SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Intracranial Aneurysm Flow Diverter
Device Trade Name:	Flow Re-Direction Endoluminal Device (FRED®) System
Device Procode:	OUT
Applicant's Name and Address:	MicroVention, Inc. 35 Enterprise Aliso Viejo, California 92656
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P180027
Date of FDA Notice of Approval:	December 16, 2019

II. INDICATIONS FOR USE

The Flow Re-Direction Endoluminal Device (FRED®) System is indicated for use in the internal carotid artery from the petrous segment to the terminus for the endovascular treatment of adult patients (22 years of age or older) with wide-necked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform intracranial aneurysms arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 mm.

III. CONTRAINDICATIONS

Use of the FRED® System is 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 FRED® System.
- Patients with an active bacterial infection.
- Patients with a pre-existing stent in place at the target aneurysm.
- Patients in whom the parent vessel size does not fall within the indicated range.
- Patients who have not received dual anti-platelet agents prior to the procedure.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the FRED® System labeling.

V. DEVICE DESCRIPTION

The FRED® System (see Figures 1, 2) consists of a self-expanding nickel titanium implant and a delivery system. The implant is designed to expand to a pre-determined diameter when released from the delivery system. The implant features integrated dual layer coverage designed to divert blood flow from entering the neck of a wide-necked intracranial aneurysm (IA). The implant has distal and proximal markers on its ends and interweaved helical marker strands delineating the inner working length of the implant to provide fluoroscopic visibility. The FRED® System is packaged sterile as a single unit with the implant, introducer sheath, and a detachable delivery pusher. It is available in 7 different implant diameters ranging from 2.5 mm to 5.5 mm and in different implant lengths ranging from 13 mm to 45 mm (see Table 1). The FRED® System 2.5 mm and 3.0 mm implants are compatible with the Headway® 21 Microcatheter. The FRED® System 3.5 mm to 5.5 mm implants are compatible with the Headway® 27 Microcatheter.

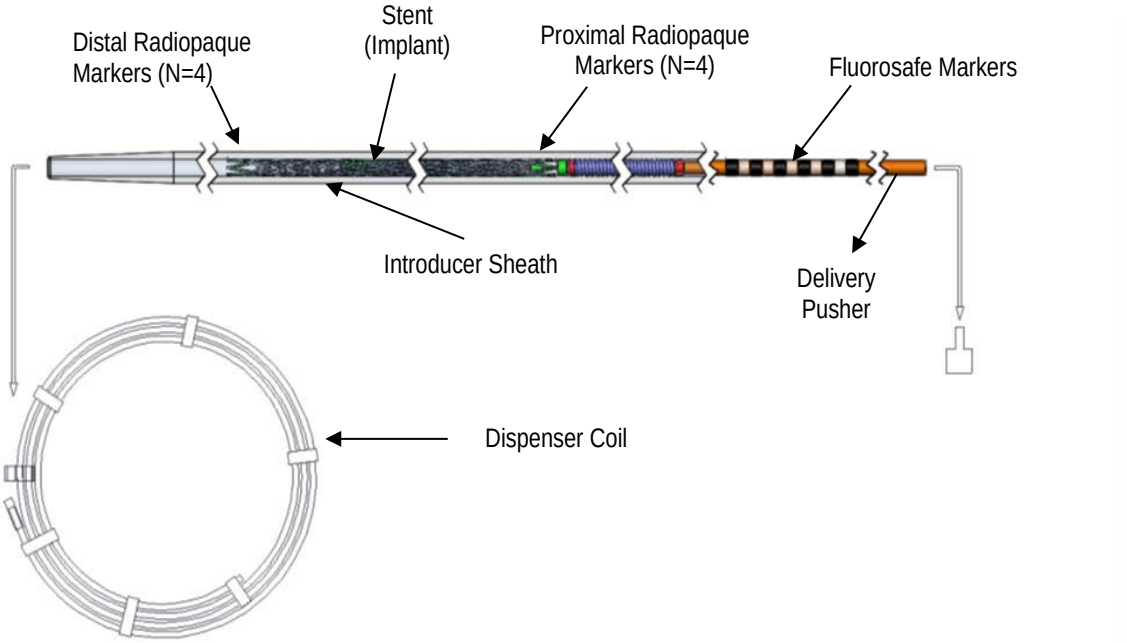


Figure 1: FRED® System

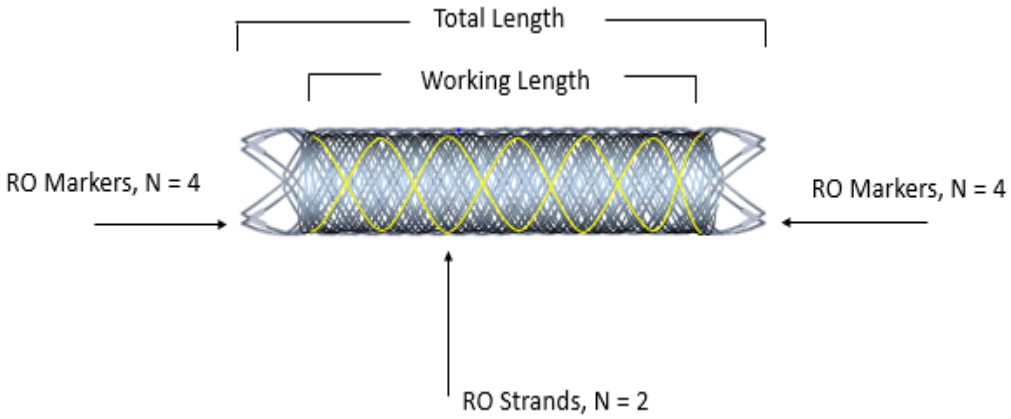


Figure 2: FRED® Implant

Table 1: Models and Dimensions of FRED® System

Device	Outer Diameter (mm)	Total Lengths (mm)	Working Lengths (mm)
FRED® System	2.5	13 to 30	8 to 26
	3.0	13 to 32	9 to 27
	3.5	13, 15, 17, 19, 22, 31, 40	7, 9, 11, 13, 16, 24, 36
	4.0	13, 15, 18, 20, 23, 32, 44	7, 9, 12, 14, 17, 26, 38
	4.5	15, 17, 20, 25, 31, 34, 45	8, 11, 13, 18, 24, 28, 39
	5.0	15, 18, 21, 26, 32, 36	9, 11, 14, 19, 26, 29
	5.5	22, 28, 32	14, 19, 26

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of wide-necked IAs including open surgical clipping, endovascular stent-assisted coiling using neurovascular stents to support embolization coils in the IA sac, balloon catheter assisted coiling of an IA, neurovascular flow diverting stents used by itself, and intrasaccular flow disruption devices. The neurovascular stents available in the United States (US) for stent-assisted coiling of wide-necked IAs were approved through the premarket approval (PMA) regulatory pathway, which include MicroVention, Inc. Low-Profile Visualized Intraluminal Support (LVIS) and LVIS Jr. (P170013) and the Stryker Neurovascular Neuroform Atlas Stent System (P180031), and the Humanitarian Device Exemption (HDE) regulatory pathway, which 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 IAs 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) and Pipeline Flex Embolizaion Device (P100018 and P100018/S015) is a PMA approved neurovascular flow diverting stent in the US and was approved with the intended use of endovascular treatment of large or giant wide-necked IAs in the internal carotid artery (ICA) from the petrous to the superior hypophyseal segment and the endovascular treatment of small and medium wide-necked IAs in the ICA up to the terminus. The Stryker Neurovascular Surpass Streamline Flow Diverter (P170024) is also a PMA approved neurovascular flow diverting stent in the US and was approved with the indicated use in the endovascular treatment of patients with unruptured large or giant saccular wide-necked or fusiform IAs in the ICA from the petrous segment to the terminus. A neurovascular flow diverting stent is implanted in the parent vessel and is placed across the neck of the IA. Its mechanism of action is to divert the blood flow from entering the IA sac and endothelialization will occur on the implant over time to further promote complete IA occlusion. The neurovascular flow diverting stent is intended to be used by itself as a stand-alone device. The subject FRED® System is also a neurovascular flow diverting stent and has the same mechanism of action as the approved PED and Pipeline Flex Embolization Device and the Surpass Streamline Flow Diverter.

There is also one neurovascular intrasaccular flow disruption device approved in the US called the MicroVention, Inc. Woven EndoBridge (WEB) Aneurysm Embolization System (P170032) indicated for use at the middle cerebral artery (MCA) bifurcation, ICA terminus, anterior communicating artery (AComm) complex, or basilar artery apex for the endovascular treatment of adult patients with saccular, wide-necked, bifurcation IAs with dome diameter from 3 mm to 10 mm and either neck size 4 mm or greater or the dome-to-neck ratio is greater than 1 and less than 2. This device is intended to be a stand-alone device that is implanted in the IA sac. The mechanism of action is to block or disrupt blood flow from entering the neck of the IA.

In addition to these alternative treatments, certain IAs 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 IAs over time. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with a physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

The FRED® System is approved for marketing in the following countries: Australia, Austria, Argentina, Belgium, Bulgaria, Belarus, Brazil, Croatia, Chile, Cyprus, Czech Republic, Columbia, Cayman Islands, Denmark, Dominican Republic, Ecuador, Egypt, El Savador, Estonia, Finland, France, Germany, Greece, Grand Cayman, Georgia, Hong Kong, Hungary, India, Iran, Ireland, Iceland, Istanbul, Italy, Jordan, Kazakhstan, Latvia, Lebanon, Liechstenstein, Lithuania, Luxembourg, Mexico, Malta, Morocco, Malaysia, Netherlands, Norway, New Zealand, Panama, Peru, Portugal, Poland, Paraguay, Romania, Russia, Saudi Arabia, Slovakia, Serbia, Slovenia, Spain, Sweden, Singapore, Sri Lanka, Switzerland, Trinidad & Tobago, Turkey, United Kingdom, United Arab Emirates, Uruguay, Ukraine, Vietnam, and Venezuela.

The applicant reports that the FRED® System has not been withdrawn from the market outside of the US for safety or effectiveness reasons.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential 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
- Amaurosis fugax or transient blindness
- Aphasia
- Blindness
- Cardiac arrhythmia
- Complications of arterial puncture including pain, local bleeding, or injury to the artery, or adjacent nerves
- Cranial neuropathy
- Death
- Device fracture, migration or misplacement
- Diplopia
- Dissection or perforation of the parent artery
- Headache
- Hemiplegia
- Hemorrhage, including intracranial hemorrhage (ICH), subarachnoid hemorrhage (SAH), and retroperitoneal
- Hydrocephalus
- Infection
- Mass effect
- Myocardial infarction
- Neurological deficits
- Pseudoaneurysm formation
- Reaction to anti-platelet or anti-coagulant agents
- Reactions due to radiation exposure, including alopecia, burns ranging in severity from skin reddening to ulcers, cataracts, and delayed neoplasia
- Reactions to anesthesia and related procedures
- Reactions to contrast agents including allergic reactions and kidney failure
- Reduced visual acuity or visual field
- Retinal artery occlusion or infarction
- Retinal ischemia
- Rupture or perforation of the aneurysm
- 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, see Section X below.

IX. SUMMARY OF NONCLINICAL STUDIES

The FRED® System underwent non-clinical mechanical, functional, biocompatibility, sterilization validation, packaging validation, shelf-life 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 FRED® System. The testing was conducted based on the recommendations in the Guidance for Industry and Food and Drug Administration (FDA) Staff, "Non-Clinical Engineering Tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems," issued on April 18, 2010, and "Select Updates for Non-Clinical Engineering tests and Recommended Labeling for Intravascular Stents and Associated Delivery Systems," issued on August 18, 2015. Applicable consensus standards were also used when available for the specific test.

Table 2: Design Verification and Validation Testing

Test	Purpose	Results
Material Characterization		
Material Composition	Determine if materials are suitable for implant.	Materials met pre-specified requirements.
Austenite Finish Transition Temperature (A_f)	Determine if the stent will achieve its pre-determined size and shape when exposed to normal body temperature.	The A_f for the FRED® stent was confirmed to comply with the specification of < 30 °C.
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.
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.
Stent (Implant) Dimensional and Functional Attributes		

Dimensional Verification	To confirm the FRED® stent is within dimensional specification.	The FRED® stent met dimensional specifications.
Percent Surface Area	Determine the surface area of the FRED® stent.	Met pre-specified criteria.
Foreshortening	Determine if the stent length shortens once deployed.	Met pre-specified criteria.
Implant Integrity	Determine if the FRED® stent remains intact after deployment through microcatheter.	All samples demonstrated the FRED® stent is able to deploy over the device shelf life of 3 years.
Hoop Force	Determine if the device exerts enough radial pressure so that it does not migrate in body when implanted in largest recommended vessel size, and the device will not injure vasculature.	Met pre-specified criteria.
Stress and Strain and Fatigue Analysis	Determine if stresses do not exceed material limits during deployment and long-term use as implant. Finite Element Analysis (FEA) model used to evaluate stresses.	No excessive localized stresses were detected. The FEA predicted the FRED® fatigue lifetime has adequate safety built into the design with a safety factor of greater than 1.0.
Accelerated Durability Testing	Accelerated durability testing to 380 million cycles (10-years equivalent) to simulate pulsing in the neurovasculature.	The FRED® stent met accelerated durability test specification with no loss in structural integrity or fragmentation.
Particulate Evaluation	Quantify the particulate matter for the FRED® System 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.
Magnetic Resonance Imaging (MRI) Safety	To assess the MRI safety and compatibility of the FRED® stent.	The test results demonstrated the FRED® stent did not pose additional unacceptable risk to the patient. The FRED® stent was determined to be MR Conditional per ASTM 2503. The MRI Conditional scanning parameters are specified in the labeling.
Radiopacity	Determine if the device is visible under fluoroscopy (imaging used during implantation).	Met the acceptance criteria for radiopacity.

Implant Bond Strength	The tensile strength of the FRED® stent is characterized.	The FRED® stent met the tensile bond strength acceptance criteria at the bond locations.
Delivery System Dimensional and Functional Attributes		
Dimensional Verification	To confirm the FRED® delivery system is within dimensional specification.	The FRED® delivery system met dimensional specifications.
Delivery, Deployment and Retraction	To confirm delivery deployment and retraction testing done as part of simulated use testing of the FRED® delivery system.	All devices tested passed the delivery, deployment and retraction testing done as part of simulated use of the FRED® delivery system.
Delivery Pusher Bond Strength	The tensile strength of the FRED® delivery pusher is characterized.	The FRED® delivery pusher met the tensile bond strength acceptance criteria at the bond locations.
Flexibility and Kink Test	Determine the flexibility and kink resistance of the FRED® stent and delivery system.	The flexibility and kink tests were assessed during the "simulated use" testing. During simulated use testing, the trackability of the devices was evaluated during advancement and retraction of the device in the microcatheter. The trackability of the FRED® System were rated favorably during the simulated use testing and did not result in any kinks.

Biocompatibility Testing

Biocompatibility testing for all materials used to manufacture the FRED® System 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 show the biocompatibility tests conducted for the FRED® stent and delivery system, respectively.

Table 3: Implant (Stent) – Biocompatibility

Test	**Purpose**	**Results**
Cytotoxicity - L929 Minimum Essential Media (MEM) Elution Test	Test for cell lysis.	Test article assessed to be Grade 0, "Non-cytotoxic."

Sensitization - Kligman Maximization Test	Test for allergenic potential or sensitization capacity of test article.	Test article assessed to be 0, "Non-sensitizer."
Irritation - Intracutaneous Injection Test in Rabbits	Test for irritation potential.	Test article assessed to be "Non-irritant."
Systemic Toxicity - Systemic Injection Test Study in Mice	Test for systemic acute toxicity in mice following intravenous and intraperitoneal injections.	Test article assessed to be "Non-toxic."
Systemic Toxicity - Rabbit Pyrogen Test (Material Mediated)	Test for pyrogenic response from the material.	Test article assessed to be "Non-pyrogenic."
Hemocompatibility - ASTM Hemolysis (Direct and Indirect Contact)	Test for red blood cell hemolysis.	Test article assessed to be "Non-hemolytic."
Hemocompatibility - Prothrombin Time (PT) Assay (Indirect Contact)	Test for coagulation response from the test material.	The PT of plasma exposed to test article was not significantly decreased when compared to both negative controls.
Hemocompatibility - Complement Activation Assay (C3a, SC5b-9) (Direct and 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 thromboresistance of medical devices that are intended for blood contact.	Test article assessed to be thromboresistant.
Genotoxicity - Bacterial Reverse Mutation Study	Test for mutagenic changes.	Test article assessed to be "Non-mutagenic" in the test species under the test conditions.
Genotoxicity - Mouse Lymphoma Mutagenesis Assay	Test to determine whether a chemical can induce a change in cultured mammalian cells.	Test article assessed to be "Non-mutagenic" in the test species under the test conditions.
Genotoxicity - Mouse Bone Marrow Micronucleus Assay	Test for toxicological screening for potential genotoxic compounds.	Test article assessed to be "Non-clastogenic" in the test species under the test conditions.
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.	Test article assessed to be Grade 0, "Non-cytotoxic."
Sensitization - Kligman Maximization Test	Test for allergenic potential or sensitization capacity of test article.	Test article assessed to be 0, "Non-sensitizer."
Irritation - Intracutaneous Injection Test in Rabbits	Test for irritation potential.	Test article assessed to be "Non- irritant."
Systemic Toxicity - Systemic Injection Test Study in Mice	Test for systemic acute toxicity in mice following intravenous and intraperitoneal injections.	Test article assessed to be "Non-toxic."
Systemic Toxicity - Rabbit Pyrogen Test (Material Mediated)	Test for pyrogenic response from the material.	Test article assessed to be "Non-pyrogenic."
Hemocompatibility - ASTM Hemolysis (Indirect Contact)	Test for red blood cell hemolysis.	Test article assessed to be "Non-hemolytic."
Hemocompatibility - PT Assay (Indirect Contact)	Test for coagulation response from the test material.	The PT of plasma exposed to test article was not significantly decreased when compared to both negative controls.
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 was not significantly decreased when compared to both negative controls.
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 thromboresistance of medical devices that are intended for blood contact.	Test article assessed to be thromboresistant.

B. Animal Studies

A Good Laboratory Practice (GLP) animal study was conducted to evaluate acute and chronic safety and performance of the device at 30, 90, 180, and 365 days. The device was implanted in New Zealand White rabbits in right common carotid arteries and abdominal aortas with microsurgically constructed sidewall aneurysms. The device performance characteristics during implantation were evaluated based on 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 and absence of migration, parent vessel patency, blood flow or vessel irregularities, and aneurysm occlusion. Excised vessels were evaluated for histology, histopathology, and vessel patency. At 365 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.

C. Additional Studies

Sterilization Validation

The FRED® System is sterilized using electron beam irradiation. The sterilization method was validated to a sterility assurance level (SAL) 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.

Bacterial Endotoxin Testing

Routine limulus amebocyte lysate (LAL) batch release testing is performed for every sterile load of the FRED System using the kinetic chromogenic method. Devices are held to the specification of < 0.06 endotoxin units (EU)/mL and < 2.15 EU/device in accordance with ANSI/AAMI ST72.

Shelf Life and Packaging Validation

The FRED® System was tested and determined to have a 3-year shelf life. The 3-year shelf life was verified on real time aged devices. The samples were pre-conditioned for simulated shipping and sterilized. The dimensional and functional attributes were tested and met acceptance criteria. In addition, packaging integrity testing (pouch and carton) was verified and met acceptance criteria to support the 3-year shelf life.

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of the FRED® System for use in the ICA from the petrous segment to the terminus for the endovascular treatment of adult patients (22 years of age or older) with wide-necked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform IAs arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 mm in the US and Japan under IDE # G120111. Data from this clinical study are the basis for the PMA approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between July 16, 2013, and December 20, 2016. The database for this PMA reflected data collected through March 6, 2018, and included 145 patients. There were 23 investigational sites: 22 in the US and 1 in Japan.

The study, titled "Pivotal Study of the MicroVention, Inc. Flow Re-Direction Endoluminal Device System in the Treatment of Intracranial Aneurysms" ["FRED"], was a 145-patient, open-label, prospective, multi-center, one-arm, clinical study. The study included follow-up at discharge, 30 days, 180 days, and 12 months. The pre-specified primary safety and effectiveness endpoints in the clinical study protocol were:

- Safety: The proportion of subjects experiencing death or major stroke within 30 days, or neurological death or major ipsilateral stroke within 12 months post-procedure.
    - A major stroke is defined as a new neurological event that persists > 24 hours and results in a ≥ 4 point increase in the National Institutes of Health Stroke Scale (NIHSS) score compared to baseline or compared to any subsequent lower score.
    - A major ipsilateral stroke is defined as a major stroke occurring within the vascular distribution of the stented artery.
    - Neurological death is defined as a death which has been adjudicated by the independent clinical events committee (CEC) to have directly resulted from a neurologic cause.

- Effectiveness: The proportion of subjects with complete occlusion (100%) of the target IA utilizing the Raymond-Roy classification scale [Raymond-Roy I] and ≤ 50% stenosis of the parent artery at the target IA assessed by digital subtraction angiography (DSA) and in whom an alternative treatment of the target IA had not been performed within 12 months post index procedure.

The control group was based on performance goals (PGs) developed using a meta-analysis of peer-reviewed published literature reporting the safety and effectiveness of endovascular treatment of IAs with neurovascular flow diverting stents. Analyses of the primary endpoints were conducted using Bayesian statistical methods consistent with the Guidance for Industry and FDA Staff, "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials," issued on February 5, 2010. Prior distributions were specified to be non-informative and no data apart from the current investigation were incorporated into the Bayesian posterior distributions. Bayesian analysis also allowed the computation of credible intervals for inference regarding primary endpoints. All analyses were performed using R version 3.3 (R Foundation for Statistical Computing, Vienna, Austria).

This study included an independent CEC, Data Safety and Monitoring Board (DSMB), angiographic imaging core laboratory ("core lab"), and study monitors who

confirmed neurological assessments, adverse events, imaging data, and study data with source documentation.

1. Clinical Inclusion and Exclusion Criteria

   Enrollment in the FRED study was limited to patients who met the following inclusion criteria:

   - Age ≥ 22 and ≤ 75 years.
   - The parent artery diameter was 2.0-5.0 mm distal and proximal to the target IA.
   - Subject fulfilled study requirements, and the subject or his/her legally authorized representative provided a signed informed consent form.
   - Negative pregnancy test (serum or urine) in a female subject who has had menses in the last 18 months.
   - Subject committed to return to the investigational site for the 30-day, 180-day, and 12-month follow-up evaluations.
   - Subject had a single target aneurysm located in:
     - Petrous through superior hypophyseal segments of the ICA
     - Communicating segment of the ICA through A1 or M1 segment
     - Posterior circulation
       - Basilar artery (not including the basilar bifurcation)
       - Vertebral artery (distal to the posterior inferior cerebellar artery (PICA))
       - Vertebral artery (proximal to the PICA)

   And any of the following inclusion criteria:

   - Subject for whom existing endovascular options (coiling, stent-assisted coiling) would had been ineffective because the aneurysm was predisposed to recurrence due to having any of the following characteristics:
     a. Aneurysm had a maximum fundus diameter less than 10 mm but ≥ 2 mm.
        i. To mitigate the risk for the treatment of subjects with small stable aneurysms that may not require treatment with respect to the possible risks and benefits associated with treatment, the treating clinician had to record a treatment justification (such as increased risk of rupture) for the aneurysms < 7 mm that were selected for treatment.
     b. Aneurysm had any of the following morphologies:
        i. No discernible neck.
        ii. Segmental parent artery dysplasia.
        iii. Aneurysm neck involving > 180 degrees of parent artery circumference.
        iv. Complex lobulations limiting stent/coiling as a treatment option.

v. Neck ≥ 4 mm or dome-to-neck ratio < 2.

OR

- Subject had a fusiform aneurysm of any size requiring treatment.

OR

- Subject was a poor candidate for open surgical treatment because of prior surgical procedures, comorbidities or location limiting conventional surgical options.

Patients were not permitted to enroll in the FRED study if they met any of the following exclusion criteria:

- Subject who suffered from a subarachnoid hemorrhage in the last 60 days.
- Subject who suffered from any intracranial hemorrhage in the last 30 days.
- Subject who presented with an intracranial mass or was currently undergoing radiation therapy for carcinoma or sarcoma of the head or neck region.
- Subject with symptomatic extracranial or intracranial stenosis of the parent artery (> 50%) proximal to the target IA.
- Subjects with an irreversible bleeding disorder, a platelet count of less than 100,000/mL < 100 x 10^3 cells/mm^3 or known platelet dysfunction or a contraindication to or inability to tolerate anticoagulants/antiplatelet agents.
- Active peptic ulcer disease, major systemic hemorrhage within 30 days, active bleeding diathesis, platelet < 100,000 or known platelet dysfunction, international normalized ratio (INR) ≥ 1.5, clotting factor abnormality, current alcohol or substance abuse, uncontrolled severe hypertension (systolic pressure > 180 mm Hg or diastolic pressure > 115 mm Hg) creatinine ≥ 3.0 mg/dL (unless on dialysis).
- Subject with contraindications or known allergies to anticoagulants or antiplatelets (aspirin, heparin, ticlopidine, clopidogrel, prasugrel, or ticagrelor).
- Subject with known hypersensitivity to metal, such as nickel-titanium and metal jewelry.
- Subject with documented contrast allergy, or other condition, that prohibits imaging.
- Evidence of active infection at the time of treatment.
- Presence of any of the following unequivocal cardiac sources of embolism: chronic or paroxysmal atrial fibrillation, mitral stenosis, mechanical valve, endocarditis, intracardiac clot or vegetation, myocardial infarction within three months, dilated cardiomyopathy, left atrial spontaneous echo contrast, ejection fraction less than 30%.
- Subject who had a previous intracranial stenting procedure associated with the target IA.
- Subject who was unable to complete the required follow-ups.

- Subject with life-threatening diseases.
- Subject who was pregnant or breastfeeding.
- Subject of childbearing potential, and unwilling to prevent pregnancy during their participation in the study.

Angiographic exclusion criteria:

- Subject had a cerebral diagnostic angiogram that demonstrated an IA that was not appropriate for endovascular treatment.
- Subject had an extracranial stenosis greater than 50% in the carotid artery of the target IA.
- Subject had an intracranial stenosis greater than 50% in the treated vessel.
- Subject had a mycotic or dissecting IA.
- Subject had a bifurcation IA for example at the bifurcation of the ICA, the MCA, or at the AComm artery such that placement of the device would fail to satisfactorily cover the entire neck of the IA or a major cerebral artery would be put at risk through "jailing."
- Subject had a posterior circulation IA with the following morphology:
  - Placement of the device would include the basilar artery bifurcation.
  - Large or giant dolichoectatic IA.
- Subject's IA had significant branch exiting from dome of IA (for example, ophthalmic artery).
- Subject was harboring more than one IA with both IAs requiring treatment at the same time.
- Subject had an arteriovenous malformation (AVM) in the area of the target IA.

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at discharge, 30 days (± 7 days), 180 days (± 30 days), and 12 months (+60 days, -30 days), postoperatively.

Preoperatively, all subjects had a neurologic and ophthalmic examination, modified Rankin Scale (mRS) assessment, hematology assessment, a pregnancy test when appropriate, and cerebral angiography. Postoperatively, the objective parameters measured during the study included cerebral angiography immediately following the procedure, at 180 days, and 12 months. Neurologic, mRS, and ophthalmic examinations were performed at 30 days, 180 days, and 12 months after the procedure (see Table 5). Adverse events and complications were recorded at all visits.

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

Table 5: Study Assessment Schedule

Summary of Events	**Pre-Procedure**	**Procedure**	**Post-Procedure**	**Discharge**	**30 days ± 7 days**	**180 days ± 30 days**	**12 months + 60 days, - 30 days**
Medical History	X						
Physical Examination	X			X	X	X	X
Informed Consent[1]	X[1]						
Neurological Examination (including NIHSS and mRS)	X			X	X	X	X
Concomitant Medications	X			X	X	X	X
Laboratory Assessment[2]	X[2]						
Pregnancy Test	X[5]	X[5]				X[5]	X[5]
Intracranial Stent Procedure		X					
Procedural Medications		X	X				
Angiogram	X	X	X			X	X
Ophthalmic Exam at Baseline (only if applicable at Follow-up)[4]	X				X[4]	X[4]	X[4]
Clinical Eye Exam	X				X	X	X
Adverse Event		X	X	X	X	X	X
Serious Adverse Event[3]		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Unanticipated Adverse Event[3]		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Protocol Deviation	X	X	X	X	X	X	X
Death, or Device Related Adverse Event[3]		X[3]	X[3]	X[3]	X[3]	X[3]	X[3]
Subject Disposition		X	X	X	X	X	X

[1] Informed consent must be signed before subject is enrolled in the study. In case of an emergency, protocol direction for obtaining a consent form should be followed.
[2] Preferably: Complete blood count (CBC) with differential, blood chemistry, PT/PTT, and blood sugar evaluation within 7 days from procedure; must conduct a pregnancy test (urine or serum) for women of childbearing age at time of enrollment and within 48 hours prior to procedure if > 48 hours has elapsed since last pregnancy test.
[3] A serious adverse event (e.g., death), protocol deviation, unanticipated adverse device effect or device related adverse event shall be 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.
[4] Ophthalmic exam is required within 30 days of procedure, a historical exam may be used. The ophthalmic exam is only required for follow up visits if there is an irregular baseline result or if concluded medically necessary due to changes in vision.
[5] Pregnancy testing may be completed through blood serum or urine testing. Pregnancy test shall be completed in accordance with standard practices at the institution prior to imaging. Pregnancy test will not be required if there is proof of hysterectomy or sterilization in the patient's medical record.

3. Clinical Endpoints

With regard to safety, the proportion of subjects experiencing death or major stroke within 30 days, or neurological death or major ipsilateral stroke within 12 months post-procedure, was analyzed based on the FRED study results.

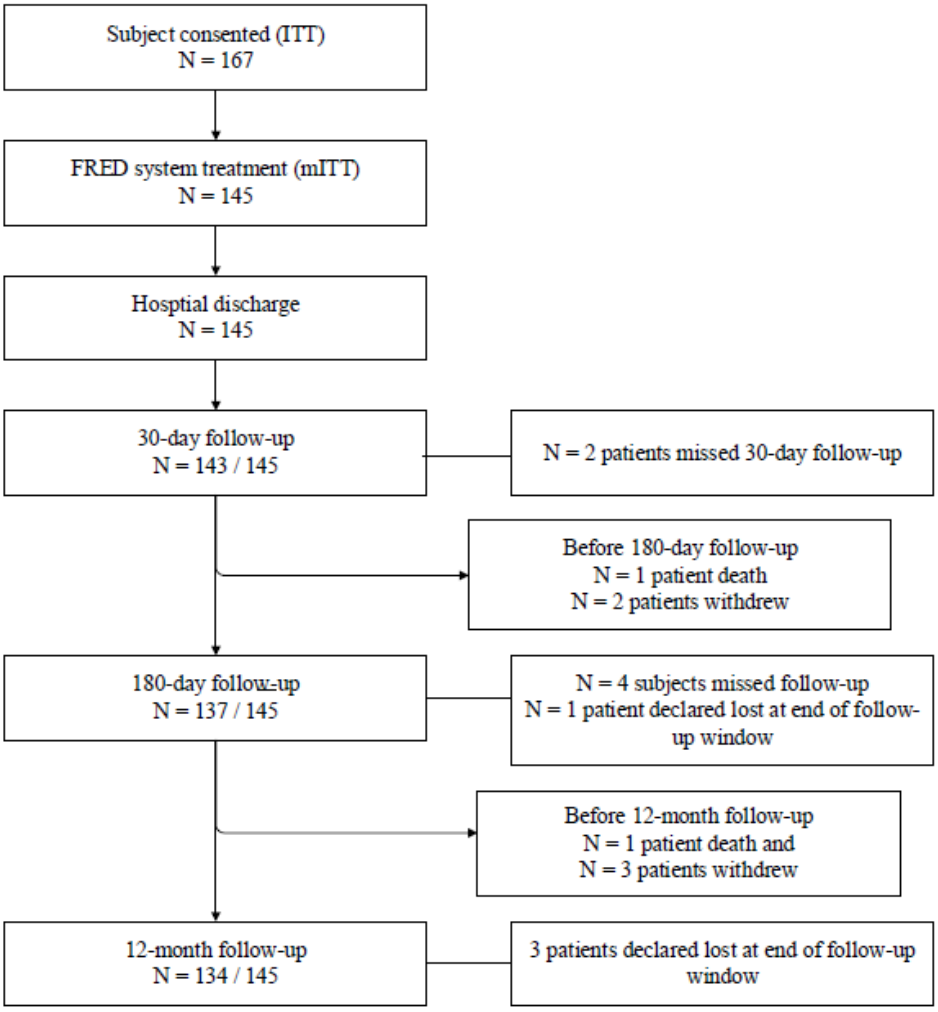
With regard to effectiveness, the proportion of subjects with complete occlusion (100%) of the target IA with a Raymond-Roy I classification, ≤ 50% stenosis of the parent artery at the target IA assessed by DSA, and in whom an alternative treatment of the target IA had not been performed within 12 months post index procedure, was analyzed based on the FRED study results.

With regard to success/failure criteria, the FRED study was designed to be successful if, using a Bayesian analysis, the two-sided 95% credible interval (CI) lower bound of the effectiveness rate exceeds the 46% PG and the two-sided 95% CI upper bound of the safety rate is below the 15% PG.

B. Accountability of PMA Cohort

At the time of database lock, of 145 patients enrolled in the PMA study, data from 92.4% (134) patients are available for analysis at the completion of the study, the 12 month post-operative visit.

Figure 3: Subject Accountability Flow Chart



Intent-to-Treat (ITT): All subjects who signed the informed consent document.
Modified ITT (mITT): ITT subjects in whom treatment with the FRED® System was attempted.

C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for an endovascular IA treatment study performed in the US. This disease predominantly affects more women than men and most patients are Caucasian. Tables 6-8 present the demographics and baseline IA characteristics of the 145 modified intent-to-treat (mITT) subjects treated in the FRED study. The 145 mITT subjects are defined as subjects in whom the FRED® System was attempted, regardless of whether the FRED® stent was implanted or not.

Baseline IA characteristics are reported per the site evaluation. The mean IA dome height was 11.5 ± 4.7 mm, mean dome width was 10.3 ± 4.9 mm, and mean neck width was 6.4 ± 3.2 mm. A total of 106 IAs (73.1%, 106/145) were considered large or giant with a maximum dimension of ≥ 10 mm. Of the 145 mITT patients, 8 patients had a previously ruptured IA and 137 patients had unruptured IAs.

Table 6: Demographics and Baseline Characteristics

Characteristic	**Mean ± Standard Deviation (SD) N=145**	**[Median] (Min, Max)**
Age (years)	59.1 ± 11.5	[60.1] (23.9, 82.9)
Gender		
Female	129 (89.0%)	
Male	16 (11.0%)	
Ethnicity		
Hispanic or Latino	19 (13.1%)	
Not Hispanic or Latino	126 (86.9%)	
Race		
American Indian or Alaska Native	1 (0.7%)	
Asian	7 (4.8%)	
Black or African American	24 (16.6%)	
Other	9 (6.2%)	
White	104 (71.7%)	
Systolic blood pressure (mm Hg)	131.5 ± 20.2	[130.0] (92.0, 208.0)
Diastolic blood pressure (mm Hg)	75.8 ± 11.7	[76.0] (49.0, 107.0)
Body temperature (°F)	97.8 ± 0.7 (N=129)	[97.9] (95.9, 100.0)
Heart rate (beats per minute (BPM))	75.8 ± 13.7	[74.0] (49.0, 123.0)

Table 7: Target Intracranial Aneurysm Locations

Location	**All N=145**	**Fusiform N=18 (12.4%)**	**Saccular N=127 (87.6%)**
Anterior Circulation, n (%)	**139 (95.9%)**	**16**	**123**
Internal Carotid Artery (ICA)	135	15	120
Carotid Cavernous	41	10	31
Carotid Ophthalmic	50	2	48
Internal Carotid Artery (Supraclinoid)	10	2	8
Superior Hypophyseal	14	1	13
Communicating segment of the ICA	20	0	20
Anterior cerebral artery	2	1	1
Anterior communicating artery (AComm)	2	0	2
Posterior Circulation, n (%)	**6 (4.1%)**	**2**	**4**
Basilar artery	2	0	2

Location	All N=145	Fusiform N=18 (12.4%)	Saccular N=127 (87.6%)
Posterior inferior cerebellar artery (PICA)	2	1	1
Vertebral artery	2	1	1

Table 8: Baseline Intracranial Aneurysm Characteristics

IA Characteristic	Mean ± SD (Range)
Dome height (mm)	11.5 ± 4.7 (3.7, 29.0)
Dome width (mm)	10.3 ± 4.9 (3.2, 27.4)
Neck width (mm)	6.4 ± 3.2 (3.5, 32.0)
Dome-to-neck ratio	1.7 ± 0.7 (0.5, 4.4)
Distal parent artery diameter (mm)	3.4 ± 0.6 (2.0, 7.9)
Proximal parent artery diameter (mm)	4.0 ± 0.7 (2.0, 7.5)
Mean parent artery diameter (mm)	3.7 ± 0.7 (2.0, 7.7)

D. Safety and Effectiveness Results

1. Safety Results

The analysis of safety was based on the mITT cohort of 145 patients available for the 12-month evaluation. The key safety outcomes for this study are presented below in Tables 9 to 13. Adverse effects are reported in Table 14.

In the mITT population, the CEC adjudicated 9 subjects to have experienced primary safety events [6.2% (9/145)]. Six (6) subjects had major strokes within 30 days and three (3) subjects sustained a major ipsilateral stroke with one subject who expired from a major ipsilateral stroke (neurological death) between 31 and 425 days post-procedure. There was one (1) subject who had a major stroke within 30 days that was counted as a primary safety endpoint failure. This subject died at day 77 from a gastric hemorrhage. Although this subject was not adjudicated as a neurological death between 31-435 days post-operative, this subject was adjudicated to be a primary safety endpoint failure from having a major stroke within 30 days. The mean of the posterior distribution of the pre-specified primary safety endpoint at 12 months post-procedure is 6.8% with an equitailed 95% credible interval (CI) of 3.3% to 11.3%. The upper bound of the CI was less than the 15% safety PG specified for the FRED study. All of the primary safety endpoint events were observed in patients treated with unruptured IAs.

Table 9: Primary Safety Endpoint Events through 12 Months - mITT Population

Pre-Specified Primary Safety Endpoint	**N=145 n (%)**	**Posterior Mean (95% CI)**	**Posterior Probability[3]**
Pre-specified Primary Safety Endpoint [1]	9 (6.2%)	6.8% (3.3%, 11.3%)	0.999
Primary safety components[2]			
Major stroke within 30 days	6 (4.1%)	4.8% (1.9%, 8.7%)	
Death within 30 days	0 (0%)	0.7% (0.0%, 2.5%)	
Major ipsilateral stroke 31-425 days	3 (2.1%)	2.7% (0.7%, 5.8%)	
Neurological death 31-425 days	1 (0.7%)	1.4% (0.2%, 3.7%)	

[1] Pre-specified primary safety endpoint defined as rate of death or major stroke within 30 days or neurologic death or major ipsilateral stroke within 12 months.
[2] Subject may have more than one failed safety component. One subject with major ipsilateral stroke expired from neurological death. Also, one subject with a major stroke within 30 days died at day 77 from a gastric hemorrhage. All subjects with primary safety endpoint events were those with unruptured IAs treated with the FRED® System. There were no primary safety endpoint events in the 8 subjects in the FRED study with a previously ruptured IA.
[3] Posterior probability that the primary safety endpoint event rate is < 15%.

There were 11 subjects in the FRED study who did not have 12-month follow-up safety data available. Of these 11 subjects, there were 2 deaths, 5 subjects who withdrew from the study, and 4 subjects lost-to-follow-up. The primary safety endpoint analysis presented in Table 9 accounts for 4 of the 11 missing data subjects because they had a primary safety endpoint event. Table 9 does not account for the additional 7 missing data subjects as primary safety endpoint failures.

Table 10 presents the baseline and 12-month mRS scores on all subjects in the mITT population (N=145) to evaluate the long-term clinical outcomes and changes in disability experienced as a result of endovascular treatment with the FRED® System for subjects with unruptured IAs. There were 10 subjects with missing mRS scores; therefore, the evaluation in the change of the mRS between the 12-month and baseline assessments could not be determined in these subjects. In the 135 subjects with available mRS data, the majority of subjects (71.1% (96/135)) experienced no change in the mRS scores during the course of the study up to 12-months post-operative. The mRS score improved in 17% (23/135) of subjects at 12 months compared to their baseline mRS. The mRS score worsened in 11.9% (16/135) of subjects at 12 months compared to their baseline mRS pre-treatment.

Table 10: Change in Modified Rankin Scale (mRS) Score through 12-Month Follow-Up Compared to Baseline – mITT Population (N=145)

12-Month Follow-up: Each cell indicates score frequency at 12-month follow-up relative to baseline score frequency. Gray shaded cells show subjects who worsened.
ND = No Data Available

Baseline	ND	0	1	2	3	4	5	6	Total
0	4	90	6	1	1	1	0	0	103
1	6	15	5	3	0	1	0	1	31
2	0	5	2	0	0	1	0	1	9
3	0	0	0	1	1	0	0	0	2
4	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0
Total	10	110	13	5	2	3	0	2	145

Of the 145 subjects in the mITT population, there were only 6 subjects with IAs located in the posterior circulation of the neurovasculature. Based on the recommendations of the April 17, 2015, meeting of the Neurological Devices Panel (the "Panel") of the Medical Devices Advisory Committee, the Panel recommended that IAs in the anterior and posterior circulations of the neurovasculature are not poolable and have different safety and effectiveness profiles and considerations. Therefore, conclusions cannot be made on the safety and effectiveness of the FRED® System for use in the treatment of IAs located in the posterior circulation of the neurovasculature. New post-hoc primary endpoint analyses were performed to remove subjects with IAs located in the posterior circulation (n=6) due to the lack of sample size to make any clinically meaningful conclusions. There were five (5) primary safety endpoint failures for subjects with IAs located in the communicating segment of the ICA to the A1 or M1 segment. Subjects with IAs located in the communicating segment of the ICA to the A1 or M1 segment were individually assessed for those who had IAs only in the ICA up to the terminus (20/24) to further identify those subjects in which benefit of treatment with the FRED® System may outweigh the risks. Based on this new modified ICA population that only includes subjects in the mITT population with IAs in the petrous segment of the ICA up to the terminus, the final indications for use for the FRED® System was modified to:

"The Flow Re-Direction Endoluminal Device (FRED®) System is indicated for use in the internal carotid artery from the petrous segment to the terminus for the endovascular treatment of adult patients (22 years of age or older) with wide-necked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform intracranial aneurysms arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 mm."

The modified post-hoc primary safety endpoint analysis based on the ICA population (N=135) is presented in Table 11 below. In the ICA population, 5.9% (8/135) of subjects were primary safety endpoint failures. Five (5) subjects had major strokes within 30 days, three (3) subjects sustained a major ipsilateral

stroke with one subject who expired from a major ipsilateral stroke (neurological death) between 31 and 425 days post-procedure. One of the subjects who had a major stroke within 30 days that was counted as a primary safety endpoint failure died at day 77 from a gastric hemorrhage. The mean of the posterior distribution of the primary safety endpoint at 12 months post-operative is 6.6% with an equitailed 95% CI of 3.1% to 11.3%. The upper bound of the CI was less than the 15% safety PG specified for the FRED study. With the post-hoc analyses of the primary endpoints based on the ICA population, the FRED study still had adequate power (80%) to make conclusions from the study data from a statistical perspective.

Table 11: Post-hoc Analysis of the Primary Safety Endpoint through 12 Months - ICA Population (N=135)

Primary Safety Endpoint	**N=135 n (%)**	**Posterior Mean (95% CI)**	**Posterior Probability[3]**
Primary Safety Endpoint [1]	8 (5.9%)	6.6% (3.1%, 11.3%)	0.999
Primary safety components[2]			
Major stroke within 30 days	5 (3.7%)	4.4% (1.6%, 8.4%)	
Death within 30 days	0 (0%)	0.7% (0.0%, 2.7%)	
Major ipsilateral stroke 31-425 days	3 (2.2%)	2.9% (0.8%, 6.3%)	
Neurological death 31-425 days	1 (0.7%)	1.4% (0.2%, 4.0%)	

[1] Primary safety endpoint defined as rate of death or major stroke within 30 days or neurologic death or major ipsilateral stroke within 12 months.
[2] Subject may have more than one failed safety component. One subject with major ipsilateral stroke expired from neurological death. Also, one subject with a major stroke within 30 days died at day 77 from a gastric hemorrhage. All subjects with primary safety endpoint events were those with unruptured IAs treated with the FRED® System. There were no primary safety endpoint events in the 8 subjects in the FRED study with a previously ruptured IA.
[3] Posterior probability that the primary safety endpoint event rate is < 15%.

The incidence of all cerebrovascular events in the ICA population is presented in Tables 12 and 13.

Table 12: Cerebrovascular Events (Death or Major/Minor Ischemic or Hemorrhagic Stroke) – ICA Population

Event	**N=135 % (n/N)**
Neurological death	0.7% (1/135)
Major stroke (ischemic or hemorrhagic)	5.9% (8/135)[1]
Minor stroke (ischemic or hemorrhagic)	5.9% (8/135)[1]
Any of the above	10.4% (14/135)[2]

[1] Two subjects experienced both major and minor strokes.
[2] One subject experienced stroke and then neurological death. One subject experienced a major stroke within 30 days and died at day 77 from a gastric hemorrhage.

Table 13: Cerebrovascular Events (Transient Ischemic Attack) – ICA Population

Event	N=135 % (n/N)
TIA (Transient Ischemic Attack)	5.2% (7/135)

Adverse effects that occurred in the PMA clinical study:

Table 14 presents the serious adverse events and non-serious adverse events that were observed through 12 months in the FRED pivotal clinical study that were adjudicated by the CEC.

Table 14: Adverse Events with > 1% Overall Frequency Through 12 Months Post-Procedure by Medical Dictionary for Regulatory Activities (MedDRA) Codes – mITT Population (N=145)

MedDRA Classification		Serious Adverse Events	Non-Serious Adverse Events	All Adverse Events*
System/Organ Class	Preferred Term	% (n) [events]	% (n) [events]	% (n) [events]
Blood and lymphatic system disorders	Anemia	0.7% (1) [1]	2.1% (3) [3]	2.8% (4) [4]
	Coagulopathy	0	1.4% (2) [2]	1.4% (2) [2]
Cardiac disorders	Arrhythmia	1.4% (2) [3]	2.1% (3) [3]	2.8% (4) [6]
Eye disorders	Visual impairment	1.4% (2) [2]	7.6% (11) [16]	9.0% (13) [18]
Gastrointestinal disorders	Diverticulum	0	1.4% (2) [2]	1.4% (2) [2]
	Nausea	0	2.1% (3) [3]	2.1% (3) [3]
	Rectal hemorrhage	0	1.4% (2) [2]	1.4% (2) [2]
	Vomiting	0	1.4% (2) [2]	1.4% (2) [2]
General disorders and administration site conditions	Chest pain	0.7% (1) [1]	2.1% (3) [3]	2.8% (4) [4]
	Device dislocation	0.7% (1) [1]	0.7% (1) [1]	1.4% (2) [2]
	Device failure	4.1% (6) [6]	2.1% (3) [3]	6.2% (9) [9]
	Fatigue	0	2.1% (3) [3]	2.1% (3) [3]
	In-stent cerebral artery stenosis	0.7% (1) [1]	2.1% (3) [3]	2.8% (4) [4]
	Puncture site hemorrhage	0.7% (1) [1]	3.4% (5) [5]	4.1% (6) [6]
	Thrombosis in device	6.9% (10) [10]	0	6.9% (10) [10]
Infections and infestations	Cellulitis	0.7% (1) [1]	0.7% (1) [1]	1.4% (2) [2]
	Nasopharyngitis	0	1.4% (2) [3]	1.4% (2) [3]
	Pneumonia	1.4% (2) [2]	0	1.4% (2) [2]
	Tooth abscess	0	1.4% (2) [2]	1.4% (2) [2]
	Urinary tract infection	1.4% (2) [2]	6.2% (9) [9]	7.6% (11) [11]
Injury, poisoning and procedural	Contusion	0	2.8% (4) [4]	2.8% (4) [4]
	Endotracheal	0	1.4% (2) [2]	1.4% (2) [2]

MedDRA Classification		Serious Adverse Events	Non-Serious Adverse Events	All Adverse Events*
System/Organ Class	**Preferred Term**	**% (n) [events]**	**% (n) [events]**	**% (n) [events]**
complications	intubation complication			
	Incision site hemorrhage	0	1.4% (2) [2]	1.4% (2) [2]
Musculoskeletal and connective tissue disorders	Arthralgia	0	2.1% (3) [3]	2.1% (3) [3]
	Back pain	0	1.4% (2) [2]	1.4% (2) [2]
	Muscular weakness	1.4% (2) [2]	0	1.4% (2) [2]
	Neck pain	0	1.4% (2) [2]	1.4% (2) [2]
Nervous system disorders	Cerebral hemorrhage	2.1% (3) [3]	0	2.1% (3) [3]
	Cerebrovascular accident	4.1% (6) [6]	0	4.1% (6) [6]
	Cognitive disorder	0	1.4% (2) [2]	1.4% (2) [2]
	Diplopia	0	2.8% (4) [4]	2.8% (4) [4]
	Dizziness	0	2.1% (3) [3]	2.1% (3) [3]
	Eyelid ptosis	0.7% (1) [1]	0.7% (1) [1]	1.4% (2) [2]
	Headache	0.7% (1) [1]	29.7% (43) [45]	29.7% (43) [46]
	Ischemic stroke	2.8% (4) [4]	0	2.8% (4) [4]
	Sciatica	0	1.4% (2) [2]	1.4% (2) [2]
	Seizure	1.4% (2) [2]	0	1.4% (2) [2]
	Transient ischemic attack	3.4% (5) [5]	1.4% (2) [3]	4.8% (7) [8]
Psychiatric disorders	Depression	0.7% (1) [1]	1.4% (2) [2]	2.1% (3) [3]
Renal and urinary disorders	Acute kidney injury	0.7% (1) [1]	0.7% (1) [1]	1.4% (2) [2]
Respiratory, thoracic and mediastinal disorders	Epistaxis	0	2.1% (3) [3]	2.1% (3) [3]
	Pulmonary embolism	1.4% (2) [2]	0	1.4% (2) [2]
Surgical and medical procedures	Aneurysm repair	7.6% (11) [11]	0	7.6% (11) [11]
Vascular disorders	Carotid artery dissection	0	2.1% (3) [3]	2.1% (3) [3]
	Hematoma	0.7% (1) [1]	6.2% (9) [9]	6.9% (10) [10]
	Hypertension	0	2.1% (3) [3]	2.1% (3) [3]
	Vasospasm	0	11.0% (16) [17]	11.0% (16) [17]

*Some subjects may have experienced both serious and non-serious adverse events.

2. Effectiveness Results

The analysis of effectiveness was based on the 135 evaluable patients at the 12-month time point in the ICA population per the final indications for use. Key effectiveness outcomes are presented in Table 15.

Table 15: Primary Effectiveness Endpoint Analysis through 12 Months – ICA Population with Imputed Data (N=135)

Endpoint	**%[2]**	**Posterior Mean (95% CI)**	**Posterior Probability[1]**
Primary effectiveness[3]	56.7%	56.6% (48.2%, 64.7%)	0.993

[1] Posterior probability that the primary effectiveness endpoint success rate is > 46%.
[2] Missing data at 12-months from subjects who died, withdrew from the study, lost-to-follow-up, unevaluable or missing imaging (n=14) were imputed per Firth's method of penalized logistic regression.
[3] Primary effectiveness endpoint was defined as the proportion of subjects with Raymond-Roy I IA occlusion with ≤ 50% parent artery stenosis and no re-treatment of the target IA within 12 months post-operative.

In the ICA population, the primary effectiveness success rate was 56.7%. Using a worst-case analysis of the primary effectiveness endpoint without imputation for missing data subjects at 12-months follow-up, the primary effectiveness endpoint rate was 54.8% (74/135) for the ICA population.

Table 16 below shows the number of FRED® stents implanted per subject. The majority of subjects (93.1%, 135/145) had a single device deployed.

Table 16: Number of FRED® Stents Placed per Subject in FRED Clinical Study

Characteristic	**Value**
Devices per subject (total subjects = 145)	
Subjects with one device deployed	135 (93.1%)
Subjects with two devices deployed	9 (6.4%)
Subjects with three devices deployed	1 (0.7%)

3. Subgroup Analyses

The following preoperative characteristics were evaluated for potential association with outcomes: age, IA size, and IA location. The subgroup analysis for age was categorized as < 60 years old, 60-69 years old, and ≥ 70 years old. The subgroup analysis for IA size was categorized as < 10 mm, 10-24.9 mm, and ≥ 25 mm. The subgroup analysis for IA location was categorized as anterior vs. the posterior circulation of the neurovasculature. None of the subgroup analyses showed any significant differences in the primary endpoint outcomes between the different subgroups for age, IA size, or IA location. There were limitations in this subgroup analysis because some of the subgroup populations had very limited

samples sizes such as the posterior (N=6) vs. the anterior circulation of the neurovasculature (N=139) to make meaningful clinical or statistical conclusions.

4. Pediatric Extrapolation

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

E. Financial Disclosure

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 46 investigators of which none were full-time or part-time employees of the sponsor and 13 had disclosable financial interests/arrangements as defined in 21 CFR 54.2(a), (b), (c) and (f) and described below:

- Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0
- Significant payment of other sorts: 13
- 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. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not applicable.

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

In accordance with the provisions of section 515(c)(3) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Neurological Devices Panel (the "Panel"), an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

The FDA previously convened a general issues meeting on March 1, 2018, of the Neurological Devices Panel (the "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 Panel at the March 1, 2018, meeting was considered during the review of this PMA. The background and meeting materials for the March 1, 2018, general issues meeting can be accessed at the following link: https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm598450.htm.

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

XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

The primary effectiveness endpoint was analyzed individually for the number of patients in the ICA population (N=135 subjects). The ICA population consists of the mITT patients who had IAs treated in the FRED study that were located in the ICA from the petrous segment to the terminus. Patients with IAs located in the posterior circulation of the neurovasculature (N=6) and patients with IAs located in the communicating segment of the ICA to A1 and M1 segments that were not within the ICA were excluded (N=4) from the mITT population of 145 patients because of weighing the benefits and risks of treatment and the lack of adequate sample size of posterior circulation IAs to make conclusions on the safety and effectiveness of the FRED® System for these patients.

Based on a worst-case analysis of the primary effectiveness endpoint without imputation for missing data subjects for the ICA population, the primary effectiveness endpoint rate was 54.8% (74/135) for the proportion of patients in the FRED study with complete (100%) occlusion of the treated IA as determined by the Raymond-Roy I classification with ≤ 50% parent artery stenosis and no re-treatment of the target IA within 12-months post-operative. Therefore, the FRED pivotal study met the primary effectiveness endpoint success criteria at one year of 46%.

B. Safety Conclusions

The risks of the device are based on non-clinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA approval as described above. The primary safety endpoint was analyzed based on the mITT and ICA populations for the proportion of patients who experienced death or major stroke within 30 days, or neurological death or major ipsilateral stroke within 12-months post-procedure. The primary safety events of stroke and neurological death are the most significant adverse events to assess the device safety for the treatment of wide-necked 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 FRED study for the mITT population was 6.2% (9/145), with a posterior mean and 95% CI of 6.8% and 3.3% to 11.3%, respectively. The nine (9) primary safety endpoint events consisted of 6 subjects who had a major stroke within 30 days and 3 subjects who suffered a major ipsilateral stroke between 31-425 days post-operative resulting in a neurological death for one of these three subjects. The primary safety endpoint rate for the ICA population was 5.9% (8/135). These analyses of the primary safety endpoint was not performed using the worst-case analysis accounting for all missing subjects as primary safety endpoint failures. Based on the primary safety endpoint analyses, the FRED study met the 15% PG.

Also, in the ICA population, the proportion of all subjects who experienced a neurological death or major or minor ischemic or hemorrhage stroke was 10.4% (14/135). The proportion of subjects in the ICA population who experienced a transient ischemic attack was 5.2% (7/135). 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 145 patients in the FRED study (mITT population), 11.9% (16/135, 10 subjects did not have paired mRS readings) had a worsening of the mRS at 12-months post-procedure compared to their baseline mRS.

C. Benefit-Risk Determination

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA approval as described above. The primary effectiveness endpoint without imputation for missing data subjects for the ICA population was 54.8% (74/135) for the proportion of patients in the FRED study with complete (100%) occlusion of the treated IA as determined by the Raymond-Roy I classification with ≤ 50% parent artery stenosis and no re-treatment of the target IA within 12-months post-procedure.

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 FRED study for the mITT population was 6.2% (9/145), with a

posterior mean and 95% CI of 6.8% and 3.3% to 11.3%, respectively. The nine (9) primary safety endpoint events consisted of 6 subjects who had a major stroke within 30 days and 3 subjects who suffered a major ipsilateral stroke between 31-425 days post-operative resulting in a neurological death for one of these three subjects. There was one (1) subject who had a major stroke within 30 days that was counted as a primary safety endpoint failure who was confirmed to have died at day 77 from a gastric hemorrhage. The primary safety endpoint rate for the ICA population was 5.9% (8/135). Of the 145 patients in the FRED study (mITT population), 11.9% (16/135, 10 subjects did not have paired mRS readings) had a worsening of the mRS at 12-months post-procedure compared to their baseline mRS.

The results of the FRED study are comparable to the SCENT study used to support PMA approval of the Surpass Streamline Flow Diverter (P170024). In the SCENT study, the results showed that 62.8% (113/180) of mITT patients met the primary effectiveness endpoint. The SCENT trial primary safety endpoint defined as the proportion of patients who experienced a major ipsilateral stroke or neurological death within 12-months post-procedure was 10.6% (19/180). Both the FRED and SCENT studies enrolled either predominantly or all patients with large or giant wide-necked IAs. The SCENT trial enrolled 100% of patients with wide-necked IAs greater than 10 mm and the FRED study enrolled 73.1% (106/145) of patients with large or giant IAs ≥ 10 mm. These types of IAs typically have the highest risk for rupture and are the most difficult to treat.

Additional factors to be considered in determining probable risks and benefits for the FRED® 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, patient age, and the patient co-morbidities (e.g., high blood pressure, family history, multiple aneurysms, diabetes). Based on natural history, it has been suggested that intracranial aneurysms have an average rupture rate of around 1% per year in patients with a diagnosed intracranial aneurysm, although that number can vary based on the study (Ishibashi et al. 2009; Juvela et al. 2013). Size and location of the intracranial aneurysm can also affect the risk of rupture. In the article by Wiebers (2003), intracranial aneurysms in the ICA, anterior communicating artery (AComm), anterior cerebral artery (ACA), or middle cerebral artery (MCA) that were < 7 mm, 7-12 mm, 13-24 mm, and > 25 mm had rupture rates of 0%, 2.6%, 14.5%, and 40%, respectively, at 5 years. 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 subarchnoid hemorrhage (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 significant co-morbidities, high risk of IA rupture, 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 may provide a safe and effective treatment option for the indicated use in the ICA from the petrous segment to the terminus for the endovascular treatment of adult patients (22 years of age or older) with wide-necked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform intracranial aneurysms arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 mm.

Additional factors to be considered in determining probable risks and benefits for the FRED® System includes some uncertainty based on the single arm pivotal trial design that may introduce some bias in patient selection for treatment and assessment of outcomes because there was no blinding or randomized concurrent control group. Since there was no active control arm in the pivotal study, there are uncertainties of whether the subject device treatment may be more or less beneficial or more or less safe than alternative treatment modalities for the proposed indicated patient population. In addition, it is unclear whether there may have been some bias in subject selection for treatment with the FRED® System to result in better clinical outcomes. Furthermore, the FRED trial did not utilize an independent vascular neurologist to perform the mRS assessments; therefore, there may be some bias introduced in the mRS scores presented. Lastly, the FRED trial only enrolled 18 patients with fusiform IAs (12.4%, 18/145). Although there was a small sample size of patients with fusiform IAs, there are limited alternative treatment options for these patients because it is difficult to treat these subjects with endovascular treatment using neurovascular embolic coils and patients may not be eligible or the risks may be too great for open surgical clipping dependent on the location of the fusiform IA. Therefore, treatment with a neurovascular flow diverting stent such as the FRED® System is a reasonable option for patients with fusiform IAs considering the benefits and risks of alternative treatment options for these patients. The IFU statement for the FRED® System includes the use of the device for fusiform IAs and a precaution was added to the labeling that advises the clinical user that the safety and effectiveness of the subject device has not been established in patients with fusiform IAs based on the FRED pivotal trial.

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 the indications for use of the FRED® System in the ICA from the petrous segment to the terminus for the endovascular treatment of adult patients (22 years of age or older) with wide-necked (neck width ≥ 4 mm or dome-to-neck ratio < 2) saccular or fusiform intracranial aneurysms arising from a parent vessel with a diameter ≥ 2.0 mm and ≤ 5.0 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 patient population. The majority of subjects enrolled and treated in the FRED study had large or giant wide-necked IAs with a higher risk of rupture in the patient's life time. While there are still risks involved with the use of the device, including major strokes and death (i.e., 6.2% (9/145)), the benefits include that 54.8% (74/135) of the ICA patient population in the FRED study had complete (100%) occlusion of the treated IA as determined by the Raymond-Roy I classification with ≤ 50% parent artery stenosis and no re-treatment of the target IA within 12-months post-operative. Based on these results, the FRED® System can be another treatment option available for the indicated patient population.

XIV. CDRH DECISION

CDRH issued an approval order on December 16, 2019.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

Ishibashi, T., et al. Unruptured Intracranial Aneurysms Incidence of Rupture and Risk Factors. Stroke 2009; 40(1):313-16.

Juvela, S., et al. Natural History of Unruptured Intracranial Aneurysms: A Long-Term Follow-Up Study. Stroke 2013; 44(9):2414-21.

Roy, D., et al. Endovascular Treatment of Unruptured Aneurysms. Stroke. 2001; 32(9):1998-2004.

Shapiro, M., et al. Stent-Supported Aneurysm Coiling: A Literature Survey of Treatment and Follow-up. Am J Neuroradiol. 2012; 33(1):159-163.

Surpass Streamline Flow Diverter (P70024), Stryker Neurovascular, "Summary of Safety and Effectiveness Data (SSED)," https://www.accessdata.fda.gov/cdrh_docs/pdf17/P170024B.pdf.

Wiebers, D.O. Unruptured Intracranial Aneurysms – Risk of Rupture and Risks of Surgical Intervention. New England Journal of Medicine 1998; 339(24):1725-33.

Wiebers, D.O. Unruptured Intracranial Aneurysms: Natural History, Clinical Outcome, and Risks of Surgical and Endovascular Treatment. The Lancet 2003; 362(9378):103-10.