional Effectiveness Endpoint Analyses

7.2.2.1 Target Intracranial Aneurysm Recurrence

The secondary effectiveness endpoint in the WEB-IT study protocol was the 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 of this secondary effectiveness endpoint is presented for the CC population in Table 22 below. 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.

Table 22. 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.

Occlusion category (complete occlusion, residual neck, residual aneurysm) at 6 and 12 months is presented in Table 23 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 (44/140), and 11% with a residual aneurysm (15/140). Based on the data presented in Table 23, it appears 6 subjects with complete IA occlusion at 6 months resulted in recanalization of their IA at 12 months with a residual neck.

Table 23. 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.

7.2.2.2 Parent Artery Stenosis

The development of a parent artery stenosis > 50% was not observed in any study subject with complete occlusion. A single subject with a residual aneurysm had a documented parent artery stenosis > 50% on the 12-month angiogram; however, this was post retreatment with a stent at 6 months. These data appear to confirm that the WEB device and its placement do not contribute to the development of a new stenosis in the parent artery of the aneurysms being treated.

7.2.2.3 Technical Success for Implantation and WEB Size Selection

Table 24 presents the technical success rates with technical success 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). Two subjects were unable to be implanted due to vessel tortuosity precluding ability to maintain catheter position during delivery of WEB and unavailability of a smaller device size after initial attempt with a larger device size. The first subject (failure to maintain catheter position), underwent subsequent aneurysm clipping prior to 30 day follow up. The other subject had no reported intervention through 30 days. 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. There were no cases where adjunctive coiling or flow diverter placement was performed.

Table 24. Procedural Success of WEB Implantation

Event	Rate 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 case)
Note: All 95% CIs presented in this table are unadjusted.

For the 150 subjects in whom device placement was attempted in the ITT population, a total of 211 device attempts resulted in 148 device placements (Table 25 and Table 26). A total of 63 inserted devices were not implanted. 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 neck width, dome width, and dome height as well as the general shape of the aneurysm. After deployment but prior to detachment, repeated DSA runs 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, similar to neurovascular coils. 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, 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 25. WEB Device Disposition

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

Table 26. Number of Attempts to Implant a WEB Device

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)

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

8 Summary

The WEB-IT study was a prospective, multi-center single-arm interventional study performed to study the safety and effectiveness of the WEB device in the treatment of wide-neck bifurcation intracranial aneurysms. A total of 179 subjects (Enrollment population) were screened and 150 subjects (ITT population) had attempted treatment with the WEB device. Of the 150 subjects with attempted placement of the device, 148 had the WEB device implanted (Per Protocol population). Technical success, defined as successful implant of the WEB device was achieved in 98.7% (148/150) of subjects allowing for supportive use of adjunctive devices (2 subjects requiring stenting). Technical success with no adjunctive device use, aside from balloon catheters, was achieved in 97.3% of subjects (146/150 subjects).

The primary effectiveness success rate in the ITT analysis population, defined as complete aneurysm occlusion at 12-month follow up without retreatment, recurrent subarachnoid hemorrhage or the development of a parent artery stenosis > 50% was 54.77% (lower bound (LB) of 90% CI of 47.97%). In the analysis performed by the applicant, pooled data was used given there was no heterogeneity identified across pseudo-sites and geographic areas, and missing data for 7 subjects without evaluable 12-month angiograms were imputed by multiple imputation. 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.

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 National Institutes of Health Stroke Scale 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 ITT analysis, missing data for 3 subjects without known primary endpoint

status at 1-year were imputed by multiple imputation. One subject (1/150, 0.67%) sustained a primary safety endpoint event (upper bound of 90% CI of 6.04%). A tipping point analysis conducted for sensitivity verified that success was achieved even under the worst-case scenario of all missing observations considered to be failures. Multivariable modeling was not done because the single endpoint event would not support the logistic regression modeling.

The secondary effectiveness endpoint of angiographic aneurysmal recurrence (defined as aneurysm recanalization or regrowth) occurred in approximately one-eighth of the studied subjects (18/143, 12.6%) at 12 months. Complete occlusion or neck remnant was achieved in over 83% (125/150) of subjects at 12 months. Durability of the aneurysm treatment assessed at 12 months as same, improved, or worse than prior assessment was determined by Core Lab to be either the same or improved in over 88% (121/137) of subjects. However, some subjects demonstrated a decrease in aneurysm occlusion between their 6-month and 12-month angiographic assessment. Retreatment was planned or performed in approximately 5% (7/148) of study subjects through 12-month follow up.

Summary to Panel: FDA is seeking discussion and recommendations on the premarket approval (PMA) P170032 application from Sequent Medical, Inc. (wholly owned subsidiary of MicroVention, Inc.) for the Woven EndoBridge (WEB) Aneurysm Embolization System for the treatment of wide-neck bifurcation intracranial aneurysms, both ruptured and unruptured, located in the anterior (middle cerebral artery (MCA) bifurcation, internal carotid artery (ICA) terminus, anterior communicating artery (Acomm) complex) and posterior (basilar apex) circulations. As discussed above, a brief review of the treatment of wide-neck bifurcation IAs, a description of the device, a review of pre-clinical studies, and the presentation of clinical data from the pivotal study titled "The WEB Intrasaccular Therapy Study (WEB-IT)" used to support the PMA P170032 has been provided and we look forward to the discussion at the September 27, 2018 Advisory Committee meeting.

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