SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Intracranial Neurovascular Stent
Device Trade Name:	Low-Profile Visualized Intraluminal Support (LVIS) and LVIS Jr.
Device Procode:	QCA
Applicant's Name and Address:	MicroVention, Inc. 1311 Valencia Avenue Tustin, CA 92780
Date(s) of Panel Recommendation:	None

Premarket Approval Application (PMA) Number: P170013

Date of FDA Notice of Approval: May 30, 2018

II. INDICATIONS FOR USE

The LVIS and LVIS Jr. are indicated for use 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.

III. CONTRAINDICATIONS

The use of the LVIS and LVIS Jr. device are contraindicated under these circumstances:

- Patients in whom anticoagulant, anti-platelet therapy or thrombolytic drugs are contraindicated.
- Patients with known hypersensitivity to metal, such as nickel-titanium and metal jewelry.
- Patients with anatomy that does not permit passage or deployment of the LVIS/LVIS Jr. device.
- Patients with an active bacterial infection.
- Patients with a pre-existing stent in place at the target aneurysm.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the LVIS and LVIS Jr. labeling.

V. DEVICE DESCRIPTION

The LVIS and LVIS Jr. consists of:

1) A self-expanding nickel titanium (nitinol) stent with radiopaque markers; and
2) A delivery system consisting of an introducer sheath and a detachable push wire.

The self-expanding nitinol stent consists of a single wire braid, compliant, closed-cell tubular design with flared ends. The nitinol stent contains radiopaque wires (tantalum) that are woven into the implant in a helical configuration and radiopaque tantalum coil markers at each end to aid in stent placement under fluoroscopy. The delivery system contains an introducer sheath that is used to protect the stent in the package and facilitates the introduction of the device into the microcatheter hub. The delivery push wire is attached to the stent and is designed to facilitate delivery of the stent to the site of implantation. On the proximal end of the delivery push wire, there are three radiopaque markers that indicate when the stent should exit the distal end of the microcatheter and aids in stent placement (see Figures 1 and 2). The LVIS are deliverable through a 0.021" inner diameter (ID) microcatheter whereas the LVIS Jr. are deliverable through a 0.017" ID microcatheter. The devices are provided sterile for single use only and are non-pyrogenic.

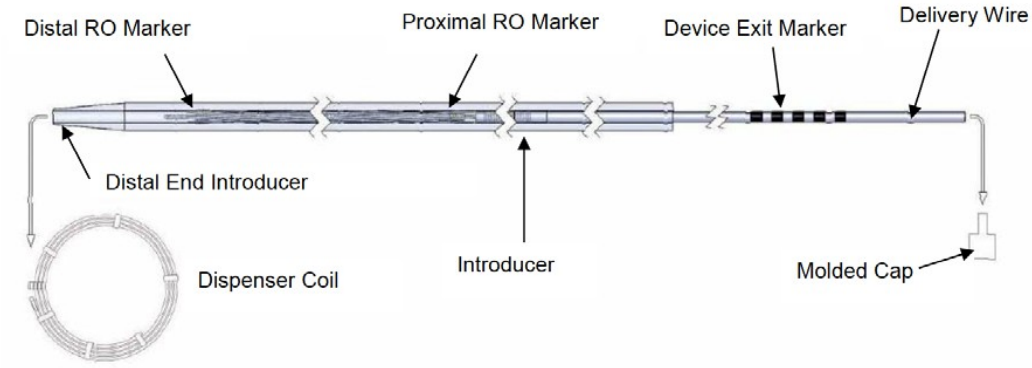


Figure 1: Overall Device Diagram

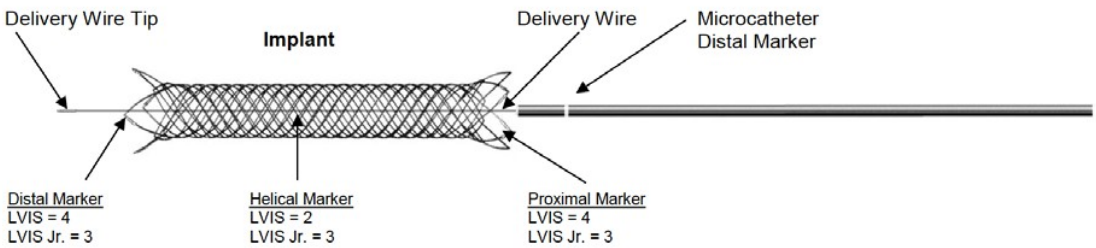


Figure 2: Device Implant and Delivery System

Table 1 shows the device sizes available for the LVIS and LVIS Jr.

Table 1: Sizes of LVIS and LVIS Jr.

Device	Outer Diameter (mm)	Lengths (mm)
LVIS	3.5	17 and 22
	4.0	12, 17, 22, 28, and 31
	4.5	18, 23, and 32
	5.5	30 and 33
LVIS Jr.	2.5	13, 17, 23, and 34
	3.5	18, 23, 28, and 33

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of wide-neck intracranial aneurysms including open surgical clipping, endovascular treatment using embolization coils supported with other Humanitarian Device Exemption (HDE) approved neurovascular stents or balloon catheter assisted coiling of the intracranial aneurysm, and flow diverters. The other neurovascular stents approved through the HDE regulatory pathway for stent-assisted coiling include the Stryker Neurovascular Neuroform EZ, 3, and Atlas Stent Systems (H020002) and the Codman & Shurtleff, Inc. Enterprise Vascular Reconstruction Device and Delivery System (H060001). A similar HDE approved device that is indicated to support neurovascular embolization coils specifically for the treatment of unruptured wide-necked intracranial aneurysms originating on or near a vessel bifurcation of the basilar tip or carotid terminus is the Pulsar Vascular, Inc. PulseRider Aneurysm Neck Reconstruction Device (H160002).

The Micro Therapeutics, Inc. d/b/a ev3 Neurovascular Pipeline Embolization Device (PED) (P100018) is the only approved flow diverter in the United States (US) and was approved with the intended use of endovascular treatment of large or giant wide-necked intracranial aneurysms in the internal carotid artery (ICA) from the petrous to the superior hypophyseal segment. The flow diverter is implanted in the parent vessel and is placed across the neck of the intracranial aneurysm. Its mechanism of action is to divert the blood flow from entering the intracranial aneurysm sac and endothelialization will occur on the implant over time to further promote complete intracranial aneurysm occlusion. The flow diverter is intended to be used by itself as a stand-alone device.

In addition to these alternative treatments, certain intracranial aneurysms may be managed medically or by observation only with no treatment but with regular imaging follow-up examinations to ensure there are no morphological changes in the intracranial aneurysm(s) over time. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The LVIS and LVIS Jr. are approved for marketing in the following countries:

Argentina, Australia, Austria, Belarus, Belgium, Brazil, Bulgaria, Canada, Chile, China, Colombia, Costa Rica, Cuba, Cyprus, Czech Republic, Denmark, Dominican Republic, Ecuador, Egypt, El Salvador, Estonia, Finland, France, Georgia, Germany, Honduras, Hong Kong, Hungary, Iceland, India, Iran, Ireland, Israel, Italy, Japan, Jordan, Kazakhstan, Korea, Latvia, Lebanon, Libya, Lithuania, Malaysia, Morocco, Mexico, Mongolia, Netherlands, New Zealand, Norway, Pakistan, Panama, Paraguay, Peru, Poland, Portugal, Puerto Rico, Romania, Russia, Saudi Arabia, Serbia, Singapore, Slovenia, Spain, Sweden, Switzerland, Thailand, Tobago, Turkey, Ukraine, United Arab Emirates, United Kingdom, United States (under HDE H130005), Uruguay, Venezuela, Vietnam.

The LVIS and LVIS Jr. have not been withdrawn from the market for safety or effectiveness reasons.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the probable adverse effects (e.g., complications) associated with the use of the device.

- Allergic reaction, including but not limited to: contrast dye, nitinol metal, and any other medications used during the procedure
- Aphasia
- Blindness
- Cardiac arrhythmia
- Coil prolapsed or migration into normal vessel adjacent to intracranial aneurysm
- Complications of arterial puncture including pain, local bleeding, local infection and injury to the artery, vein or adjacent nerves
- Cranial neuropathy
- Death
- Device fracture, migration or misplacement
- Dissection or perforation of the parent artery
- Headache
- Hemorrhage (i.e., intracranial hemorrhage (ICH), subarachnoid hemorrhage (SAH), retroperitoneal (or in other locations))
- Hemiplegia
- Hydrocephalus
- Infection
- Injury to normal vessel or tissue
- Ischemia
- Mass effect
- Myocardial infarction

- Neurological deficits
- Occlusion of non-target side branches
- Pseudo aneurysm formation
- Reactions to anti-platelet/anti-coagulant agents
- Reactions due to radiation exposure (i.e., alopecia, burns ranging in severity from skin reddening to ulcers, cataracts, delayed neoplasia)
- Reactions to anesthesia and related procedures
- Reactions to contrast agents
- Renal failure
- Aneurysm rupture
- Stenosis of stented segment
- Seizure
- Stent thrombosis
- Stroke or TIA (transient ischemic attack)
- Thromboembolic event
- Vasospasm
- Visual impairment

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

IX. SUMMARY OF NONCLINICAL STUDIES

The LVIS and LVIS Jr. underwent non-clinical mechanical, functional, biocompatibility, sterilization validation, bacterial endotoxin, and animal testing to support the proposed intended use.

A. Laboratory Studies

Design Verification and Validation Testing

Table 2 shows the design verification and validation testing conducted on the LVIS and LVIS Jr. Much of the testing was conducted based on the recommendations in the Guidance for Industry and FDA Staff, "Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems," issued on April 18, 2010.

Table 2: Design Verification and Validation Testing

Test	Purpose	Results
Material Composition	Verify if materials are suitable for implant.	Materials met pre-specified requirements.
Austenite Finish Transition Temperature (A_f)	The implant will achieve its predetermined size and shape when exposed to normal body temperature.	The A_f for the LVIS and LVIS Jr. implant was confirmed to comply with the specification of < 30 °C.
Pitting, Crevice, and Fretting Corrosion Potential	Determine the corrosion susceptibility of the stent.	No breakdown potential was reached.
Galvanic Corrosion	Assess the galvanic corrosion susceptibility of two dissimilar metals (nitinol and tantalum).	No corrosion susceptibility was observed.
Percent Surface Area	To determine the surface area of the LVIS/LVIS Jr. device.	Met pre-specified criteria.
Foreshortening	To determine if the stent length shortens once deployed.	Met pre-specified criteria.
Stent Integrity	Determine if there are any abnormalities on the LVIS/LVIS Jr. device.	All samples demonstrated the LVIS/LVIS Jr. device is able to deploy over the device shelf life of 3 years.
Mechanical Properties	To specify the mechanical properties of incoming and post processing stent material.	The post processed nitinol wire is equivalent to the raw nitinol material.
Stress/Strain and Fatigue Analysis	Fatigue resistance of the LVIS/LVIS Jr. stents were analyzed based on a 0.4% endurance limit.	No excessive localized stresses were detected. The finite element analysis (FEA) predicted the LVIS/LVIS Jr. fatigue lifetime has adequate safety built into the design with a safety factor of > 2.39.
Accelerated Durability Testing	Following 380,000,000 cycles (10-yrs equivalent), the LVIS/LVIS Jr. device was tested for percent strain.	The LVIS/LVIS Jr. device met accelerated durability test specification with no loss in structural integrity or fragmentation.
Particulate Evaluation	Quantify the particulate matter in injections for the LVIS/LVIS Jr. device under simulated use conditions in a neurovascular tortuosity model.	The particulate test was validated by demonstrating > 90% recovery for > 10 µm and > 25 µm particle size ranges.

Test	Purpose	Results
Magnetic Resonance Imaging (MRI) Safety	To assess the MRI safety and compatibility of the LVIS/LVIS Jr. device.	The test results demonstrated the LVIS/LVIS Jr. device does not pose additional unacceptable risk to the patient. The LVIS/LVIS Jr. device was determined to be MRI Conditional per ASTM2503. The MRI Conditional scanning parameters are specified in the labeling.
Radiopacity	Determine if the LVIS/LVIS Jr. device and delivery system are visible under fluoroscopy (imaging used during implantation).	The LVIS/LVIS Jr. device was verified to meet the acceptance criteria for radiopacity.
Tensile Bond Strength	The tensile strength of the LVIS/LVIS Jr. implant is characterized at the: - Implant wire ends; - Proximal implant marker coil; and - Distal implant marker coil.	The LVIS/LVIS Jr. device met the tensile bond strength acceptance criteria at the bond locations.
Dimensional Attributes – Delivery System and Stent	To confirm the delivery system and stent is within dimensional specifications.	The delivery systems and stents for the LVIS and LVIS Jr. met dimensional specifications.
Radial Outward Force	The radial force of the LVIS/LVIS Jr. implant is characterized.	The LVIS/LVIS Jr. implant met the radial outward force acceptance criteria.
Simulated Use Testing	Verify performance attributes in an in-vitro model simulating tortuous intracranial anatomy. - Compatibility with delivery catheter - Trackability through delivery catheter while advancing stent - Trackability through delivery catheter while retracting stent - Ease of stent deployment - Ease of stent detachment - Accuracy of stent placement - Wall apposition/conformance to vessel - Stent stability - Ability to cross/re-cross deployed stent with microcatheter	All devices tested passed the simulated use testing.

Test	Purpose	Results
	- Compatibility with ancillary microcatheter used for deploying embolic coils - Compatibility with embolic coils - Overall performance	
Flexibility and Kink Test	The flexibility and kink test for the LVIS/LVIS Jr. were assessed during the "simulated use" testing of the device. During simulated use testing, the trackability of the devices is evaluated during advancement/retraction of the device in the microcatheter. The device including the delivery system needs to be flexible and kink resistant to be able to advance the device through tortuous anatomy. If not, the trackability of the device would be affected.	The trackability of the LVIS and LVIS Jr. were rated favorably during the simulated use testing and did not result in any kinks observed.

Biocompatibility Testing

Biocompatibility testing for all materials used to manufacture the LVIS and LVIS Jr. were performed in accordance with ISO 10993-1:2009/(R)2013, Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing within a Risk Management Process. Tables 3 and 4 shows the biocompatibility tests conducted for the LVIS/LVIS Jr. implant and delivery system, respectively.

Table 3: Implant - Biocompatibility

Test	Purpose	Results
Cytotoxicity - L929 MEM Elution Test	Test for cell lysis.	No evidence of biological reactivity.
Sensitization - Kligman Maximization Test	Test for allergenic potential or sensitization capacity of test article.	The test article extracts showed no reaction at the challenge.
Irritation - Intracutaneous Injection Test in Rabbits	Test for irritation potential.	The test article sites did not show a significantly greater biological reaction than the sites injected with the control article.
Systemic Toxicity - Systemic Injection Test Study in Mice	Test for systemic acute toxicity in mice following intravenous and intraperitoneal injections.	The test article did not induce a significantly greater biological reaction than the control extracts, when tested in mice.
Systemic Toxicity - Rabbit Pyrogen Test (Material Mediated)	Test for pyrogenic response from the material.	The increases in temperature did not exceed the test limit for the maximum individual temperature rise.
Hemocompatibility -	Test for red blood cell	The test article exhibited 0.29% hemolysis

Test	Purpose	Results
ASTM Hemolysis (Indirect Contact)	hemolysis.	above the level of hemolysis exhibited by the negative control via the indirect method.
Hemocompatibility - Prothrombin Time Assay (Indirect Contact)	Test for coagulation response from the test material.	The mean value for the test article and each individual replicate value did not differ from the mean of the negative and untreated controls by more than one second.
Hemocompatibility - Complement Activation Assay (C3a, SC5b-9) (Indirect Contact)	Test the potential for activation of the complement system.	The test article did not induce complement activation of C3 or C5 proteins in human plasma.
Hemocompatibility - Thrombogenicity Study	Test to determine comparative thromboresistence of medical devices that are intended for blood contact.	No significant thrombosis was observed in test sites and control sites.
Genotoxicity - Bacterial Reverse Mutation Study	Test for mutagenic changes.	A statistically significant increase in the number of relevant colonies was not observed with either of the test article extracts as compared to the negative controls in both non-activated and activated conditions.
Genotoxicity - Mouse Lymphoma Mutagenesis Assay	Test to determine whether a chemical is can induce a change in cultured mammalian cells.	Extracts of the test article showed no significant increase in the frequency of homozygous mutants in cells exposed to sodium chloride (NaCl) or polyethylene glycol (PEG) extracts of test articles as compared to the respective controls.
Genotoxicity - Mouse Bone Marrow Micronucleus Assay	Test for toxicological screening for potential genotoxic compounds.	The test article extracts did not induce a statistically significant increase in micro-nucleated erythrocytes as compared to the respective negative controls.
Implantation - 7-Day, 13-Week, and 26-Week Muscle Implantation	Test for local effects of implant material on living tissue.	Macroscopic evaluation of the test article implant sites indicated no significant signs of inflammation, encapsulation, hemorrhage, necrosis, or discoloration as compared to the control article sites.

Table 4: Delivery System – Biocompatibility

Test	Purpose	Results
Cytotoxicity - L929 MEM Elution Test	Test for cell lysis.	No evidence of biological reactivity.
Sensitization - Kligman Maximization Test	Test for allergenic potential or sensitization capacity of test article.	The test article extracts showed no reaction at the challenge.
Irritation - Intracutaneous Injection Test in Rabbits	Test for irritation potential.	The test article sites did not show a

Test	Purpose	Results
		significantly greater biological reaction than the sites injected with the control article.
Systemic Toxicity - Systemic Injection Test Study in Mice	Test for systemic acute toxicity in mice following intravenous and intraperitoneal injections.	The test article did not induce a significantly greater biological reaction than the control extracts, when tested in mice.
Systemic Toxicity - Rabbit Pyrogen Test (Material Mediated)	Test for pyrogenic response from the material.	The increases in temperature did not exceed the test limit for the maximum individual temperature rise.
Hemocompatibility - ASTM Hemolysis (Indirect Contact)	Test for red blood cell hemolysis.	The test article exhibited 0.00% hemolysis above the level of hemolysis exhibited by the negative control via the indirect method.
Hemocompatibility - Prothrombin Time Assay (Indirect Contact)	Test for coagulation response from the test material.	The mean value for the test article and each individual replicate value did not differ from the mean of the negative and untreated controls by more than one second.
Hemocompatibility - Unactivated Partial Thromboplastin Time (UPTT) Assay (Indirect Contact)	Test to measure the ability to form blood clots.	The UPTT of the plasma exposed to the test article extract was not significantly decreased as compared to the untreated plasma and the plasma exposed to the negative control article.
Hemocompatibility - Complement Activation Assay (C3a, SC5b-9) (Indirect Contact)	Test the potential for activation of the complement system.	The test article did not induce complement activation of C3 or C5 proteins in human plasma.
Hemocompatibility - Thrombogenicity Study	Test to determine comparative thromboresistence of medical devices that are intended for blood contact.	No significant thrombosis was observed in the test sites and control sites.

Sterilization Validation

The LVIS and LVIS Jr. are sterilized using electron beam irradiation. The sterilization method was validated to a sterility assurance level of 10^{-6} per ISO 11137-1:2006/(R)2010, Sterilization of Health Care Products – Radiation – Part 1: Requirements for Development, Validation, and Routine Control of a Sterilization Process for Medical Devices. The device was tested and met specifications for sterilization.

Shelf Life

The LVIS and LVIS Jr. were tested and determined to have a 3-year shelf-life. The 3-year shelf life was verified on accelerated aged devices. The samples were pre-conditioned for

simulated shipping and sterilization. The dimensional and functional attributes were tested and met acceptance criteria. In addition, packaging integrity testing (pouch) was verified and met acceptance criteria to support the 3-year shelf-life.

B. Animal Studies

A Good Laboratory Practice (GLP) animal study was conducted to evaluate acute and chronic safety and performance of the device at 0, 30, 90, and 180 days. The device was implanted in 20 rabbits in which elastase-induced aneurysms were created. The device performance characteristics during implantation were evaluated based upon a scaled scoring system used by the neurointerventionalists conducting the procedure. Prior to sacrifice, the animals were angiographically assessed for stent performance such as stability of the implant in the artery (absence of migration), parent vessel patency, embolization coil stability, blood flow or vessel irregularities, and aneurysm occlusion. Excised vessels were evaluated for histology – histopathology and vessel patency. At 180 days, minimal inflammation was observed. The results at all time points in the in vivo study demonstrated safety of the device for use in humans in the pivotal clinical study.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of stent assisted coiling (SAC) with the LVIS and LVIS Jr. for use with neurovascular embolization coils in the treatment of wide-necked saccular intracranial aneurysms in the US under IDE # G110188. Data from this clinical study were the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between July 30, 2013 and October 28, 2014. The database for this PMA reflected data collected through February 24, 2017 and included 171 patients. There were 22 investigational sites, all in the US.

The study, titled "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms,*" was a multi-center, prospective, single-arm, open label clinical study. The pivotal study included follow-up at discharge, 30 days, 6 months, and 12 months. The pre-specified primary endpoints in the clinical study protocol were:

- Safety: Any major stroke or death within 30 days, or major ipsilateral stroke or neurological death within 12 months.
- Effectiveness: Successful aneurysm treatment with LVIS/LVIS Jr. as defined by complete (100%) aneurysm angiographic occlusion at 12 months without retreatment and no significant (≥ 50%) stenosis of the treated artery at 12 months.

The primary endpoint results were compared to performance goals (PGs) developed using prior published data from the other HDE approved neurovascular stents including the Neuroform Stent Systems (H020002) and the Enterprise Vascular Reconstruction Device and Delivery System (H060001). Study analyses were conducted using Bayesian statistical methods described in the Guidance for Industry and FDA Staff, "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials," issued on February 5, 2010. The Bayesian approach allows for incorporation of prior (external to the proposed study) information in decision-making. Bayesian analyses also allows the computation of one-sided 97.5% credible intervals and multivariate regression analyses.

Bayesian analyses were performed using the program OpenBUGS, Version 3.2.3 (Lunn et al., The BUGS Project: Evolution, Critique and Future Directions. Statistics in Medicine 2009; 28(25): 3049-67). Posterior inferences were carried out by sampling from the posterior distribution of the parameters. Other analyses, including summaries, were conducted using SAS (version 9.2 or greater). Descriptive statistics were presented for continuous variables included mean, standard deviation, median, quartiles, minimum, maximum, and sample size for each treatment group. Categorical variables were summarized using counts and percentages. Proportions were calculated using known non-missing values.

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

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms*" was limited to patients who met the following inclusion criteria.

   - Subject whose age is ≥ 18 and ≤ 75 years.
   - Subject with an unruptured or ruptured (> 30 days since occurrence), wide-necked (neck ≥ 4 mm or dome to neck ratio < 2) intracranial, saccular aneurysms (≥ 4 mm and < 20 mm maximum diameter in any plane) arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 4.5 mm who are candidates for endovascular coil embolization.
   - Subject or his/her Legally Authorized Representative understands the nature of the procedure, consents to participation in the study and provides a signed informed consent form.
   - Subject (woman of child-bearing potential) with a current negative pregnancy test who has agreed to an appropriate method of contraception throughout the trial.
   - Subject lives at a permanent address within commuting range of the investigational site and will be residing at that address during their 12 months of study participation.

- Subject is willing to return to the investigational site for the 30-day, 6-month and 12-month follow-up evaluations.

Patients were not permitted to enroll in the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms*" if they met any of the following exclusion criteria.

- Subject who presents with ruptured aneurysm, unless rupture occurred 30 days or more prior to screening.
- Subject who presents with an intracranial mass (other than a meningioma) or currently undergoing radiation therapy for carcinoma or sarcoma of the head or neck region.
- Subject with significant extracranial or intracranial stenosis of the parent artery (> 50%) proximal to the target aneurysm.
- Subject with an irreversible bleeding disorder, a platelet count of less than 100,000/ml (< 100x103 cells/mm^3) or known platelet dysfunction or a contraindication to or inability to tolerate anticoagulants and/or antiplatelet agents.
- Subject with serum creatinine level > 3.0 mg/dL at time of enrollment (this will restrict the use of contrast) and not on dialysis.
- Subject with known allergies to nickel-titanium metal, jewelries.
- Subject with known allergies or contraindications to required anti-platelet and/or heparin medications required for treatment.
- Subject with a life-threatening allergy to radiographic contrast (unless treatment for allergy is tolerated or can be managed medically).
- Subject with a contraindication to CT (Computed Tomography) and MRI (Magnetic Resonant Imaging).
- Subject who has a known cardiac disorder, likely to be associated with cardioembolic symptoms such as AFIB (atrial fibrillation).
- Subject with any condition which in the opinion of the treating physician would place the subject at a high risk of embolic stroke.
- Subject who is currently participating in another clinical research study with a conflicting protocol.
- Subject who has had a previous intracranial stenting procedure associated with the target aneurysm.
- Subject who is unable to complete the required follow-up.
- Subject who is pregnant or breastfeeding;
- Subject who has participated in a drug study within the last 30 days.

Angiographic Exclusion Criteria

- Subject has a cerebral diagnostic angiogram that demonstrates an aneurysm that is not appropriate for endovascular treatment.
- Subject has a fusiform or dissecting aneurysm.

- Subject is harboring more than one aneurysm with each aneurysm requiring treatment within 30 days.
- Subject has an arteriovenous malformation (AVM) in the territory of the target aneurysm.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at discharge, 30 days (± 7 days), 6 months (± 4 weeks), and 12 months (± 4 weeks) postoperatively. Preoperatively, the patients underwent a review of their concomitant medications, medical history, physical, clinical, neurological, laboratory, and angiographic evaluations. Postoperatively, the objective parameters measured during the study included a review of the concomitant medications, physical, clinical, neurological, and angiographic evaluations (see Table 5). Postoperatively, the angiographic examination was only conducted at the 12 month visit to evaluate intracranial aneurysm occlusion and parent artery patency. Adverse events and complications were recorded at all visits.

The key timepoints are shown below in tables summarizing safety and effectiveness.

Table 5: Study Timeline

	Pre-Procedure	**Procedure**	**Post-Procedure**	**Discharge**	**30 days ± 7 days**	**6 months ± 4 weeks**	**12 months ± 4 weeks**
Medical History	X						
Physical Examination	X			X	X	X	X
Informed Consent (1)	X						
Clinical Evaluation	X			X	X	X	X
Neurological Evaluation	X			X	X	X	X
Concomitant Medications	X			X	X	X	X
Laboratory Assessment (2)	X						
Intracranial Stent Procedure		X					
Procedural Medications		X	X				
Angiographic Evaluation	X	X	X				X
Adverse Event	X	X	X	X	X	X	X
Serious Adverse Event (3)	X	X	X	X	X	X	X
Unanticipated Adverse Event (3)	X	X	X	X	X	X	X
Protocol Deviation (3)	X	X	X	X	X	X	X
Death, or Device Related Adverse Event (3)	X	X	X	X	X	X	X

(1) Informed consent was signed before the patient was enrolled in the study.

(2) Complete Blood Count (CBC) with differential, blood chemistry, PT/PTT, and blood sugar evaluation within 14 days from procedure and a pregnancy test for women of childbearing age at the time of enrollment.
(3) A serious adverse event (e.g., death), protocol deviation, unanticipated adverse device effect or device related adverse event were reported to the Sponsor as soon as possible (i.e., within 24 hours) and no more than 10 working days from the date of becoming aware of the event or effect**.**

3. Clinical Endpoints

With regards to safety, the number of patients who had a disabling stroke (defined as modified Rankin Scale (mRS) score ≥ 3 assessed at a minimum of 90 days post-stroke event) or neurological death within 12 months post-procedure was used to analyze the clinical study results.

With regards to effectiveness, the number of patients who had complete (100%) occlusion (equivalent to Raymond-Roy I intracranial aneurysm occlusion classification) of the target intracranial aneurysm without clinically significant in-stent stenosis ($\geq$ 50%) or target aneurysm re-treatment within 12 months post-procedure was used to analyze the clinical study results. In addition, the number of patients who had stable intracranial aneurysm occlusion assessed via two (2) imaging scans taken at a minimum of 6 months apart equivalent to a Raymond-Roy II intracranial aneurysm occlusion classification (~90-99% occlusion) without clinically significant in-stent stenosis or re-treatment of the target intracranial aneurysm were also considered a successful treatment with respect to effectiveness.

These primary safety and effectiveness endpoints were determined to be most clinically meaningful for evaluating the safety and performance of the LVIS and LVIS Jr., and are consistent with the recommendations from a March 1, 2018 general issues meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee to discuss the evaluation of benefits vs. risks of new endovascular medical devices intended to treat intracranial aneurysms. The pre-specified primary endpoints for the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms*" are described in Section X (A. Study Design).

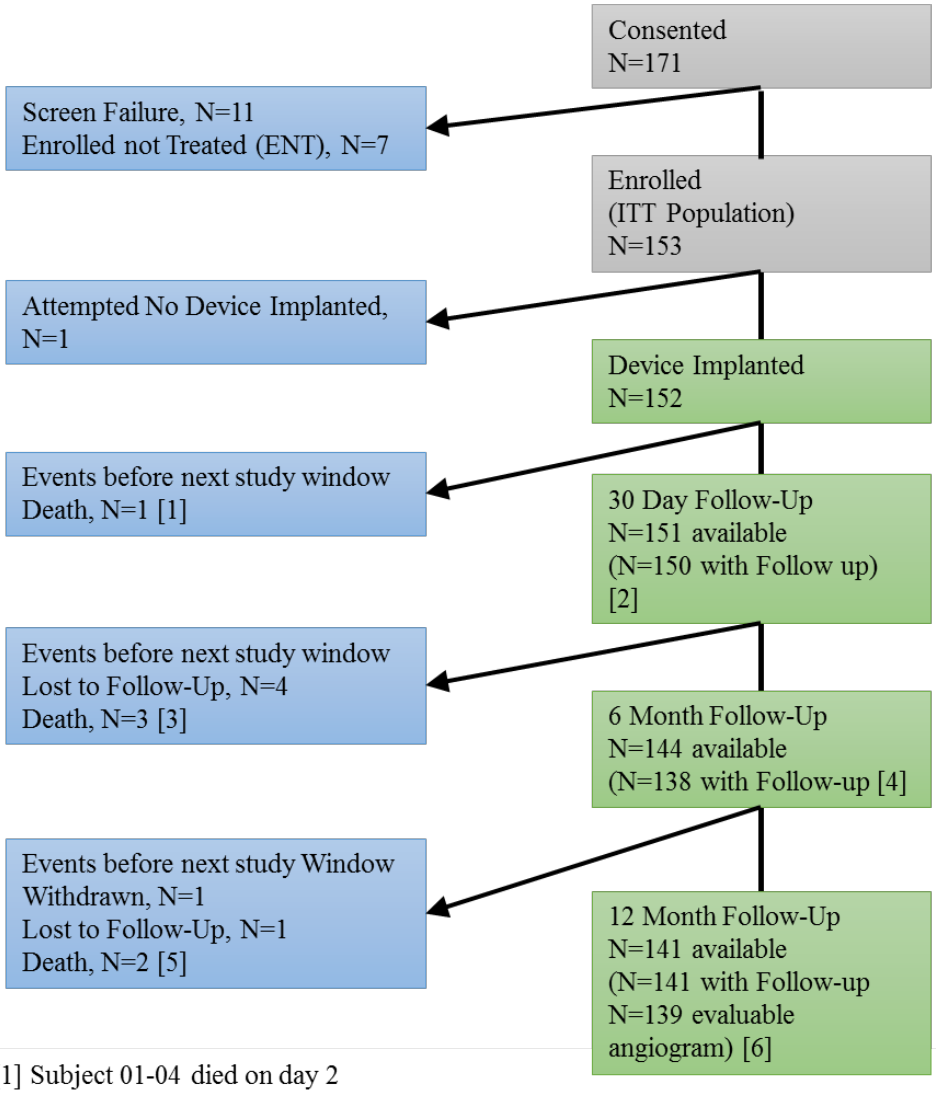
With regard to success/failure criteria, the primary endpoints were compared to PGs. The clinical study would be considered a success for effectiveness if the primary effectiveness endpoint based on the rate of patients who had complete (100%) intracranial aneurysm occlusion without clinically significant in-stent stenosis or retreatment of the target aneurysm was greater than 46%. This PG for effectiveness was based on evaluable patient level data obtained from 514 patients from five (5) published studies using the HDE approved Neuroform Stent Systems (H020002) (Bondi et al. 2007; Fiorella et al.; Maldonado et al.; Yahia et al.; Sedat et al. 2009). The clinical study would be considered a success for safety if the primary safety endpoint was less than 20%. This PG for safety was calculated based on the rate of major stroke or

neurological death observed in the prior clinical studies used to support HDE approval of the Neuroform Stent Systems (H020002) and the Enterprise Vascular Reconstruction Device and Delivery System (H060001), which was approximately 10% with an added non-inferiority margin of 10% to equal 20%. As part of the decision-making process for the subject PMA, the FDA did not consider the safety PG of 20% to be acceptable and utilized the observed 10% rate for primary safety events to be the PG when determining the safety profile of the LVIS and LVIS Jr. for study success.

B. Accountability of PMA Cohort

At the time of database lock, of 171 patients enrolled in the PMA study, 82% (141) patients are available for analysis at the completion of the study, the 12 month post-operative visit (see Figure 3).

Figure 3: Subject Accountability Flow Chart



[1] Subject 01-04 died on day 2
[2] Subject 22-05 had a missed 30 day visit
[3] Subject 01-05 died on day 63
[4] Subjects 06-25, 09-02, 11-03, 12-04, 12-06, and 19-23 missed the 6 month visit
[5] Subject 03-03 died on day 393; however, this subject completed the 12 month follow-up visit and is included.
[6] Subjects 06-25 and 05-05 had a 12 month visit. 06-25 did not have an angiogram, 05-05 had an angiogram that was not evaluable.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an intracranial aneurysm treatment study performed in the US. This disease predominantly affects more women than men, and most patients are White, similar to the demographic and baseline characteristics of the patient population in the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-*

Necked Intracranial Artery Aneurysms" (see Table 6). The study population used to analyze the clinical study results are based on the Intent-to-Treat (ITT) population of 153 patients (N) who signed the informed consent form, met inclusion/exclusion criteria, and in which the device was attempted.

Table 6: Demographics and Baseline Characteristics

Characteristic	Summary Statistic
Age (years)	
Mean ± Standard Deviation (std) (N)	58.3 ± 10.49 (153)
Median (min, max)	59.0 (18, 75)
Gender, % (n/N)	
Male	28.1% (43/153)
Female	71.9% (110/153)
Ethnicity, % (n/N)	
Hispanic or Latino	5.2 % (8/153)
Not Hispanic or Latino	94.1% (144/153)
No willing to provide	0.0 % (0/153)
Unknown	0.7 % (1/153)
Missing[1]	0.0 % (0/153)
Race, % (n/N)	
American Indian or Alaska Native	0.7 % (1/153)
Asian	1.3 % (2/153)
Black or African American	15.7% (24/153)
Native Hawaiian or other Pacific Islander	0.0 % (0/153)
White	80.4% (123/153)
Other	2.0 % (3/153)
Missing[1]	0.7 % (1/153)
Systolic Blood Pressure	
Mean ± std (N)	130.9 ± 17.80 (153)
Median (min, max)	131.0 (93, 179)
Diastolic Blood Pressure	
Mean ± std (N)	74.8 ± 11.35 (153)
Median (min, max)	75.0 (40, 102)
Temperature (°F)	
Mean ± std (N)	97.8 ± 0.90 (144)
Median (min, max)	97.9 (94.5, 99.5)
Heart Rate (Beats per Minute (BPM))	
Mean ± std (N)	73.0 ± 15.04 (153)
Median (min, max)	71.0 (45, 124)

Pre-procedure data is considered for this table.
One subject is considered in both "Black or African American" and "Other"
[1] Missing information are considered under the category Missing.

Baseline intracranial aneurysm characteristics are reported per the site evaluation. The target intracranial aneurysm locations in the neurovasculature are presented in Table 7, and Table 8 presents the intracranial aneurysm sizes and parent artery dimensions. The

mean intracranial aneurysm dome height was 6.0 ± 2.15 mm and mean dome width was 5.5 ± 2.33 mm. All intracranial aneurysms were wide-neck as defined by a neck width ≥ 4 mm or a dome to neck ratio < 2. There were only 12 intracranial aneurysms that were classified as large or giant since they had at least one aneurysm dimension (dome height or width) ≥ 10 mm.

Table 7: Target Aneurysm Location

Location and Sublocation (site reported)	% of subjects (n/N)
Internal Carotid Artery (ICA)	28.1% (43/153)
Carotid Cavernous	2.0% (3/153)
Carotid Ophthalmic	5.9% (9/153)
Superior Hypophyseal	6.5% (10/153)
Posterior Communication Artery	5.9% (9/153)
Anterior Choroidal Artery	1.3% (2/153)
Internal Carotid Artery (Supraclinoid)	4.6% (7/153)
Carotid Bifurcation	2.0% (3/153)
Anterior Cerebral Artery (ACA)	37.3% (57/153)
Anterior Communicating Artery (AComm)	33.3% (51/153)
Pericallosal	3.9% (6/153)
Middle Cerebral Artery (MCA)	11.1% (17/153)
Posterior Cerebral Artery	3.9% (6/153)
Basilar Artery	17.6% (27/153)
Basilar Tip	17.0% (26/153)
Anterior Inferior Cerebellar Artery	0.0% (0/153)
Basilar Trunk	0.7% (1/153)
Superior Cerebellar Artery	0.7% (1/153)
Vertebral Artery	1.3% (2/153)
Posterior Inferior Cerebellar Artery (PICA)	0.7% (1/153)
Vertebrobasilar (VB) Junction	0.7% (1/153)

Table 8: Target Aneurysm Characteristics

Characteristic	Mean ± std (N)	Median (min, max)
Dome Height	6.0 ± 2.15 (153)	5.8 (2.0, 14.0)
Dome Width (perpendicular to height)	5.5 ± 2.33 (153)	5.0 (1.4, 17.0)
Neck Width	4.2 ± 1.41 (153)	4.0 (1.8, 10.0)
Dome to Neck Ratio	1.3 ± 0.38 (153)	1.3 (0.5, 3.3)
Distal Parent Artery Diameter (landing zone)	2.5 ± 0.64 (153)	2.2 (1.6, 4.8)
Proximal Parent Artery Diameter (landing zone)	2.8 ± 0.70 (153)	2.5 (2.0, 4.5)
Mean Parent Artery Diameter	2.6 ± 0.64 (153)	2.4 (2.0, 4.6)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the ITT cohort of 153 patients available for the 12-month evaluation. The key safety outcomes for this study are presented below in Table 9. Adverse effects are reported in Table 10.

Table 9: Primary Safety Events through 12 Months - ITT Population

Event Type	**% of Subjects with Observations (n/N)**	**Posterior Mean, 95% Confidence Interval (CI) [1]**	**Posterior Probability [2]**
Primary Safety Composite Rate (disabling stroke with mRS score ≥ 3 or neurological death within 12 months)	5.9% (9/153)	6.2% (3.0% - 10.5%)	1
Primary Safety Failure Reasons [3]			
Disabling stroke with mRS score ≥ 3 through 12 months*	3.9% (6/153)	4.2% (1.7% - 7.9%)	N/A
Neurological death through 12 months	2.0% (3/153)	2.3% (0.6% - 5.1%)	N/A

[1]Posterior mean and 95% CI. Confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.

[2]Posterior probability that the primary safety endpoint event rate is < 20% (PG proposed by applicant).

[3]Subjects may have more than one failed safety component. Three (3) subjects with stroke expired from neurological deaths.

*mRS score ≥ 3 at any time point between 90 days and last available follow-up.

There were nine (9) subjects who met the primary safety endpoint definition of disabling stroke or neurological death within 12 months post-procedure for a rate of 5.9% (9/153). Three (3) of the 9 primary safety events were deaths caused by strokes from which two (2) subjects expired from major ipsilateral strokes at 2 and 63 days post-procedure and the third subject sustained a fatal contralateral stroke 393 days post-procedure. Of the remaining six (6) disabling strokes out of the total of nine (9) primary safety events, two (2) strokes were determined by the CEC to have occurred in vessel territories that are distinct from those territories treated with LVIS/LVIS Jr. and may be caused by pre-existing conditions unrelated to the device or procedure. These two (2) disabling stroke events are analyzed within the primary safety endpoint as a worst-case analysis and it cannot be fully confirmed that the strokes were unrelated to the device and treatment. The posterior mean is 6.2% with a one-sided 97.5% CI upper bound of 10.5%.

Adverse effects that occurred in the PMA clinical study:

Tables 10-12 present all adverse events, device-related serious adverse events, and procedure-related serious adverse events that were observed through 12 months in the pivotal study for the ITT population as adjudicated by the CEC, respectively. Tables 10-12 are also presented based on time of adverse event occurrence, whether peri-procedural or post-procedure. In Tables 10-12, percentage of subjects with events may not match the number of events if more than one event occurred in the same subject.

Table 10: All Adverse Events Observed through 12 Months - ITT Population

Adverse Event	Peri Procedure		Post Procedure	
	# of Events	% of subjects with event (n/N)	# of Events	% of subjects with event (n/N)
Any Adverse Event	145	39.9% (61/153)	159	30.1% (46/153)
Cardiac	8	4.6% (7/153)	10	5.2% (8/153)
Cardiac arrhythmias	4	2.6% (4/153)	2	1.3% (2/153)
Death	0	0.0% (0/153)	1	0.7% (1/153)
Myocardial Infarction	0	0.0% (0/153)	1	0.7% (1/153)
Other	4	2.6% (4/153)	6	3.9% (6/153)
Gastrointestinal	2	1.3% (2/153)	13	5.9% (9/153)
Bleeding	0	0.0% (0/153)	2	0.7% (1/153)
Hemorrhage	1	0.7% (1/153)	0	0.0% (0/153)
Infection	0	0.0% (0/153)	1	0.7% (1/153)
Ischemia	0	0.0% (0/153)	1	0.7% (1/153)
Other	1	0.7% (1/153)	9	4.6% (7/153)
Infectious / Inflammatory	0	0.0% (0/153)	8	1.3% (2/153)
Infection	0	0.0% (0/153)	8	1.3% (2/153)
Musculoskeletal	9	5.2% (8/153)	17	9.8% (15/153)
Ischemia	0	0.0% (0/153)	1	0.7% (1/153)
Other	9	5.2% (8/153)	16	9.8% (15/153)
Neurological / Neurovascular	74	26.8% (41/153)	50	19.0% (29/153)
Aneurysm rupture	4	2.6% (4/153)	0	0.0% (0/153)
Aphasia	1	0.7% (1/153)	0	0.0% (0/153)
Device Failure	10	6.5% (10/153)	0	0.0% (0/153)
Dissection or perforation of the parent artery	2	1.3% (2/153)	0	0.0% (0/153)
Headache	9	5.2% (8/153)	8	4.6% (7/153)
Hydrocephalus	1	0.7% (1/153)	1	0.7% (1/153)
Intra-Parenchymal Hemorrhage	2	1.3% (2/153)	2	1.3% (2/153)
Neurological deficits	6	3.3% (5/153)	3	1.3% (2/153)
Other	5	3.3% (5/153)	12	7.2% (11/153)
Seizure	4	2.0% (3/153)	1	0.0% (0/153)
Stent Thrombosis	3	2.0% (3/153)	2	1.3% (2/153)
Stroke	6	3.3% (5/153)	6	3.3% (5/153)
Sub-Arachnoid Hemorrhage (SAH)	2	1.3% (2/153)	1	0.7% (1/153)
Sub-Dural Hematoma (SDH)	1	0.7% (1/153)	2	1.3% (2/153)
TIA (Transient Ischemic Attack)	3	2.0% (3/153)	3	2.0% (3/153)
Target aneurysm retreatment	0	0.0% (0/153)	6	3.9% (6/153)

Adverse Event	Peri Procedure		Post Procedure	
	# of Events	% of subjects with event (n/N)	# of Events	% of subjects with event (n/N)
Thromboembolic event	1	0.7% (1/153)	0	0.0% (0/153)
Vasospasm	10	5.9% (9/153)	0	0.0% (0/153)
Visual impairment	4	1.3% (2/153)	3	2.0% (3/153)
Other	22	10.5% (16/153)	35	11.8% (18/153)
Allergic reaction	1	0.7% (1/153)	0	0.0% (0/153)
Bleeding	2	1.3% (2/153)	0	0.0% (0/153)
Death	0	0.0% (0/153)	1	0.7% (1/153)
Headache	0	0.0% (0/153)	1	0.7% (1/153)
Infection	0	0.0% (0/153)	1	0.7% (1/153)
Other	17	8.5% (13/153)	31	9.2% (14/153)
Reactions due to radiation exposure	1	0.7% (1/153)	0	0.0% (0/153)
Reactions to anesthesia and related procedures	1	0.7% (1/153)	0	0.0% (0/153)
Visual impairment	0	0.0% (0/153)	1	0.7% (1/153)
Renal / Genitourinary	5	3.3% (5/153)	8	3.9% (6/153)
Infection	3	2.0% (3/153)	2	0.7% (1/153)
Other	2	1.3% (2/153)	5	3.3% (5/153)
Renal failure	0	0.0% (0/153)	1	0.7% (1/153)
Respiratory / Pulmonary	8	5.2% (8/153)	13	4.6% (7/153)
Death	0	0.0% (0/153)	1	0.7% (1/153)
Emboli	0	0.0% (0/153)	1	0.7% (1/153)
Infection	3	2.0% (3/153)	1	0.7% (1/153)
Other	5	3.3% (5/153)	10	3.9% (6/153)
Vascular	17	11.1% (17/153)	5	3.3% (5/153)
Bleeding	4	2.6% (4/153)	1	0.7% (1/153)
Complications of arterial puncture	9	5.9% (9/153)	0	0.0% (0/153)
Ecchymosis	0	0.0% (0/153)	2	1.3% (2/153)
Hemorrhage	2	1.3% (2/153)	0	0.0% (0/153)
Other	2	1.3% (2/153)	1	0.7% (1/153)
Vascular complication	0	0.0% (0/153)	1	0.7% (1/153)

Table 11: Device-Related Serious Adverse Events through 12 Months – ITT Population

Adverse Event	Peri procedure		Post Procedure	
	# of Events	% of subjects with event (n/N)	# of Events	% of subjects with event (n/N)
Any Serious Device Related Adverse Events	22	11.1% (17/153)	5	3.3% (5/153)
Neurological / Neurovascular	22	11.1% (17/153)	5	3.3% (5/153)
Device Failure*	6	3.9% (6/153)	0	0.0% (0/153)
Dissection or perforation of the parent artery	1	0.7% (1/153)	0	0.0% (0/153)
Other	3	2.0% (3/153)	0	0.0% (0/153)
Stent Thrombosis†	3	2.0% (3/153)	2	1.3% (2/153)
Stroke	4	2.6% (4/153)	2	1.3% (2/153)
TIA (Transient Ischemic Attack)	1	0.7% (1/153)	1	0.7% (1/153)
Vasospasm	1	0.7% (1/153)	0	0.0% (0/153)
Visual impairment	3	1.3% (2/153)	0	0.0% (0/153)

Table 12: Procedure-Related Serious Adverse Events through 12 Months – ITT Population

Adverse Event	Peri procedure		Post Procedure	
	# of Events	% of subjects with event (n/N)	# of Events	% of subjects with event (n/N)
Any Serious Procedure Related Adverse Events	61	28.8% (44/153)	8	3.9% (6/153)
Cardiac	1	0.7% (1/153)	0	0.0% (0/153)
Cardiac arrhythmias	1	0.7% (1/153)	0	0.0% (0/153)
Gastrointestinal	1	0.7% (1/153)	1	0.7% (1/153)
Bleeding	0	0.0% (0/153)	1	0.7% (1/153)
Hemorrhage	1	0.7% (1/153)	0	0.0% (0/153)
Neurological / Neurovascular	43	20.9% (32/153)	6	2.6% (4/153)
Aneurysm rupture	4	2.6% (4/153)	0	0.0% (0/153)
Aphasia	1	0.7% (1/153)	0	0.0% (0/153)
Device Failure	9	5.9% (9/153)	0	0.0% (0/153)
Dissection or perforation of the parent artery	1	0.7% (1/153)	0	0.0% (0/153)
Hydrocephalus	1	0.7% (1/153)	0	0.0% (0/153)
Intra-Parenchymal Hemorrhage	2	1.3% (2/153)	0	0.0% (0/153)
Neurological deficits	2	1.3% (2/153)	0	0.0% (0/153)
Other	1	0.7% (1/153)	0	0.0% (0/153)
Seizure	1	0.7% (1/153)	0	0.0% (0/153)
Stent Thrombosis	3	2.0% (3/153)	0	0.0% (0/153)
Stroke	5	3.3% (5/153)	1	0.0% (0/153)
Sub-Arachnoid Hemorrhage (SAH)	2	1.3% (2/153)	0	0.0% (0/153)
TIA (Transient Ischemic Attack)	1	0.7% (1/153)	1	0.7% (1/153)
Target aneurysm retreatment	0	0.0% (0/153)	3	2.0% (3/153)
Thromboembolic event	1	0.7% (1/153)	0	0.0% (0/153)
Vasospasm	7	4.6% (7/153)	0	0.0% (0/153)
Visual impairment	2	1.3% (2/153)	1	0.7% (1/153)
Other	4	2.6% (4/153)	1	0.7% (1/153)
Other	4	2.6% (4/153)	1	0.7% (1/153)
Renal / Genitourinary	2	1.3% (2/153)	0	0.0% (0/153)
Infection	2	1.3% (2/153)	0	0.0% (0/153)
Respiratory / Pulmonary	3	2.0% (3/153)	0	0.0% (0/153)
Infection	1	0.7% (1/153)	0	0.0% (0/153)
Other	2	1.3% (2/153)	0	0.0% (0/153)
Vascular	7	4.6% (7/153)	0	0.0% (0/153)
Bleeding	2	1.3% (2/153)	0	0.0% (0/153)
Complications of arterial puncture	4	2.6% (4/153)	0	0.0% (0/153)
Hemorrhage	1	0.7% (1/153)	0	0.0% (0/153)

Table 13 below presents all the stroke events observed in the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms,"* which was 16 events total that occurred in 14 subjects (9.2%, 14/153).

Table 13: All Stroke Events through 12 Months (ITT Population)

#	Subject ID*	mRS pre-procedure baseline	mRS at discharge	mRS at 30 days	mRS at 180 days	mRS at 12 months
Strokes resulting in neurological death						
1	01-04	0	mRS = 6, neurological death	n/a	n/a	n/a
2	01-05	0	0	0	mRS = 6, neurological death	n/a
3	03-03 €	0	0	Not done	0	mRS = 0 at 12 months. Subject expired from a neurological cause 393 days post-procedure
Disabling strokes (mRS ≥ 3 at a minimum of 90 days)						
4	03-02 ¥	0	4	1	3	1
5	09-09 €	0	3	2	2	3
6	12-04	3	3	4	Not done	4
7	14-18	1	1	0	5	5
Disabling strokes caused by pre-existing conditions						
8	03-18 ¥	1	1	0	3	1
9	04-09	3	3	3	3	3
Non-Disabling strokes						
10	03-03 €	0	0	Not done	0	0
11	03-19	1	1	1	1	0
12	06-07	0	0	1	1	0
13	09-05	1	1	1	1	1
14	09-09 €	0	3	2	2	3
15	09-13	0	0	0	0	0
16	16-01	0	0	1	0	0

*16 strokes occurred in 14 subjects, ID=Patient Identification.

€Subjects 03-03 & 09-09 each sustained both a minor stroke peri-operatively and a major stroke post-operatively.

¥Subjects 03-02 & 03-18 sustained strokes that did not result in permanent neurological disability.

One of the key secondary safety endpoints was assessment of the number of subjects who had a worsening in the mRS (measurement of patient disability) at 12 months post-procedure compared to their baseline mRS prior to the treatment. Table 14 shows all of the subjects in the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms*" who had a worsening of the mRS at 12 months post-procedure compared to their baseline mRS, 16% (25/153). Fourteen

(14) out of the 25 patients with a deterioration in the mRS at 12 months post-procedure compared to baseline had a bad clinical outcome (mRS ≥ 3) resulting in a rate of 9.2% (14/153). This rate in bad clinical outcome based on the mRS score is less than the observed safety PG estimated for the pivotal study of 10%.

Table 14: Subjects (n=25) with Worsening mRS Scores at 12 Months Compared to Baseline

Subject #	Baseline mRS	Discharge mRS	mRS at 30 days	mRS at 6 months	mRS at 12 months	Reason for Change
Neurological Death						
1*	0	6				
2*	0	0	0			
3*	0	0		0	0	
Non-Neurological Death						
4*	1	1	1			Cardiac arrest
5*	0	0	0			Drug overdose
6*	2	2	2			Suicide
Neurological Decline from New Neurological Deficits						
7	0	3	2	2	3	Ataxia, Major Stroke
8	1	1	0	5	5	Major stroke
9	0	0	0		4	Subdural Hematoma
10	0	0	0	2	3	New diagnosis of multiple sclerosis
11	2	2	1	0	3	Depression
12	3	4	4	3	4	General Debilitation from visual impairment, anxiety, depression
Neurological Decline from Pre-Existing Neurological Deficits						
13	1	1	1	3	3	Preexisting neuropathy
14	1	1	1	1	2	General debilitation from right upper intrinsic weakness, right leg weakness, mild motor aphasia
15	3	3	4		4	Preexisting bilateral leg paresthesia & weakness
Other (No New Neurological Deficit)						
16	0	0	0	1	1	Lightheaded episode
17	0	4	1	3	1	Left foot weakness

18	0	1	0	0	1	Persisting headaches
19	0	0	0	1	1	Left-sided weakness
20	0	0	0	0	1	Headaches & Fatigue
21	0	0	0	1	1	Arthritis
22	0	0	0	1	1	Dizziness
23	0	0	1	1	1	Exacerbation of pre-existing low back pain
24	0	0	1	1	1	Headaches & dizziness
25	0	0	0	0	2	Fatigue, CPAP issues

Six (6) subjects footnoted above died throughout the course of the LVIS study.
*Subject (1) died 2 days post procedure, subject (2) died 63 days post procedure, subject (3) died 393 days post procedure, subject (4) died 310 days post procedure, subject (5) died 92 days post procedure, subject (6) died 202 days post procedure.

2. Effectiveness Results

The analysis of effectiveness was based on the 153 evaluable patients at the12-month time point. Key effectiveness outcomes are presented in Table 15.

Table 15: Primary Effectiveness Endpoint Analysis through 12 Months – ITT Population

Endpoint [1]	**% of Subjects with Observations (n/N)**	**Posterior Mean, 95% CI [2]**	**Posterior Probability [3]**
Imputed Analysis per the Prespecified Primary Effectiveness Endpoint			
Primary Effectiveness Composite Success (100% Aneurysm Occlusion without Clinically Significant In Stent Stenosis or Target Aneurysm Retreatment)	70.6% (108/153)	70.5% (63.0% – 77.4%)	1
Imputed Analysis per the Modified Primary Effectiveness Endpoint			
Modified Primary Effectiveness Composite Success (90% - 99% Aneurysm Occlusion without Clinically Significant In Stent Stenosis or Target Aneurysm Retreatment) $^{\Sigma}$	10.4% (16/153)		
Modified Primary Effectiveness Composite Success (90% - 100% Aneurysm Occlusion without Clinically Significant In Stent Stenosis or Target Aneurysm Retreatment)	81.0% (124/153)	80.8% (74.3% - 86.6%)	1
Primary Effectiveness Endpoint Subcomponents			
90%-100% Aneurysm Occlusion*	83.7% (128/153)	83.4% (77.2% - 88.9%)	n/a

Endpoint [1]	% of Subjects with Observations (n/N)	Posterior Mean, 95% CI [2]	Posterior Probability [3]
Imputed Analysis per the Prespecified Primary Effectiveness Endpoint			
Without Clinically Significant In Stent Stenosis (≥ 50%) of Parent Artery	90.8% (139/153)	90.6% (85.5% - 94.7%)	n/a
No Target Aneurysm Retreatment	96.1% (147/153)	95.8% (92.1% - 98.4%)	n/a
Evaluable Only Analysis per the Prespecified Primary Effectiveness Endpoint	% of Subjects with Observations (n/N)		
Primary Effectiveness Composite Success (100% Aneurysm Occlusion without Clinically Significant In Stent Stenosis or Target Aneurysm Retreatment)	77.7% (108/139)	77.5% (70.3% - 84%)	1
Evaluable Only Analysis per the Modified Primary Effectiveness Endpoint			
Modified Primary Effectiveness Composite Success (90% - 99% Aneurysm Occlusion without Clinically Significant In Stent Stenosis or Target Aneurysm Retreatment) ∑	11.5% (16/139)		
Modified Primary Effectiveness Composite Success (90% - 100% Aneurysm Occlusion without Clinically Significant In Stent Stenosis or Target Aneurysm Retreatment)	89.2% (124/139)	82.5% (75.3% - 88.6%)	1
Modified Primary Effectiveness Composite Success (90% - 100% Aneurysm Occlusion without Clinically Significant In Stent Stenosis or Target Aneurysm Retreatment) using only DSA at 12 months ¥	88.6% (117/132) [124-7 / 139-7]	88.3% (82.4%- 93.2%)	1
Primary Effectiveness Endpoint Subcomponents			
90%-100% Aneurysm Occlusion*	91.4% (127/139)	91.2% (84.4% - 97.4%)	n/a
Without Clinically Significant In Stent Stenosis (≥ 50%) of Parent Artery	100.0% (139/139)	99.6% (98.2% - 100%)	n/a
No Target Aneurysm Retreatment	95.7% (133/139)	95.4% (91.3% - 98.2%)	n/a

∑ Only subjects with stable or positively progressing Raymond-Roy II occlusion between baseline and 12 months are included.

¥ Seven subjects who were assessed using magnetic resonance angiography (MRA) in lieu of digital subtraction angiography (DSA) are excluded.

[1] Includes primary effectiveness data collected on all ITT subjects at or through 12-month follow-up visit.

[2] Posterior mean and two-sided 95% CI. The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.
[3] Posterior probability that the primary effectiveness endpoint success rate exceeds the pre-specified PG at 12 months.
*Subjects having negative progression from post-procedure to 12 months are considered failures. Missing data imputed as failures.
The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.

Table 15 presents the primary effectiveness endpoint analyses individually for the number of patients in the ITT population who had complete (100%) occlusion (equivalent to Raymond-Roy I intracranial aneurysm occlusion classification) of the target intracranial aneurysm without clinically significant in-stent stenosis (≥ 50%) or target aneurysm re-treatment within 12 months post-procedure, and the number of patients who had stable intracranial aneurysm occlusion assessed via two imaging scans taken at a minimum of 6 months apart equivalent to a Raymond-Roy II intracranial aneurysm occlusion classification (~90-99% occlusion) without clinically significant in-stent stenosis or re-treatment of the target intracranial aneurysm, and a combined composite primary effectiveness rate with these two (2) results combined. The additional analysis of the primary effectiveness endpoint to include intracranial aneurysms with Raymond-Roy II classifications as a satisfactory outcome was based on the recommendations at the March 1, 2018 general issues meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee.

The additional analysis of the primary effectiveness endpoint to include "stable" Raymond-Roy II classification of treated intracranial aneurysms identified seventeen (17) patients from the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms*" with stable or improved Raymond-Roy II intracranial aneurysm occlusions. Four (4) of the 17 subjects had "stable" intracranial aneurysm occlusion between post-procedure and 12 months and 13 had improved intracranial aneurysm occlusion at 12 months as compared to the immediate post-procedure angiogram. Of the 17 subjects, 16 subjects are included in the primary effectiveness endpoint composite analysis which includes freedom from clinically significant in-stent stenosis and target aneurysm retreatment (since one subject was retreated). As with the original ITT analysis, missing data were imputed as failures (not a primary endpoint success). Thus, 81.0% (124/153) of the subjects met the success criteria of the composite primary effectiveness endpoint analysis as shown in Table 15.

The posterior mean for the composite primary effectiveness endpoint success proportion at 12 months post-treatment was 80.8% with an equitailed 95% CI of 74.3-86.6%, with the lower bound exceeding the 46% effectiveness PG. If using the primary effectiveness endpoint analysis of only those subjects who had complete (100%) intracranial aneurysm occlusion without clinically significant in-stent stenosis

or retreatment of the target aneurysm, the posterior mean for success was 70.5% with an equitailed 95% CI of 63-77.4%, which still exceeded the effectiveness PG of 46%. The posterior probability of the alternative hypothesis was > 0.9999; therefore, exceeding the pre-defined one-sided threshold of 0.975 (0.95 equitailed), and confirms the primary effectiveness analysis in the ITT population.

Table 15 also presents an "Evaluable Only" analysis that excludes 14 subjects with missing angiographic data at 12 months. It is also noted that seven (7) subjects evaluated for this modified effectiveness endpoint were evaluated using magnetic resonance angiography (MRA) instead of digital subtraction angiography (DSA) at the 12 month follow-up visit, which is a protocol violation. With the MRA-evaluated subjects excluded, 88.6% (117/132) of the evaluable subjects with imaging available at the 12 month follow-up visit met the success criteria of the primary effectiveness endpoint as shown in Table 15. These results further support that the primary effectiveness endpoint was met and exceeds the effectiveness PG of 46%.

Because the subject devices are intended to support neurovascular embolization coils in the treatment of saccular wide-neck intracranial aneurysms, FDA also evaluated two (2) key secondary effectiveness endpoints of successful delivery of the LVIS and LVIS Jr. and stent migration within 12 months post-procedure (see Table 16). There were no events of stent migration within 12 months post-procedure. There were 10 cases of technical success failure associated with delivery and implantation of the LVIS/LVIS Jr., and failures were primarily associated with inadequate sizing of the device resulting in poor or lack of apposition to the parent vessel walls and/or coil prolapse.

Table 16. Secondary Endpoints of LVIS/LVIS Jr. Delivery Success and Stent Migration

Secondary Endpoint [1]	**% Subjects with Observations (n/N)**	**Posterior Mean, 95% CI [2]**
LVIS/LVIS Jr. Delivery and Implant Success [3]	93.5% (143/153)	0.932 (0.888-0.966)
Stent Migration	0% (0/153)	0.003 (0.000-0.016)

[1] Includes secondary endpoint data collected on all ITT patients at or through the 12-month follow-up visit.
[2] Posterior mean and 95% CI. The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.
[3] Successful delivery of LVIS/LVIS Jr. is evaluated at the completion of the procedure.

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: intracranial aneurysm rupture status, intracranial aneurysm size, location in the neurovasculature (anterior vs. posterior circulation), sex, and use of device with hydrocoils or bare metal embolic coils.

Primary Safety Endpoint Sub-Group Analyses

Subgroup analyses of the primary safety endpoint was performed based on sex, intracranial aneurysm rupture status, location in the neurovasculature, size, and use with hydrocoils or bare metal neurovascular embolic coils, and the subgroup analyses are presented in Tables 17-21. For sex (male vs. female), it appears there is a higher rate of probability of primary safety event occurrence in female patients as shown in Table 17. However, this result has limitations in that the pivotal study sample size was primarily female (71.9% (110/153)) and the primary safety event rates were small to make any definitive conclusions from this subgroup analysis that there may be a difference in clinical safety outcomes based on sex.

Table 17: Subgroup Analysis of Primary Safety Endpoint through 12 Months Based on Sex - ITT Population

Event Type	Gender	% of Subjects with Observations (n/N)	Posterior Mean, 95% CI [1]
Modified Primary Safety Composite Rate* (Disabling stroke with mRS score ≥ 3 or neurological death within 12 months)	Male	7.0% (3/43)	0.070 (0.015 - 0.162)
	Female	5.5% (6/110)	0.059 (0.023 - 0.109)
Modified Primary Safety Failure Reasons [2]			
Disabling stroke with mRS score ≥ 3 through 12 months *	Male	7.0% (3/43)	0.070 (0.015 - 0.163)
	Female	2.7% (3/110)	0.032 (0.008 - 0.072)
Neurological death through 12 months	Male	0.0% (0/43)	0.000 (0.000 - 0.001)
	Female	2.7% (3/110)	0.031 (0.008 - 0.071)

[1] Posterior mean and 95% CI. The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.

[2] Subjects may have more than one failed safety component.

[*] mRS score ≥ 3 at any time point between 90 days and last available follow-up. Three (3) subjects with stroke resulted in neurological deaths.

Subgroup analyses were conducted for the primary safety endpoint based on intracranial aneurysm rupture status (unruptured vs. previously ruptured aneurysms that were treated with device > 30 days after rupture), intracranial aneurysm location in the neurovasculature (anterior vs. posterior circulation), and intracranial aneurysm

size (≤ 5 mm vs. > 5 mm) for the ITT population (see Tables 18-20). The analysis supports comparability of these subgroups of intracranial aneurysm type, location, and size for the primary safety endpoint events although there is limited data available for previously ruptured intracranial aneurysms that were treated with LVIS/LVIS Jr. > 30 days after rupture, posterior circulation aneurysms, and small aneurysms. Also, the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms*" only enrolled and treated 12 (12/153 = 7.8%) intracranial aneurysms ≥ 10 mm and there were 0% (0/12) primary safety events in this subgroup and all nine (9) primary safety events occurred in patients with intracranial aneurysms < 10 mm (9/141 = 6.4%). This information is descriptive only and should not be used to make any definitive statistical or clinical conclusions on safety outcomes.

Table 18: Subgroup Analysis of Primary Safety Endpoint through 12 Months Follow-Up by Intracranial Aneurysm Type – ITT Population

Event Type	Aneurysm Type	% of Subjects with Observations (n/N)	Posterior Mean, 95% CI [1]
Modified Primary Safety Composite Rate* (Disabling stroke with mRS score ≥ 3 or neurological death within 12 months)	Ruptured [3]	0.0% (0/22)	0.022 (0.000 - 0.103)
	Unruptured	6.9% (9/131)	0.069 (0.032 - 0.118)
Modified Primary Safety Failure Reasons [2]			
Disabling stroke with mRS score ≥ 3 through 12 months *	Ruptured [3]	0.0% (0/22)	0.021 (0.000 - 0.105)
	Unruptured	4.6% (6/131)	0.046 (0.017 - 0.088)
Neurological death through 12 months	Ruptured [3]	0.0% (0/22)	0.021 (0.000 - 0.101)
	Unruptured	2.3% (3/131)	0.023 (0.005 - 0.055)

[1] Posterior mean and 95% CI. The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.

[2] Subjects may have more than one failed safety component.

[3] Device treatment was initiated > 30 days since occurrence of intracranial aneurysm rupture.

[*] mRS score ≥ 3 at any time point between 90 days and last available follow-up. Three (3) subjects with stroke resulted in neurological deaths.

Table 19: Subgroup Analysis of Primary Safety Endpoint through 12 Months Follow-Up by Intracranial Aneurysm Location – ITT Population

Event Type	Aneurysm Location	% of Subjects with Observations (n/N)[#]	Posterior Mean, 95% CI [1]
Modified Primary Safety Composite Rate* (Disabling stroke with mRS score ≥ 3 or neurological death within 12 months)	Anterior circulation	6.8% (8/118)	0.071 (0.032 - 0.125)
	Posterior circulation	2.9% (1/34)	0.029 (0.001 - 0.106)
Modified Primary Safety Failure Reasons [2]			
Disabling stroke with mRS score ≥ 3 through 12 months*	Anterior circulation	5.1% (6/118)	0.055 (0.021 - 0.103)
	Posterior circulation	0.0% (0/34)	0.000 (0.000 - 0.001)
Neurological death through 12 months	Anterior circulation	1.7% (2/118)	0.021 (0.004 - 0.053)
	Posterior circulation	2.9% (1/34)	0.029 (0.001 - 0.105)

[1] Posterior mean and 95% CI. The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.

[2] Subjects may have more than one failed safety component.

[*] mRS score ≥ 3 at any time point between 90 days and last available follow-up. Three (3) subjects with stroke resulted in neurological deaths.

[#]One subject 16-03 has missing aneurysm location.

Table 20: Subgroup Analysis of Primary Safety Endpoint through 12 Months Follow-Up by Intracranial Aneurysm Size – ITT Population

Event Type	% of Subjects with Observations	Posterior Mean, 95% CI [1]	Posterior Probability [2]
Primary Safety Composite Rate* (Disabling stroke with mRS score ≥ 3 or neurological death within 12 months)	Size ≤ 5 mm 6.8% (3/44)	7.8% (1.9% - 17.1%)	0.992
	Size > 5 mm 5.5% (6/109)	5.9% (2.3% - 11.0%)	1

[1] Posterior Mean and 95% Credible Interval (CI). The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.

[2] Posterior probability that the primary safety endpoint event rate is < 20% (PG proposed by applicant).
[*] mRS score ≥ 3 at any time point between 90 days and last available follow-up.

An additional subgroup analysis was conducted for the primary safety endpoint based on neurovascular embolization coil type used for treatment with the LVIS and LVIS Jr. for the ITT population (see Table 21). The analysis supports comparable safety outcomes for both coils types (hydrogel and non-hydrogel coils).

Table 21: Subgroup Analysis of Primary Safety Endpoint through 12 Months Follow-Up by Type of Neurovascular Embolization Coil used with LVIS/LVIS Jr. – ITT Population

Event Type	Coil Type	% of Subjects with Observations (n/N)[#]	Posterior Mean, 95% CI [1]
Modified Primary Safety Composite Rate* (Disabling stroke with mRS score ≥ 3 or neurological death within 12 months)	Hydrogel Coils	6.8% (5/74)	0.073 (0.026 - 0.142)
	Non-Hydrogel Coils	5.2% (4/77)	0.052 (0.014 - 0.111)
Modified Primary Safety Failure Reasons [2]			
Disabling stroke with mRS score ≥ 3 through 12 months*	Hydrogel coils	4.1% (3/74)	0.047 (0.012 - 0.104)
	Non-Hydrogel coils	3.9% (3/77)	0.039 (0.008 - 0.092)
Neurological death through 12 months	Hydrogel coils	2.7% (2/74)	0.033 (0.006 - 0.084)
	Non-Hydrogel coils	1.3% (1/77)	0.013 (0.000 - 0.048)

[1] Posterior mean and 95% CI. The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.
[2] Subjects may have more than one failed safety component.
[*] mRS score ≥ 3 at any time point between 90 days and last available follow-up. Three (3) subjects with stroke resulted in neurological deaths.
[#]Two subjects 06-06 and 06-19 have missing coil type.

Primary Effectiveness Endpoint Sub-Group Analyses

Subgroup analyses were conducted for the primary effectiveness endpoint based on sex, intracranial aneurysm type, location in the neurovasculature, size, and use with

type of neurovascular embolic coil (see Tables 22-26). For the subgroup analysis based on sex (male vs. female), the primary effectiveness endpoint results appear comparable between both groups with female patients exhibiting slightly less effectiveness. For the subgroup analysis of the primary effectiveness endpoint based on intracranial aneurysm type (unruptured vs. previously ruptured intracranial aneurysm with device implanted > 30 days after rupture), the results show that previously ruptured intracranial aneurysms with the device implanted > 30 days after rupture tended to have a higher primary effectiveness endpoint rate of success. Based on the limited sample size of male subjects and the number of previously ruptured intracranial aneurysms treated with the device > 30 days after rupture in the pivotal study, it is difficult to draw any statistical or clinical conclusions from these subgroup analyses.

Table 22: Subgroup Analysis of Primary Effectiveness Endpoint through 12 Months by Sex – ITT Population

Primary Effectiveness Endpoint [1]	**Sex**	**% of Subjects with Observations (n/N)**	**Posterior Mean, 95% CI [2]**
Primary Effectiveness Composite Success* [100% Aneurysm Occlusion (Equivalent to Raymond-Roy I Classification) without Clinically Significant In Stent Stenosis or Target Aneurysm Retreatment]	Male	74.4% (32/43)	0.744 (0.606-0.862)
	Female	69.1% (76/110)	0.689 (0.600-0.772)

[1] Includes primary effectiveness data collected on all ITT subjects at or through 12 month follow-up visit.

[2] Posterior mean and two-sided 95% CI. The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.

*Missing data imputed as failures.

Table 23: Subgroup Analysis of Primary Effectiveness Endpoint through 12 Months by Intracranial Aneurysm Type – ITT Population

Primary Effectiveness Endpoint [1]	Intracranial Aneurysm Type	% of Subjects with Observations (n/N)	Posterior Mean, 95% CI [2]
Primary Effectiveness Composite Success* [100% Aneurysm Occlusion (Equivalent to Raymond-Roy I Classification) without Clinically Significant In Stent Stenosis or Target Aneurysm Retreatment]	Ruptured [3]	81.8% (18/22)	0.803 (0.619-0.934)
	Unruptured	68.7% (90/131)	0.687 (0.606-0.764)

[1] Includes primary effectiveness data collected on all ITT subjects at or through 12 month follow-up visit.

[2] Posterior mean and two-sided 95% CI. The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.

[3] Device treatment initiated > 30 days from intracranial aneurysm rupture.

*Missing data imputed as failures.

Table 24: Subgroup Analysis of Primary Effectiveness Endpoint through 12 Months by Intracranial Aneurysm Location – ITT Population

Primary Effectiveness Endpoint [1]	Location	% of Subjects with Observations (n/N)[#]	Posterior Mean, 95% CI [2]
Primary Effectiveness Composite Success* [100% Aneurysm Occlusion (Equivalent to Raymond-Roy I Classification) without Clinically Significant In Stent Stenosis or Target Aneurysm Retreatment]	Anterior Circulation	74.6% (88/118)	0.744 (0.662-0.817)
	Posterior Circulation	58.8% (20/34)	0.588 (0.421-0.746)

[1] Includes primary effectiveness data collected on all ITT subjects at or through 12 month follow-up visit.

[2] Posterior mean and two-sided 95% CI. The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.

*Missing data imputed as failures.

[#]One subject 16-03 has missing intracranial aneurysm location by Core Lab assessment. Therefore, the total N=152.

As an additional subgroup analysis, the primary effectiveness endpoint was evaluated by intracranial aneurysm location (anterior vs. posterior circulation) per Core Lab assessment (see Table 24). The distribution of anterior versus posterior intracranial aneurysms in the LVIS and LVIS Jr. pivotal trial is representative of the prevalence of intracranial aneurysms located in these regions. In prior published studies, the initial International Study of Unruptured Intracranial Aneurysms (ISUIA) was a retrospective study that evaluated 1449 angiographically confirmed intracranial aneurysms, which showed only 207 (14%) were in the posterior circulation (Wiebers 1998). In a 2003 follow-up study by Wiebers, the results showed that 12% of the 4060 participating patients had intracranial aneurysms located in the posterior circulation (Wiebers 2003). The subgroup analysis results show that there is decreased device and treatment effectiveness for posterior circulation intracranial aneurysms. This result is not unexpected because there may be a greater quantity of sources of blood supply and small arteries in the posterior circulation and it may be more procedurally challenging to access and implant the device in the posterior circulation resulting in a decreased effectiveness to fully occlude the intracranial aneurysm to achieve a Raymond-Roy I occlusion classification.

Table 25: Subgroup Analysis of Primary Effectiveness Endpoint through 12 Months by Intracranial Aneurysm Size – ITT Population

Primary Effectiveness Endpoint [1]	**Size**	**% of Subjects with Observations (n/N)**	**Posterior Mean, 95% CI [2]**	**Posterior Probability [3]**
Primary Effectiveness Composite Success* [90% - 100% Aneurysm Occlusion (Equivalent to Raymond-Roy I and "Stable" Raymond-Roy II Classifications) without Clinically Significant In Stent Stenosis or Target Aneurysm Retreatment]	≤ 5 mm	86.4% (38/44)	85.6% (74% - 94.1%)	1
	> 5 mm	78.9% (86/109)	78.6% (70.5% - 85.7%)	1

[1] Includes primary effectiveness data collected on all ITT subjects at or through 12-month follow-up visit.

[2] Posterior mean and two-sided 95% CI. The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.

[3] Posterior probability that the primary effectiveness endpoint success rate is > 46% at 12 months.

*Subjects having negative progression from post-procedure to 12 months are considered failures. Missing data imputed as failures.

Table 25 presents a subgroup analysis of the primary effectiveness endpoint based on intracranial aneurysm size delineated by aneurysms ≤ 5 mm and those that are > 5 mm. The results show that there is a minimal increase in effectiveness for device treatment of small intracranial aneurysms. As the intracranial aneurysms get larger in size, the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms"* showed that device and treatment effectiveness decreased. For example, when only comparing the rate of patients who achieved a Raymond-Roy I aneurysm occlusion classification (100%) without clinically significant in-stent stenosis or retreatment of the target intracranial aneurysm, 25% of patients with intracranial aneurysms ≥ 10 mm (3/12) in the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms"* were able to meet this effectiveness endpoint compared to 74.5% of patients with intracranial aneurysms < 10 mm (105/141) who met this endpoint. Although there were only 12 patients in the pivotal study who had intracranial aneurysms ≥ 10 mm and there is limited clinical data available, the decreased device and treatment effectiveness may be correlated with the difficulty in treating large and giant wide-neck intracranial aneurysms simply because of the intracranial aneurysm size and the probability to fully thrombose the aneurysm to achieve 100% complete occlusion as compared to small or medium wide-neck intracranial aneurysms.

Table 26: Subgroup Analysis of Primary Effectiveness Endpoint through 12 Months by Type of Neurovascular Embolization Coil used with LVIS/LVIS Jr. – ITT Population

Primary Effectiveness Endpoint [1]	Embolic Coil Type	% of Subjects with Observations (n/N)[#]	Posterior Mean, 95% CI [2]
Primary Effectiveness Composite Success* [100% Aneurysm Occlusion (Equivalent to Raymond-Roy I Classification) without Clinically Significant In Stent Stenosis or Target Aneurysm Retreatment]	Non-Hydrogel Coils	74.0% (57/77)	0.740 (0.637-0.832)
	Hydrogel Coils	68.9% (51/74)	0.686 (0.578-0.786)

[1] Includes primary effectiveness data collected on all ITT subjects at or through 12 month follow-up visit.

[2] Posterior mean and two-sided 95% CI. The confidence intervals are calculated without multiplicity adjustment. As such, the confidence intervals are provided to show the variability only and should not be used to draw any statistical conclusions.

*Missing data imputed as failures.

[#]There were two (2) subjects (06-06 and 06-19) with missing coil type. Therefore, the total N=151.

Table 26 presents a subgroup analysis of the primary effectiveness endpoint based on patients implanted with non-hydrogel neurovascular embolization coils with the LVIS and LVIS Jr. compared to patients implanted with hydrogel neurovascular embolization coils. Approximately an equal proportion of patients in the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms*" were enrolled and treated with both types of neurovascular embolization coils and the effectiveness results are comparable for both groups when assessing those patients who had 100% intracranial aneurysm occlusion without clinically significant in-stent stenosis or target aneurysm retreatment.

4. Pediatric Extrapolation

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

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 82 investigators of which 0 were full-time or part-time employees of the sponsor and 8 investigators had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 2
- Significant payment of other sorts: 6
- Proprietary interest in the product tested held by the investigator: 0
- Significant equity interest held by investigator in sponsor of covered study: 0

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

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

During the review of this PMA, the FDA convened a general issues meeting on March 1, 2018 of the Neurological Devices Panel of the Medical Devices Advisory Committee regarding factors to consider in the evaluation of benefits and risks when reviewing clinical evidence of new endovascular medical devices intended to treat intracranial aneurysms. Feedback from the Neurological Devices Panel at the March 1, 2018 meeting was considered during the review of this PMA, primarily based on the modified definitions of the primary safety and effectiveness endpoints to assess

safety and effectiveness of the subject device as described within the SSED in Section X. The background and meeting materials for the March 1, 2018 general issues meeting can be accessed at the following link: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm598450.htm.

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint was analyzed individually for the number of patients in the ITT population who had complete (100%) occlusion (equivalent to Raymond-Roy I intracranial aneurysm occlusion classification) of the target intracranial aneurysm without clinically significant in-stent stenosis (≥ 50%) or target aneurysm re-treatment within 12 months post-procedure, and the number of patients who had stable intracranial aneurysm occlusion assessed via two (2) imaging scans taken at a minimum of 6 months apart equivalent to a Raymond-Roy II intracranial aneurysm occlusion classification (~90-99% occlusion) without clinically significant in-stent stenosis or re-treatment of the target intracranial aneurysm, and a combined composite primary effectiveness rate with these two results combined. The additional analysis of the primary effectiveness endpoint to include intracranial aneurysms with Raymond-Roy II classifications as a satisfactory outcome was based on the recommendations at the March 1, 2018 general issues meeting of the Neurological Devices Panel of the Medical Devices Advisory Committee.

The effectiveness results show that 70.6% (108/153) of patients in the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms*" had complete (100%) intracranial aneurysm occlusion without clinically significant in-stent stenosis or retreatment of the target aneurysm, an additional 10.4% (16/153) patients had stable or improved Raymond-Roy II intracranial aneurysm occlusions without clinically significant in-stent stenosis or target aneurysm treatment, for a total composite effectiveness rate of 81.0% (124/153). Therefore, the pivotal study met the primary effectiveness endpoint success criteria at one year, and the majority of the patients in the clinical trial exhibited a good effectiveness outcome.

Subgroup analyses showed that effectiveness, evaluated using complete (100%) intracranial aneurysm occlusion without clinically significant in-stent restenosis or target aneurysm retreatment, was not significantly different with respect to sex, aneurysm location (i.e., anterior versus posterior circulation), use with non-hydrogel vs. hydrogel neurovascular embolization coils, or aneurysm rupture status. The subgroup analysis did show that effectiveness may be lower for device treatment in large or giant intracranial aneurysms but the results are not conclusive because there were only 12 out of 153 patients with intracranial aneurysms > 10 mm in the pivotal study. Even with the potential for decreased effectiveness with the device and treatment in large or giant wide-neck intracranial aneurysms, these aneurysms have a greater risk for rupture

(Wiebers 1998 and Ishibashi et al. 2009) and must be treated because the overall mortality rate can be as high as 66% observed in the ISUIA trial if the intracranial aneurysm ruptures (Wiebers 1998).

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The primary safety endpoint was analyzed based on the ITT population for the rate of patients who exhibited a disabling stroke (ischemic or hemorrhagic) or neurological death within 12 months post-procedure. These two (2) primary safety events are the most significant adverse events to assess the device safety for the treatment of wide-neck intracranial aneurysms because these events are the most debilitating, can result in permanent disability, or expiration of the patient. The primary safety endpoint rate observed in the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms*" was 5.9% (9/153), with six (6) of the nine (9) primary safety endpoint events being a disabling stroke (3.9% (6/153)) and the remaining three (3) primary safety events being neurological deaths caused by a significant stroke (2.0% (3/153)). There was a total of 16 stroke events (10.5% (16/153)) that occurred in the pivotal study observed through 12 months post-procedure of which three (3) resulted in death, six (6) were categorized as disabling strokes, and seven (7) were categorized as non-disabling strokes. The mRS scores (measurement of patient disability) was also assessed to determine the rate of patients who had a worsening mRS score 12 months post-procedure compared to their baseline mRS prior to device treatment. Of the 153 patients in the ITT population in the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms*," 16% (25/153) had a worsening of the mRS at 12 months post-procedure compared to their baseline mRS. Fourteen (14) out of the 25 patients with a deterioration in the mRS at 12 months post-procedure compared to baseline had a bad clinical outcome (mRS $\geq$ 3) resulting in a rate of 9.2% (14/153). The primary safety event rates are similar to the rates published in the literature for the treatment of wide-neck intracranial aneurysms and below the estimated 10% safety PG.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The effectiveness results show that 70.6% (108/153) of patients in the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms*" had complete (100%) intracranial aneurysm occlusion without clinically significant in-stent stenosis or retreatment of the target aneurysm, an additional 10.4% (16/153) patients had stable or improved Raymond-Roy II intracranial aneurysm occlusions without clinically significant in-stent stenosis or target aneurysm treatment, for a total composite effectiveness

success rate of 81.0% (124/153) one year post-procedure. Because the LVIS and LVIS Jr. are permanent implants and the pivotal study with 1 year follow-up data was used to support the PMA, the long-term durability of treatment after 1 year post-procedure is currently unknown. If there is recurrence of the target intracranial aneurysm, the subject device allows for retreatment by placing additional neurovascular embolization coils within the intracranial aneurysm sac. Retreatment may carry additional procedural related risks to the patient(s). With endovascular intracranial aneurysm treatment with neurovascular stents for SAC, the stability of intracranial aneurysm occlusion at 1 year may be a good predictor of long-term stability because the use of the device with neurovascular embolization coils implanted within the intracranial aneurysm sac aids in the promotion of thrombosis to occlude the aneurysm from blood flow.

The probable risks of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The primary safety endpoint rate observed in the "*Pivotal Study of the MicroVention, Inc. Neurovascular Self-Expanding Retrievable Stent System LVIS in the Treatment of Wide-Necked Intracranial Artery Aneurysms*" was 5.9% (9/153), with six (6) of the nine(9) primary safety endpoint events being a disabling stroke (3.9% (6/153)) and the remaining three (3) primary safety events being neurological deaths caused by a significant stroke (2.0% (3/153)). There was a total of 27 device-related serious adverse events (SAEs) experienced in 153 patients, with 17 patients who experienced SAEs that occurred peri-procedural (11.1% (17/153)) and five (5) patients with SAEs that occurred post-procedure (3.3% (5/153)), including device failures, dissection or perforation of the parent artery, stent thrombosis, transient ischemic attack (TIA), vasospasm, and visual impairment. There was a total of 69 procedure-related SAEs experienced in 153 patients, with 44 patients who experienced SAEs that occurred peri-procedural (28.8% (44/153)) and six (6) patients with procedure-related SAEs that occurred post-procedure (3.9% (6/153)).

Additional factors to be considered in determining probable risks and benefits for the LVIS and LVIS Jr. device included: weighing the benefits and risks of device treatment with the patient's risk of intracranial aneurysm rupture. The risk of rupture of an untreated unruptured intracranial aneurysm is dependent on multiple factors including aneurysm size, shape, and morphology, and the patient co-morbidities (e.g., high blood pressure, family history, multiple aneurysms, diabetes). Based on natural history, it has been suggested that intracranial aneurysms have an average rupture rate of around 1% per year in patients with a diagnosed intracranial aneurysm, although that number can vary based on the study (Ishibashi et al. 2009; Juvela et al. 2013). Size and location of the cerebral aneurysm in the neurovasculature can also affect the risk of rupture. In the article by Wiebers (2003), intracranial aneurysms in the ICA, AComm, ACA, or MCA that were < 7 mm, 7-12 mm, 13-24 mm, and > 25 mm had rupture rates of 0%, 2.6%, 14.5%, and 40%, respectively, at 5 years. In addition, from this same study, rupture rates of 2.5%, 14.5%, 18.4%, and 50% were seen, for the same distribution of sizes, for aneurysms located in the posterior circulation and posterior communicating artery. Several additional studies have suggested that

smaller aneurysms (< 7 mm) rarely rupture, with a rupture rate reported at 0.7%, and therefore, may inform an opinion that these aneurysms be best treated conservatively by observation only ("The Natural Course of Unruptured Cerebral Aneurysms in a Japanese Cohort" 2012; Rinkel et al. 1998; Komotar, Mocco, and Solomon 2008). For patients with an unruptured aneurysm without a history of SAH (Type 1), the risk of rupture rate drops to 0.1% for aneurysms < 7 mm in diameter (Ishibashi et al. 2009; Wiebers 2003). Conversely, larger aneurysms are at a greater risk for rupture (i.e., the rupture rate for aneurysms > 25 mm have a reported 6% rupture rate in the first year (Wiebers 1998) with other studies reporting an annual rupture rate as high as 43.1% (Ishibashi et al. 2009)).

Based on the natural history of patients who are at high risk for intracranial aneurysm rupture from these prior published studies, it appears that patients who will benefit the most from device treatment are those with larger intracranial aneurysms, intracranial aneurysms located in the posterior circulation, those with significant co-morbidities, and/or those with longer life-expectancies. Therefore, based on the complexity of the disease, the physician-patient relationship in deciding which intracranial aneurysms should be treated with the device is particularly important based on the patient's individual risk of intracranial aneurysm rupture within their lifetime. If the patient's risk of intracranial aneurysm rupture is high within their lifetime, then the use of the subject device would provide a safe and effectiveness treatment for the indicated use 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.

One additional factor to be considered in determining probable risks and benefits for the LVIS and LVIS Jr. device include some uncertainty based on the single arm pivotal trial design that may introduce some bias in patient selection for treatment because there was no blinding or randomized concurrent control group. Since there was no active control arm in the pivotal study, there are uncertainties of whether the device treatment was more beneficial than no treatment at all for certain patients such as those with small intracranial aneurysms or with limited life expectancies. This additional factor further highlights the importance of patient selection for treatment with this disease and the important role of the physician-patient relationship.

1. Patient Perspectives

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

In conclusion, given the available information above, the data support that for use 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, the probable benefits outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. The overall risk to benefit ratio is favorable for the intended population. While there are still risks involved with the use of this device, including disabling strokes and death (i.e., 5.9% (9/153)), the benefits include that 81.0% (124/153) of the ITT population in the pivotal clinical study achieved a good effectiveness outcome of Raymond-Roy I and stable Raymond-Roy II occlusions of their treated wide-neck intracranial aneurysm without clinically significant in-stent stenosis or retreatment within one year post-procedure.

XIII. CDRH DECISION

CDRH issued an approval order on May 30, 2018. The final conditions of approval cited in the approval order are described below.

OSB Lead PMA Post-Approval Study – Post-Market Surveillance Study to Evaluate the Long-Term Safety and Effectiveness of the LVIS and LVIS Jr.: The Office of Surveillance and Biometrics (OSB) will have the lead for studies initiated after device approval. The Post-Market Surveillance Study to Evaluate the Long-Term Safety and Effectiveness of the LVIS and LVIS Jr. is a retrospective post-market surveillance study to evaluate the long-term safety and effectiveness of all LVIS and LVIS Jr. device models, including the 212517-LVIS, 212525-LVIS, 213015-LVIS, 213025-LVIS, 213041-LVIS, 214035-LVIS, and 214049-LVIS, for its intended use up to a minimum of five (5) years follow-up. The safety and effectiveness endpoints are the rate of disabling strokes or neurological deaths and the rate of patients who had complete (100%) or stable Raymond-Roy II intracranial aneurysm occlusion without clinically significant in-stent stenosis or retreatment of the target aneurysm.

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

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

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