SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: Intracranial Aneurysm Flow Diverter

Device Trade Name: Pipeline™ Embolization Device

Applicant's Name and Address: ev3 Inc.
173 Jefferson Drive
Menlo Park, CA 94025

Date(s) of Panel Recommendation: March 18, 2011

Premarket Approval Application (PMA) Number: P100018

Date of FDA Notice of Approval: April 06, 2011

Expedited: Granted on June 16, 2010 because the device will be used to treat a life-threatening condition, its technology and treatment approach are significantly different from the available options for the condition and it appears to provide a clinically significant advantage compared to current treatment options.

II. INDICATIONS FOR USE

The Pipeline™ Embolization Device is indicated for the endovascular treatment of adults (22 years of age or older) with large or giant wide-necked intracranial aneurysms (IAs) in the internal carotid artery from the petrous to the superior hypophyseal segments.

III. CONTRAINDICATIONS

Use of the Pipeline™ Embolization Device is contraindicated in:

- Patients with active bacterial infection
- Patients in whom antiplatelet therapy is contraindicated
- Patients who have not received dual antiplatelet agents prior to the procedure
- Patients in whom a pre-existing stent is in place in the parent artery at the target aneurysm location

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Pipeline™ Embolization Device labeling.

V. DEVICE DESCRIPTION

The Pipeline Embolization Device™ (PED) consists of a permanent implant combined with a guidewire-based delivery system.

The PED implant is a braided, multi-alloy, mesh cylinder woven from Platinum/8% Tungsten and 35NLT (cobalt chromium nickel) alloy wires. The woven wires of the device provide nominally 30-35% metal coverage of the arterial wall surface area. Radial wall pressures are in the 1-7 mmHg range for the entire device when it is expanded to the labeled diameters. PED is provided with the implant mounted on a 304 stainless steel guidewire and compressed inside an introducer sheath (Figure 1a, 1b). It may be deployed using commercially available 3F (0.027 inch inner diameter) microcatheters.

The PED delivery system is a 175 - 190 cm micro-guidewire-based technology. The core wire is 304SS with a polytetrafluoroethylene coating. The tip and protective coils are made of platinum-tungsten alloy, the proximal marker a platinum-iridium alloy, and the distal, mid and proximal solder joints are a tin-silver mixture. The protective coil is designed to hold PED in the collapsed state until the operator deploys PED. Rotating the proximal delivery wire "unscrews" the coil from the distal tip of PED, allowing it to spontaneously expand into the parent artery. Other than being held in place by the protective coil, PED is not physically attached to the guidewire. The proximal pusher allows the user to push PED out of the microcatheter when the wire is advanced. A proximal marker soldered to the core wire allows for localization.

PED implant is available in diameters from 2.5 to 5.0 mm and lengths from 10 to 35 mm. Table 1 shows the available sizes of the PED. The expanded or un-constrained diameter is 0.25 mm larger than the labeled diameter.

Please see the Operator's Manual for deployment details.

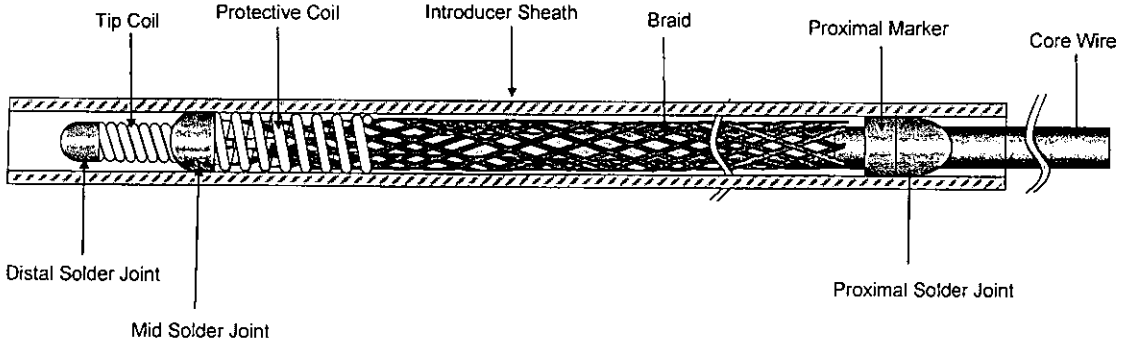

Figure 1a: The Pipeline Embolization Device.

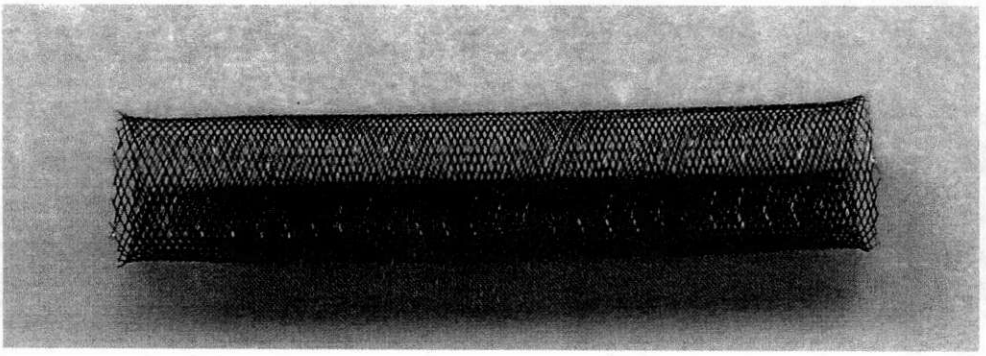

Figure 1b: The Pipeline Embolization Device.

Table 1. Size range of PEDs

Labeled Diameter (mm)	Self Expanded Diameter (mm)	Labeled Lengths (mm)
2.5	2.75	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35
2.75	3.00	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35
3.0	3.25	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35
3.25	3.50	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35
3.5	3.75	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35
3.75	4.00	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35
4.0	4.25	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35
4.25	4.50	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35
4.5	4.75	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35
4.75	5.00	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35
5.0	5.25	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 25, 30, 35

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several alternatives for the treatment of wide-necked intracranial aneurysms. 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. Surgical approaches to the treatment of wide-necked intracranial aneurysms include clipping and trapping or wrapping. A bypass may be required with some surgical procedures. Endovascular approaches to the treatment of wide-necked intracranial aneurysms include placement of embolic coils or liquid embolic material into the fundus of the aneurysm, stent-assisted coiling and parent vessel occlusion. If left untreated, aneurysms can rupture, causing death or significant permanent morbidity.

VII. MARKETING HISTORY

PED is approved for marketing in the following countries: Argentina, Australia, Austria, Belgium, Bulgaria, Canada, Chile, Columbia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, Iran, Ireland, Israel, Italy, Jordan, Latvia, Lebanon, Lithuania, Luxembourg, Malaysia, Malta, Netherlands, New Zealand, Peru, Philippines, Poland, Portugal, Romania, Russia, Saudi Arabia, Singapore, Slovakia, Slovenia, South Africa, Spain, Sweden, Thailand, Tunisia, Turkey, United Arab Emirates, United Kingdom, Uruguay, Venezuela, and Vietnam.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

The following are potential adverse effects of the use of PED, the PED placement procedure and general anesthesia, some of which can be fatal.

- Bleeding, including intracerebral, retroperitoneal or in other locations
- Blindness
- Complications of arterial puncture including pain, local bleeding, local infection and injury to the artery, vein or adjacent nerves
- Confusion, coma or other change in mental status
- Cranial neuropathy
- Device fracture, migration or misplacement
- Dissection or perforation of the parent artery
- Embolism of air, blood clots, cholesterol fragments or device components
- Headache
- Hydrocephalus
- Infection
- Mass effect
- Neurologic deficits
- Perforation or rupture of aneurysm sac or parent artery
- Reactions to antiplatelet/anticoagulant agents
- Reactions due to radiation exposure
- Reactions to anesthesia and related procedures
- Reactions to contrast agents including allergic reactions and renal failure

- Seizure
- Stenosis or thrombosis of the parent artery within PED or a branch vessel covered by PED
- Transient ischemic attack (TIA) or ischemic stroke
- Vasospasm
- Visual impairment

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

IX. SUMMARY OF PRECLINICAL STUDIES

The PED underwent rigorous mechanical, functionality, biocompatibility, and animal tests to evaluate its suitability for deployment and as a long term implant in the neurovasculature. The device was found to have a 3-year shelf-life in package and ageing tests. The device is sterilized by ethylene oxide with a sterility assurance level that exceeds 10^{-6}. The PED was found to be suitable for use in humans based on preclinical testing results.

The following tables summarize the preclinical tests that were performed with PED.

Table 2. Laboratory Studies

Test	Purpose	Acceptance Criteria	Results
Material characterization	Determine if materials are suitable for implant	Blood path contact – implant - platinum-tungsten (Pt/W 92%/8%) and nickel-cobalt-chromium alloy wire (ASTM F562). Core wire – 304 SS coated with PTFE*	Pass Materials found to be biocompatible
Dimensional verification	Device must conform to aneurysm location and anatomy, remain in specification after simulated use in vasculature model, have adequate surface area coverage	2.50 - 5.0 mm dia 10-35 mm lengths. Minimum 20% surface area coverage, picks-per-inch criteria (PPI), # of wire crossing per inch in axial direction	Pass N = 40 tested Dimensions met labeled requirements and surface area 27.1-30.7%
PED integrity	PED must remain intact after deployment through catheter	PED free of kinks or bends and PPI uniform after deployment	Pass N = 40 tested
Delivery and deployment tests	PED must be able to be deployed through 0.027 in ID catheter in	Benchtop vasculature model, access, positioning, stability,	Pass N = 40 tested

Test	Purpose	Acceptance Criteria	Results
	neurovasculature	migration, visual inspection for PED integrity	
Delivery system corrosion, tensile strength and particulate	Delivery system used to deliver PED must pass tensile tests, coating integrity, corrosion testing	No visual corrosion, adequate tensile strength, particles meet USP <788>	Pass
Foreshortening	Device axial length should be adequate when deployed, % difference between in-catheter length and deployed length	Proprietary Deployed device must meet labeled size specification and have designed area coverage	Pass N = 55 tested
Radial pressure test	Device exerts enough radial pressure so that it does not migrate in body when implanted in largest recommended vessel size, device will not injure vasculature. The device is not designed to support artery open as with a stent	Proprietary Pressure adequate to prevent device migration	Pass N = 5 tested of each available size
PED material tensile strength	Mechanical strength adequate in raw material and post-processing	Ultimate tensile strength, yield strength, % elongation	Pass N = 10 tested for each wire diameter
Stress analysis	Determine if stresses do not exceed material limits during deployment and long-term use as implant, finite element model used to evaluate stresses	Von Mises stresses were below limits on Goodman plot	Pass
Durability test	Accelerated durability testing to 400 million cycles (10-year life) to simulate pulsing in neurovasculature	No wire failures	Pass, N = 36 tested, no wire fatigue failures were observed
Corrosion resistance	Materials must have at least 10-year life (400 million cycles)	ASTM F2129 Cyclic Potentiodynamic tests – pitting corrosion resistance in phosphate buffered saline (PBS) ASTM G71-81 Galvanic corrosion tests – meet minimum corrosion current	Pass N = 3 tested ASTM 2129 N = 5 tested ASTM G71-81 Minimal fretting observed

Test	Purpose	Acceptance Criteria	Results
		Fretting corrosion tests – 400 million cycles in PBS – no stress cracking, minimum fatigue fractures	
MRI compatibility	Device must be MRI compatible to assure this diagnostic procedure for patients with aneurysms	No significant deflection, attraction, torque and heating during MRI ASTM 2052-06 ASTM 2182-02a	Pass N = 5 tested MRI artifact within 2-3 mm of implant, minimal heating 0.6 deg C at 3.0 T for 80 kg patient
Radiopacity	Device should be visible under fluoroscopy	Likert scale criteria ≥ 3 Animal and benchtop model	Pass N = 32 tested Device exceeds criteria, verified in PITA** study

*PTFE; Poly(tetrafluoroethylene);
**PITA; Pipeline for Intracranial Treatment of Aneurysms

Table 3. Biocompatibility

Test	Purpose	Acceptance Criteria	Results
Acute systemic toxicity	Test for systemic acute toxicity in mice following intravenous and intraperitoneal injections	Injections must not cause the following: •2 grams weight loss in 3+ animals •Mortality o Abnormal clinical signs	Pass
Lymph Node Assay for sensitization	Test for allergenic potential or sensitization capacity of test article	Stimulation Index <3.0	Pass
Acute intracutaneous reactivity	Test for irritation potential	Primary Irritation Index < 1.0)	Pass
Genotoxicity: Bacterial reverse mutation study	Test for mutagenic changes. Based on OECD* Guidelines.	Mean number of revertants ≤2-fold negative control	Pass
Cytotoxicity	Test for cell lysis	≤Grade 2 lysis	Pass
Hemolysis	Test for red blood cell lysis	Non-hemolytic (0-2% hemolytic index).	Pass
Genotoxicity: In-vitro	Test for clastogenecity, i.e., structural changes to	No significant increase in	Pass

Test	Purpose	Acceptance Criteria	Results
chromosomal aberration study in mammalian cells	chromosomes	chromosome aberrations	
Mouse peripheral blood micronucleus study	*In vivo* test for clastogenecity, i.e., structural changes to chromosomes	No significant increase in chromosome aberrations	Pass
ASTM Partial thromboplastin time	Test for effect on intrinsic pathway of coagulation cascade	≥ 50% result of the negative control	Pass
C3a Complement activation assay	Test for component activation	No activation of complement system via C3a	Pass
SC5b-9 Complement activation assay	Test for activation of SC5b-9, a component of complement activation	No activation of complement system via SC5b-9	Pass

*OECD;Organization for Economic Cooperation and Development

Table 4. Animal Studies

Test	Purpose	Acceptance Criteria	Study Model / Results
Acute delivery in rabbits with elastase-induced surgical aneurysms	Assess PED performance (deliverability) into parent artery affected by aneurysm	Adequate radiopacity, flow disruption, ease of use, vessel patency, distal access, accuracy in placement and anchoring	Pass PED easily placed in parent artery across aneurysm.
Acute delivery in pigs	Assess PED compatibility with catheter, deliverability, radiopacity, expansion, anchoring, side branch patency	Adequate radiopacity, flow disruption, ease of use, vessel patency, distal access, accuracy in placement and anchoring	Pass PED compatible with microcatheter, easily delivered into target vessel, sufficient radiopacity, expanded well and anchored. Covered side branches patent.
Acute delivery in rabbits with elastase-induced surgical aneurysms	Assess PED deliverability, radiopacity, compatibility with catheter, detachment,	Avg score <3 of 5 for access, compatibility, and ease of use, 100% score for radiopacity, expansion, accuracy, anchoring, flow	Pass PED compatible with microcatheter, easily delivered into target

Test	Purpose	Acceptance Criteria	Study Model / Results
	expansion, migration, flow disruption and side branch patency	disruption, patency of side branches	vessel, sufficiently radiopaque, expanded well, anchored well without distal migration. Covered side branches patent.
Chronic outcomes from PED in elastase-induced surgical aneurysms in rabbits	Assess PED effectiveness to occlude elastase-induced surgical aneurysms at 1, 3 and 6 months, parent artery injury by histological score, histology of aneurysm	Histological evidence of healing response, endothelialization, and side branch patency at all time points	Pass High rate of aneurysm occlusion with single PED. Low artery injury scores histologically. No migration or stenosis in parent vessel. All covered side branches patent.
Chronic outcomes from PED placement in rabbits	Assess angiographic and histologic patency of side branches of rabbit abdominal aorta covered by 1, 2 or 3 PEDs at 6 and 12 months	Side branches patent angiographically and histologically, low injury scores, evidence of neoendothelialization	Pass At 6 and 12 months, lumbar arteries covered by 1, 2 or 3 PEDs were patent angiographically and histologically. Histology consistent with neointimal growth. Very low injury scores.

Table 5. Additional Studies

Test	Acceptance Criteria	Results	Analysis Type
Shelf life Testing			
Device performance	Device meets performance specifications after 3-year accelerated aging	Pass	Variables & Attribute
Packaging integrity	Packaging integrity is maintained after 3-year accelerated aging	Pass	Variable & Attribute
Sterilization			
Sterilization	100% Ethylene Oxide sterilization process with sterility assurance of at least 10^{-6}	Pass	Variable & Attribute

X. SUMMARY OF PRIMARY CLINICAL STUDY

Data from the Pipeline™ for Uncoilable or Failed Aneurysms (PUFS) study form the basis for the PMA approval decision of the PED. The study was conducted in the US, Hungary and Turkey under an approved Investigational Device Exemptions (IDE) application #G080093. The clinical study is summarized below.

A. Study Design

The first subject was enrolled in the pivotal clinical trial on November 3, 2008 and the last on July 17, 2009. The study is ongoing with planned follow-up continuing to 5 years after treatment. The database for this PMA reflected data collected through October 22, 2010 and included 111 enrolled subjects. There were 10 investigational sites, 8 in the US, one in Hungary and one in Turkey.

The study was a prospective, multi-center, single-arm, open label clinical study. The primary safety and effectiveness endpoints were analyzed using a Bayesian statistical approach. Although prior information regarding safety and effectiveness of the Pipeline™ Embolization Device from a preceding feasibility study was used to power the study, a non-informative prior distribution was assumed. Sample size was based on assumptions regarding the probable safety and effectiveness of the device in the target population and the proposed thresholds for interpretation of study success. With a maximum sample size of 100, statistical power was sufficient to meet both study co-primary endpoints (see primary endpoints in section X.A.3 below) provided that the underlying but unknown success rate was at least 70% and the stroke/neurologic death rate was <7%.

An independent Clinical Events Committee adjudicated all serious adverse events and selected non-serious adverse events and made the determination as to whether a subject met the criteria for a primary safety failure. An independent Core Radiology Laboratory made the determination of aneurysm occlusion status using the Raymond Scale[1] and the degree of parent artery stenosis using the method described in the WASID study[2].

Study results for the primary effectiveness and safety endpoints were compared to pre-determined thresholds of 50% and 20%, respectively, based on information derived from a pre-study review of available information in the medical literature.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the PUFS study was limited to subjects who were between the ages of 21 and 75 and who had a single target intracranial aneurysm that was located in the petrous, cavernous or paraophthalmic (including paraclinoid, ophthalmic and hypophyseal segments) regions of the internal carotid artery. The target aneurysm must have had a neck ≥ 4 mm or no discernible neck and a maximum fundus

diameter ≥ 10 mm. The parent artery diameter must have been 2.5 to 5.0 mm distal and proximal to the target aneurysm.

Patients were not permitted to enroll in the PUFS study if they had a subarachnoid hemorrhage within the preceding 60 days, or an intracerebral hemorrhage or major surgery in the preceding 42 days. Patients were excluded if they had an irreversible bleeding disorder, a platelet count less than 100 X $10^3/mm^3$ or a contraindication to or inability to tolerate antiplatelet agents. Patients with an allergy to radiographic contrast agents that could not be managed medically and those with a relative contraindication to angiography, including a creatinine >2.5mg/dL were excluded. Patients were not enrolled if they had a stenosis of the extracranial carotid artery or of the IA parent artery of >50%. Those with a known severe allergy to the components of PED including platinum or cobalt/chromium alloys were also excluded. Women of child-bearing potential were required to have a current negative pregnancy test to be enrolled.

2. Follow-up Schedule

All subjects were scheduled to return for follow-up examinations post-procedure/prior to discharge and at 30 ± 7days, 180 +40/-20 days and 1, 3, and 5 years ± 42 days after treatment. Telephone assessments were scheduled for 90 ±14 days, 2 and 4 years ± 42 days after treatment.

Prior to the procedure, all subjects had a neurologic and ophthalmologic examination, modified Rankin scale, blood hematology, a pregnancy test when appropriate and cerebral angiography.

Post-procedure, the objective parameters measured included cerebral angiography immediately following the procedure and at 180 days, at 1 year and are scheduled for follow-up angiography at 3 and 5 years following treatment. Neurologic examination and modified Rankin scale score were assessed at discharge and 30 days, 180 days and 1 year and are scheduled for 3 and 5 years after the procedure. An ophthalmologic examination was completed at 180 days after treatment. Adverse events and complications were or are scheduled to be recorded at all visits.

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

Table 6. Assessment schedule in PUFS

Assessment	Pre-procedure	Procedure, Second Procedure or Salvage Procedure	Post-procedure/Prior to Discharge	30-Days Follow-up (+/- 7 days)	†90 days (+/- 14 days)	180-Day follow-up (day -+40/-20 days)	2,4 years (+/- 42 days)	1,3,5 years (+/- 42 days)
Inclusion/exclusion criteria	X							
Demographics and medical history	X							
Intercurrent medical history and medication use				X	X	X	X	X
Neurologic exam	X		X	X		X		X
Fundus photograph	X							
Ophthalmologic examination	X					X		
Hematocrit/platelet count	X							
Pregnancy test	X							
Modified Rankin Scale	X		X	X		X		X
Angiogram		X				X		X
Adverse events review	X	X	X	X	X	X	X	X
Medications	X	X	X	X	X	X	X	X
Termination								X

†: telephone contact

3. Clinical Endpoints

The study's primary safety endpoint was the proportion of subjects who experienced either death due to neurologic causes or major ipsilateral stroke by 180 days after the last IA treatment procedure.

The primary effectiveness endpoint was the proportion of subjects who had complete occlusion of the target aneurysm and ≤ 50% stenosis of the parent artery at the target IA location on 180-day angiography and in whom an alternative treatment on the target IA had not been performed. The proportion of subjects with complete IA occlusion and the proportion with parent artery stenosis at 180 day and one year angiography were key secondary effectiveness endpoints.

The study was to be considered successful if, using a Bayesian analysis, the posterior probability that the effectiveness rate (pE) exceeded 50% given trial data

was at least 0.975 and the posterior probability that the safety rate (pS) given trial data was less than 20% was at least 0.975.

B. Accountability of PMA Cohort

At the time of database lock, 111 subjects were enrolled in PMA study. The intracranial aneurysms (IAs) attempted population was comprised of the 108 subjects with 110 qualifying IAs (2 subjects had a second qualifying IA treated with PED per protocol) in whom treatment with PED was attempted. The attempt was unsuccessful in one subject. The safety population therefore was comprised of the 107 subjects treated with PED. Three subjects treated with PED were subsequently determined by the Core Radiology Laboratory to have target IAs that did not qualify for the study by location and/or aneurysm size. The remaining 104 subjects with 106 qualifying IAs formed the IAs treated population. These analysis populations are summarized in Table 7.

Table 7. Analysis populations in PUFS

Category	Subjects	Aneurysms	Population
Enrolled	111		
Treatment attempted	108	110	IAs attempted
Treated with PED	107		Safety
Qualifying IA treated	104	104	Subjects treated
	104	106	IAs treated

Of 108 subjects in whom treatment with PED was attempted, 92.6 % (100) were available for analysis at the safety and effectiveness time point of 180 days post-procedure and 92 (85.2%) were available for analysis one year post-procedure. Table 8 summarizes subject accountability for the study.

Table 8. Subject accountability

	Pre-procedure	30 days	90 days	180 days	1 year
Theoretical	111	108	108	108	108
Deaths (cumulative)		3	3	3	3
Failures (cumulative)		1	1	1	1
Expected		104	104	104	104
Actual[A]				100	92
Actual[B]		102	101	100	100
% Follow-up[A]		98.1%	97.1%	96.2%	88.5%

[A]Patients with angiographic data for each endpoint, evaluated per protocol, in the window timeframe.
[B]Patients with any follow up data reviewed or evaluated by investigator ("all evaluated" accounting).

C. Study Population Demographics and Baseline Parameters

The demographics of the study population were typical for a study of large and giant wide-necked intracranial aneurysms performed in the US (Table 9). Subjects were predominantly female. There was a history of subarachnoid hemorrhage in 8 (7.4%), one of which had occurred within 60 days of treatment. There was a history of hypertension in 55.6% of the PUFS subjects. The target aneurysm had been previously treated in 8 subjects. The study thus includes predominantly unruptured and previously untreated IAs.

Table 9. Baseline characteristics - PUFS (n=108).

Characteristic	Value
Age, mean (SD, range)	57.0 (11.3, 30.2 – 75.1)
Female gender, n (%)	96 (88.9%)
Race	
White	99 (91.7%)
Black	6 (5.6%)
Not reported	3 (2.8%)
Ethnicity, % Hispanic or Latino	6 (5.6%)
Medical history	
Subarachnoid hemorrhage	8 (7.4%)
Stroke	7 (6.5%)
Coronary artery disease	6 (5.6%)
Hypertension	60 (55.6%)
Diabetes	7 (6.5%)
Previous cocaine use	1 (0.9%)
Smoking	
Never smoker	46 (42.6%)
Current smoker	31 (28.7%)
Previous smoker	31 (28.7%)
Prior treatments for target IA	
Coil embolization	6 (5.6%)
Surgery	1 (0.9%)
Other	1 (0.9%)

The characteristics of the target aneurysms in the PUFS study are displayed in Table 10. Target IAs were predominantly in the cavernous and paraophthalmic portions of the internal carotid artery.

Table 10 .Target IA characteristics in PUFS (n=108).

Characteristic	N (%) or Mean (range)
Side	
Left	57 (52.8%)
Right	51 (47.2%)
Location	
Petrous	4 (3.7%)
Cavernous	45 (41.7%)
Carotid cave	2 (1.9%)
Superior hypophyseal	10 (9.3%)
Lateral clinoidal	2 (1.9%)
Paraophthalmic	35 (32.4%)
Supraclinoid	9 (8.3%)
Posterior communicating	1 (0.9%)
Maximum fundus diameter (mm), mean (SD, range)	18.2 (6.4, 6.2 – 36.1)
"Small" (<10 mm), N (%)	1 (0.9%)
"Large" (>10 mm), N (%)	85 (78.7%)
"Giant" (>25 mm), N (%)	22 (20.4%)
Neck (mm), mean (SD, range)	8.8 (4.3, 4.1-36.1)
Dome (mm), mean (SD, range)	14.6 (5.5, 4.4 – 29.5)
Dome/neck ratio, mean (SD, range)	1.8 (0.6, 0.6 – 4.1)
Target IA partially thrombosed, N (%)	17 (15.7%)

D. Technical results

1. PED was placed successfully in 107 of 108 attempted (99.0%) subjects. In one subject, the parent artery distal to the IA could not be catheterized and the Pipeline procedure was abandoned. The subject was treated with additional coils and had safety follow-up but was not included in the safety analysis population.

2. PED was delivered using both the Renegade Hi-Flo catheter (52 subjects) and with the Marksman Catheter (55subjects). Although there were 5 reports of excessive friction when attempting to deliver PED with the Renegade Hi-Flo catheter compared to no reports of friction with the Marksman catheter, there was no apparent difference in safety or effectiveness with the use of these two catheters in the PUFS study.

3. Table 11 shows the number of PEDs used to treat subjects in PUFS. A mean and median of approximately 3 PEDs per subject was required.

Table 11. Number of PEDs placed per subject in PUFS (n = 107 subjects)

# of PEDs placed	N (%)
1	2 (2%)
2	34 (32%)
3	50 (47%)
4	12 (11%)
5 or more	9 (8%)
Mean (range)	3.1 (1-15)

4. Table 12 shows the lengths and diameters of PEDs used to treat aneurysms in PUFS. Lengths greater than 20 mm were not available during the study.

Table 12. Length and diameter of PEDs used in PUFS

Length, mm	N
10	13
12	55
14	62
16	67
18	63
20	81
Diameter, mm	**N**
3.25	3
3.50	31
3.75	88
4.00	91
4.25	64
4.50	39
4.75	12
5.00	13
Total	341

5. Table 13 displays the procedure and fluoroscopy time in PUFS subjects.

Table 13. Procedure and fluoroscopy time information

	Mean (SD, range)
Procedure duration (min)	123.8 (62.8, 39 – 427)
Total fluoroscopy time (minutes), N = 89	48.4 (31.5, 8.0 – 205.6)

6. Angioplasty balloons were permitted per protocol and were used 22 times in 18 PUFS subjects. Angioplasty balloons were used to address narrowing or distortion of the parent vessel (10 subjects), to aid in guide wire navigation (2 subjects) or to fully open and/or appose PED to the parent vessel wall.

7. The protocol-recommended dosing of antiplatelet agents prior to the procedure was aspirin 325 mg daily for 2 days and clopidogrel 75 mg daily for 7 days or a 600 mg bolus the day prior to the procedure. Following the procedure the protocol required aspirin 325 mg daily for at least 6 months and clopidogrel 75 mg daily for at least 3 months, after which the medications could be continued at the investigator's discretion.

8. PED was placed under general anesthesia.

9. Following a baseline activated clotting time (ACT), a bolus of heparin was administered at 50-100U/kg and subsequent doses as needed to maintain the ACT at 2 to 3.5 times normal.

E. Safety and Effectiveness Results

1. Safety Results

The analysis of the primary safety endpoint was based on the safety cohort of 107 subjects treated with PED. The key safety outcomes for this study are presented below in tables 14 to 15. Adverse events have been collected through one year after treatment and are reported in Tables 16 to 19.

Primary safety endpoint (major stroke or death due to neurologic cause)

Ipsilateral major stroke (5 events) or neurologic death (3 events) as adjudicated by the Clinical Events Committee occurred in 6 subjects (5.6%, 95% posterior credible interval CI 2.6 - 11.7%). The posterior probability that the major safety endpoint rate was less than 20%, the predetermined safety success threshold, was 0.999979. This probability value exceeded the pre-study probability threshold of 0.975, was statistically significant and met the pre-specified primary safety endpoint.

Table 14. Primary safety failures in PUFS

Cause of safety failure	Number of subjects
Major stroke	5
Neurologic death	3
Total	6*

*: 2 subjects in both categories

There were no statistically significant differences in the primary safety outcome in any exploratory subgroup analyses (Table 15). More subjects with hypertension met the primary safety endpoint compared to those without a history of hypertension (unadjusted p-value = .087). All 6 primary safety failures were in the group with a history of hypertension.

Table 15. Subgroup analysis of primary safety endpoint failures in PUFS (Safety population)

Subgroup	No. failures/n
Gender	
Male	2/12 (17%)
Female	4/95 (4%)
Aneurysm location	
Cavernous	1/49 (2%)
Ophthalmic	3/36 (8%)
Supraclinoid	2/22 (9%)
Aneurysm size	
≥25 mm	0/22 (0%)
< 25 mm	6/85 (7%)
Neck size	
< 6 mm	1/22 (5%)
≥ 6 mm	5/85 (6%)
Current/former smoker	
No	4/45 (72%)
Yes	2/62 (75%)
IA partially thrombosed	
No	6/90 (7%)
Yes	0/17 (69%)
Age range	
< 55 yrs	1/40 (3)
55-65 yrs	2/39 (5%)
> 65 yrs	3/28 (11%)
History of hypertension	
No	0/47 (0%)
Yes	6/59 (10%)
Unknown	0/1 (0%)
Site geography	
US	4/75 (5%)
OUS	2/32 (6%)
Number of PEDs used	
1 or 2	2/36 (6%)
3 or 4	3/62 (5%)
5 or more	1/9 (11%)

Mean length of PEDs used	
10-15	1/38 (3%)
16-20	5/69 (7%)
Mean diameter of PEDs used	
<4.0	2/53 (4%)
4.0-<4.5	3/44 (7%)
4.5-5.0	1/10 (10%)
Procedure duration	
< 2 hours	3/55 (6%)
2-4 hours	2/47 (4%)
> 4 hours	1/5 (20%)

Serious adverse events (SAE)

Thirty-seven SAEs occurred in PUFS to the 180 day assessment (Table 16). Ten (10) SAEs occurred between the 180 day and one year assessment. Hemorrhagic or ischemic strokes were the most common neurologic events and are listed in greater detail in Table 17.

Table 16. Serious adverse events in PUFS by MedDRA® *category and term – cumulative incidence at 180 days and one year (N=107 subjects).

MedDRA® category	MedDRA® term	180 days	1 year
Nervous system disorders		17 (15.9%)	19 (17.8%)
	Headache	5 (4.7%)	5 (4.7%)
	Haemorrhage intracranial	4 (3.7%)	4 (3.7%)
	Amaurosis fugax	3 (2.8%)	5 (4.7%)
	Ischemic stroke	3 (2.8%)	3 (2.8%)
	Cerebral haematoma	1 (0.9%)	1 (0.9%)
	Thrombotic stroke	1 (0.9%)	1 (0.9%)
Neurological disorders NEC	Dizziness	0 (0%)	2 (0.9%)
Vascular disorders NEC	Arteriovenous fistula	2 (1.9%)	2 (1.9%)
Arteriosclerosis, stenosis, vascular insufficiency and necrosis	Compartment syndrome	1 (0.9%)	1 (0.9%)
	Carotid artery occlusion	0 (0%)	1 (0.9%)
Cardiac arrhythmias	Atrial fibrillation	1 (0.9%)	1 (0.9%)
	Sinus bradycardia	1 (0.9%)	1 (0.9%)

MedDRA® category	MedDRA® term	180 days	1 year
	Sudden cardiac death	1 (0.9%)	1 (0.9%)
Decreased and nonspecific blood pressure disorders and shock	Procedural hypotension	1 (0.9%)	1 (0.9%)
Ear and labyrinth disorders	Tinnitus	1 (0.9%)	1 (0.9%)
Embolism and thrombosis	Deep vein thrombosis postoperative	1 (0.9%)	1 (0.9%)
	Retinal artery thrombosis	1 (0.9%)	1 (0.9%)
Gastrointestinal hemorrhages	Colitis (excl infective)	1 (0.9%)	1 (0.9%)
	Rectal haemorrhage	1 (0.9%)	1 (0.9%)
Infections - pathogen unspecified	Urinary tract infection	1 (0.9%)	1 (0.9%)
Neoplasms benign, malignant and unspecified	Breast cancer recurrence	0 (0%)	1 (0.9%)
Pulmonary vascular disorders	Post procedural pulmonary embolism	1 (0.9%)	1 (0.9%)
Reproductive system and breast disorders	Female genital tract fistula	1 (0.9%)	1 (0.9%)
Respiratory tract neoplasms	Lung squamous cell carcinoma stage 1	0 (0%)	1 (0.9%)
Vascular disorders	Aneurysms and dissections site specific NEC	1 (0.9%)	1 (0.9%)
Vascular hemorrhagic disorders	Epistaxis	1 (0.9%)	1 (0.9%)
	Retroperitoneal haemorrhage	1 (0.9%)	1 (0.9%)
Vision disorders	Diplopia	1 (0.9%)	1 (0.9%)
Visual field disorders	Visual field defect	1 (0.9%)	1 (0.9%)
Total		**37 (34.6%)**	**44 (41.1%)**

*MedDRA®: Medical Dictionary for Regulatory Activities

Adverse cerebrovascular events in the PUFS trial are listed in Table 17. Ten strokes occurred in 9 subjects (9.3%), 5 ischemic and 4 hemorrhagic. Five occurred in the peri-procedural period (prior to discharge) and 5 in the post-procedural period. Two of the events were fatal, both intracerebral hemorrhages. One peri-procedural ischemic stroke and 2 post-procedural ischemic strokes were associated with parent artery occlusion.

Table 17. Adverse cerebrovascular events in PUFS at 1 year after treatment (Safety population N = 107)

Adverse event	Peri-procedural	Post-procedural
Intracerebral hemorrhage	2	2
Ischemic stroke	2	3
Cilioretinal artery occlusion	1	
Amaurosis fugax		5

Non-serious adverse events in PUFS are listed in Table 18. Headache was the most common non-serious adverse event. Various types of hemorrhagic events occurred in 21 subjects including 14 vascular hemorrhagic events, 4 ecchymoses, 2 uterine bleeding and 1 lower gastrointestinal hemorrhage. Hair loss (alopecia) in one subject was attributed to prolonged radiation exposure.

Table 18. Non-serious adverse events occurring in PUFS by 180 days – by decreasing incidence (N=107 subjects).

MedDRA® Category	MedDRA® Term	180 Days
Nervous system disorders – headache		19 (17.8%)
	Headache	18 (16.8%)
	Post-traumatic headache	1 (0.9%)
Procedural and device related injuries and complications NEC*	Procedural headache	16 (15%)
Vascular hemorrhagic disorders		14 (13.1%)
	Conjunctival haemorrhage	1 (0.9%)
	Epistaxis	3 (2.8%)
	Subcutaneous haematoma	1 (0.9%)
	Urogenital haemorrhage	2 (1.9%)
	Vessel puncture site hemorrhage	7 (6.5%)
Gastrointestinal signs and symptoms		13 (12.1%)
	Nausea	5 (4.7%)
	Procedural nausea	7 (6.5%)
	Procedural vomiting	1 (0.9%)
Vision disorders		10 (9.3%)
	Diplopia	6 (5.6%)
	Photopsia	3 (2.8%)
	Vision blurred	1 (0.9%)
Ocular neuromuscular disorders		9 (8.4%)
	Eyelid ptosis	4 (3.7%)
	IIIrd nerve disorder	1 (0.9%)

MedDRA® Category	MedDRA® Term	180 Days
	IVth nerve disorder	1 (0.9%)
	VIth nerve disorder	3 (2.8%)
Infections - pathogen unspecified		6 (5.6%)
	Acute sinusitis	1 (0.9%)
	Pharyngitis	2 (1.9%)
	Puncture site infection	1 (0.9%)
	Urinary tract infection	2 (1.9%)
Neurological disorders NEC		5 (4.7%)
	Dizziness	2 (1.9%)
	Hyperesthesia	1 (0.9%)
	Hypoesthesia	1 (0.9%)
	Hypoesthesia facial	1 (0.9%)
Vascular disorders	Ecchymosis	4 (3.7%)
Visual field disorders	Visual field defect	3 (2.8%)
Blood and lymphatic system disorders	Anemia	2 (1.9%)
Body temperature conditions	Postoperative fever	2 (1.9%)
Embolism and thrombosis	Deep vein thrombosis postoperative	2 (1.9%)
Allergic conditions	Drug eruption	1 (0.9%)
Ear and labyrinth disorders	Tinnitus	1 (0.9%)
Epidermal and dermal conditions	Pruritis	1 (0.9%)
Eye disorders NEC	Eye pain	1 (0.9%)
Gastrointestinal disorders	Constipation	1 (0.9%)
Gastrointestinal hemorrhages	Lower gastrointestinal haemorrhage	1 (0.9%)
General system disorders	Discomfort	1 (0.9%)
	Facial pain	1 (0.9%)
	Peripheral edema	1 (0.9%)
Injuries NEC	Corneal abrasion	1 (0.9%)
Musculoskeletal and connective tissue disorders NEC	Back pain	1 (0.9%)
	Pain in extremity	1 (0.9%)
Reproductive system and breast disorders	Menometrorrhagia	1 (0.9%)
	Menorrhagia	1 (0.9%)
Skin and subcutaneous tissue disorders	Skin bacterial infection	1 (0.9%)
Skin appendage conditions	Application site alopecia	1 (0.9%)
Total		**122**

*NEC; not elsewhere classified

2. Effectiveness Results

The analysis of effectiveness was evaluated in three populations (see Table 7, Analysis populations in PUFS) at 180 days and at 1 year after treatment. The three populations were: the IAs treated population, the subjects treated population, and the IAs attempted population. Key effectiveness outcomes are presented in Tables 19 to 24.

The study met the primary effectiveness endpoint an all three of the populations analyzed.

Table 19. Analyses of proportion of PUFS subjects who met the primary effectiveness endpoint.

Population	180 day	1 year
Intracranial aneurysms treated (N=106)	78/106; 73.6% (64.4, 81.0)*	75/106; 70.8% (61.1, 79.2)**
Subjects treated (N=104)	76/104; 73.1% (63.8, 80.7)*	73/104; 70.2% (60.4, 78.7)**
Intracranial aneurysms attempted (N=110)	80/110; 72.7% (63.7, 80.2)*	77/110; 70.7% (58.6, 76.7)**

*: 95% posterior credible interval
**: 95% exact confidence interval

The reasons for failure to meet the primary effectiveness endpoint at 180 days for 28 PUFS subjects/IAs are shown in Table 20. Residual aneurysm neck or dome (Raymond grade 2 or 3) accounted for 14 of the 28 failures. In 5 subjects failure was due to occlusion or >50% stenosis of the parent artery.

Table 20. Reasons for primary effectiveness endpoint non-success at 180 days in PUFS.

Reason for Non-success	**Number**
Residual neck	8
Residual aneurysm	6
Death	3
Spontaneous parent artery occlusion	3
Withdrew or lost to follow-up	2
Refused 180 day angiogram	2
Stenosis of parent artery >50%	2
Coils used in fundus. Target IA was completely occluded and there was no stenosis	1
Carotid-cavernous fistula	1
Total	**28**

3. Subgroup Analyses

Table 21 shows an analysis of the primary effectiveness success in relationship to baseline characteristics. The table lists number and proportion of subjects in a subgroup who met the primary effectiveness endpoint of complete aneurysm occlusion in the absence of stenosis > 50% of the parent artery and without the use of any other IA treatment or retreatment. There were no statistically significant relationships.

Table 21. Subgroup analysis of the primary effectiveness endpoint

Subgroup	No. successes/n
Gender	
Male	6/10 (60%)
Female	72/96 (75%)
Aneurysm location	
Cavernous	33/47 (70%)
Ophthalmic	29/37 (78%)
Supraclinoid	16/22 (73%)
Aneurysm size	
≥25 mm	15/22 (68%)
< 25 mm	63/84 (75%)
Neck size	
< 6 mm	18/21 (86%)
≥ 6 mm	60/85 (71%)
Current/former smoker	
No	31/43 (72%)
Yes	47/63 (75%)
IA partially thrombosed	
No	67/90 (74%)
Yes	11/16 (69%)
Age range	
< 55 yo	36/41 (88)
55-65 yo	21/36 (58%)
> 65 yo	21/29 (72%)
History of hypertension	
No	37/47 (79%)
Yes	41/59 (70%)
Site geography	
US	52/73 (71%)
OUS	26/33 (79%)

Of the 104 subjects with 106 IAs in the IAs treated population, 97 subjects with 99 treated IAs had angiography 180 days after treatment. Table 22 shows that the incidence of parent artery stenosis of greater than 50% including total occlusion in

this population was 5.1% at 180 days and 3.3% at one year after treatment. Two subjects in this population had total parent artery occlusion at 180 days but did not have angiography at 1 year. Inclusion of these two subjects as total occlusion at one year yields an incidence of significant stenosis or total occlusion at one year of 5/93 or 5.4%.

Table 22. Parent artery stenosis and occlusion at 180 days and 1 year for subjects with angiographic data

Percent stenosis	180 days (N=99 IAs)	1 year (N=91 IAs)
0 - ≤25%	84 (84.8%)	85 (93.4%)
25 - ≤ 50%	10 (10.1%)	1 (1.1%)
50 - ≤ 75%	0 (0%)	1 (1.1%)
75 – 100%	5* (5.1%)	3** (3.3%)
Other		1*** (1.1%)
Total	99 (100%)	91 (100%)

*: includes 3 subjects with carotid occlusion
**: 2 subjects with carotid occlusion
***: 1 subject in whom visualization of the parent artery blocked by coils.

Table 23 displays the status of ophthalmic artery flow at 180 days. For those 76 subjects whose ophthalmic artery was evaluable, patent prior to treatment and covered by treatment with the PED, antegrade flow in the ophthalmic artery was seen with internal carotid angiography in 63 and not seen in 13 (17.1%) at 180 days after treatment. The five adverse events of amaurosis fugax occurred in 4 of the 13 subjects in whom antegrade flow in the ophthalmic artery was not seen. Antegrade flow was seen in the ophthalmic artery in the one subject with an SAE of cilioretinal artery occlusion. The ophthalmic artery was patent in all 19 subjects in whom it was not covered by PED.

Table 23. Ophthalmic artery flow at 180 days

Ophthalmic artery covered by PED	Antegrade ophthalmic artery flow at 180 days		Total
	Yes	No	
Yes	63	13	76
No	19	0	19

Of the 104 subjects with 106 IAs in the IAs treated population, 97 subjects with 99 treated IAs had angiography 180 days after treatment and 89 subjects with 91 treated IAs had angiography 1 year after treatment. Complete IA occlusion was seen in 81.8% of this population 180 days after treatment and in 85.7% 1 year after treatment (Table 24).

Table 24. IA occlusion status at 180 days and 1 year for subjects with angiographic data

Occlusion ranking	180 days (N=99 IAs)	1 year (N=91 IAs)
Complete occlusion	81 (81.8%)	78 (85.7%)
Residual neck	8 (8.1%)	5 (5.5%)
Residual aneurysm	6 (6.1%)	5 (5.5%)
Other	4* (4.0%)	3** (3.3%)
Total	99 (100%)	91 (100%)

*: 1 subject with carotid-cavernous fistula and 3 subjects with carotid occlusion in whom IA not visualized

**: 2 subjects with carotid occlusion, 1 transvenous coil embolization in whom IA not visualized

Of the 7 subjects who did not have angiography at 180 days, 3 had died and 4 refused angiography, had withdrawn or were lost to follow-up. One year after treatment 89 subjects with 91 treated IAs had angiography. Of the 15 subjects who did not have angiography at one year 3 had died, 2 had known total carotid artery occlusion at 180 days and 4 had withdrawn or were lost to follow-up (1 of whom had 180 day angiography with total IA occlusion and no parent artery stenosis) and 6 refused or were unable to undergo the procedure (all with complete IA occlusion and no parent artery stenosis at 180 days).

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not Applicable

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

A. Panel Meeting Recommendation

At an advisory meeting held on March 18, 2011, the Neurological Devices Panel indicated unanimously that the data submitted by Chestnut Medical Technologies in the PMA for the Pipeline™ Embolization Device provided adequate assurance of safety, effectiveness and a favorable risk/benefit ratio. The meeting transcript may be accessed at the following webpage:
http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/NeurologicalDevicesPanel/ucm240924.htm

B. FDA's Post-Panel Action

Although the panel recommended that there be no age restriction in the Indications for Use, in the absence of any data in subjects in the pediatric age group FDA believes that restriction to use in adults only is appropriate.

XIII. CONCLUSION.S DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA approval as described above. The study met the primary safety success criterion. The overall incidence and types of serious and non-serious adverse events did not raise safety issues that were not anticipated for the population studied. The conclusion is supported by a unanimous vote of the Neurological Devices Panel.

B. Effectiveness Conclusions

The study met the primary effectiveness success criteria at both 180 days and one year after treatment. The result is supported by key secondary effectiveness endpoints at both 180 days and one year after treatment. The conclusion is supported by a unanimous vote of the Neurological Devices Panel.

C. 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 adequate for the intended population for whom the benefit of currently available treatments is limited.

XIV. CDRH DECISION

CDRH issued an approval order on April 06, 2011. The final conditions of approval cited in the approval order are described below.

As a condition of approval, you must conduct the following post-approval study:

Continued Follow-up of Premarket Cohorts Study: Per the protocol outline submitted by email dated February 3, 2011 and email correspondence on March 30, 2011, continued follow-up of individuals in the pivotal clinical cohort (PUFS) as well as in the continued access cohort (PUFS-CA) for a total of five years will be conducted to provide additional long-term safety and effectiveness data for patients receiving Pipeline Embolic Device (PED). This prospective, observational, open-label, single-arm cohort study anticipates enrolling 131 subjects from the aforementioned studies and performing clinical exams and angiograms at the 3- and 5-year visits and conducting telephone interviews at the 2- and 4-year visits. A minimum of 70 subjects are required for the primary endpoint analysis, as described below. If less than 70 subjects complete the 5-year follow-up, FDA may require you to enroll new patients or consider other regulatory options to reach the required study sample size. The main study endpoints include: ipsilateral stroke and/or neurovascular death (primary endpoint), complete occlusion of the aneurysm, stenosis of the parent artery, and device-related adverse events. Subgroup analyses will be performed based on the

anatomic location of the aneurysm as well as the hypertensive status of the subjects. The study protocol with its stated assumptions has adequate power to test the study hypothesis at 5-years for the overall cohort as well as for subgroups of interest.

The applicant's manufacturing facilities were 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. REFERENCE

1. Roy D, Milot G, Raymond J. Endovascular treatment of unruptured aneurysms. Stroke 2001;32(9):1998-2004.

2. Chimowitz MI, Lynn MJ, Howlett-Smith H et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. N Engl J Med 2005;352(13):1305-1316.