SSED (Summary of Safety and Effectiveness Data)

Summary of Safety and Effectiveness
Pipeline Embolization Device
P100018

Chestnut Medical Technologies Inc.
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1 General Information

Device generic name	Neurovascular embolization device
Device trade name	Pipeline™ Embolization Device
Applicant's name and address	Chestnut Medical Technologies 173 Jefferson Drive Menlo Park, CA 94025
PMA number	P090014
Date of Panel Recommendation	TBD
Date of notice of approval to the applicant	TBD

2 Indications for Use

The Pipeline™ Embolization Device (PED) is indicated for the endovascular treatment of large or giant wide-necked intracranial aneurysms (IAs) in the cavernous and paraclinoid regions of the internal carotid artery.

3 Device Description

PED consists of a braided, multi-alloy, mesh cylinder shaped implant combined with a simple guidewire based delivery system. PED is provided sterile (EtO) with the implant loaded onto the wire delivery system and compressed inside an introducer sheath. **Table 1** shows the size range of the PED implant. The system is designed to be introduced into commercially available 3F neurovascular microcatheters for delivery to the target vessel adjacent to the intracranial aneurysm. The PED delivery system is a 175cm micro-guidewire whose primary components consist of a 304SS core wire with a PTFE coating. The tip and protective coils are a platinum-tungsten alloy, the proximal marker a platinum-iridium alloy, and the distal, mid and proximal solder joints are a tin-silver mixture. A protective coil holds PED in the collapsed state until the operator deploys PED. A proximal marker is soldered to the core wire; the function of the proximal pusher is to push PED out of the microcatheter when the wire is advanced.

Table 1. Size range of PED.

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
2.75	3.00	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20
3.0	3.25	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20
3.25	3.50	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20
3.5	3.75	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20
3.75	4.00	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20
4.0	4.25	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20
4.25	4.50	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20
4.5	4.75	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20
4.75	5.00	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20
5.0	5.25	10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20

4 Contraindications, Warnings, and Precautions

4.1 Contraindications

- Patients with active bacterial infection.
- Patients in whom dual antiplatelet therapy (aspirin and clopidogrel) is contraindicated.
- Patients who have not received dual antiplatelet agents prior to the procedure.

4.2 Warnings

- While advancing the PED inside the microcatheter, do not pull back on or torque the wire. This may make device release more difficult or impossible.
- Do not rotate the delivery wire for more than 10 full turns. Over-rotation may cause delivery wire breakage. If PED does not open after 10 turns, remove the entire system (microcatheter and PED delivery system) simultaneously.
- If the capture coil tip of the delivery system becomes stuck in the mesh of a delivered PED, rotate the wire clockwise while advancing the wire to try to release it, then slowly pull back on the delivery wire.

4.3 Cautions

- Do not use PED in patients in whom angiography demonstrates inappropriate anatomy, such as severe pre- or post-aneurysmal narrowing.
- PED should be used only by physicians trained in percutaneous, intravascular techniques and procedures at medical facilities with the appropriate fluoroscopic equipment.
- Physicians should undergo appropriate training prior to using PED in patients.
- PED is provided sterile for single use only. Store in a cool, dry place.
- Carefully inspect the sterile package and device components prior to use to verify that they have not been damaged during shipping. Do not use kinked or damaged components.
- Use PED system prior to the “Use Before” date printed on the package.

- The appropriate anti-platelet and anti-coagulation therapy should be administered in accordance with standard medical practice.
- A thrombosed aneurysm may aggravate pre-existing, or cause new, symptoms of mass effect and may require medical therapy.
- Placement of multiple PEDs may increase the risk of ischemic complications.
- Select an appropriately sized PED such that it is fully expanded diameter is equivalent to that of the proximal parent vessel. An incorrectly sized PED may result in inadequate device placement, incomplete opening or distal migration.
- Anchor PED approximately 2-3 mm into the proximal and distal segments of the parent artery, preferably in a straight portion of the parent artery.
- Use fluoroscopy to carefully monitor the tip of the core wire during PED deployment.
- PED foreshortens substantially (50-60%) during deployment. Take device foreshortening into account when deploying PED.
- If the delivery wire cannot be retracted into the microcatheter, carefully remove the delivery core wire and microcatheter simultaneously.
- Rotate the delivery wire only in a clockwise direction. Rotating in a counter-clockwise direction may make device release more difficult or impossible.
- Use of Marksman Catheter (ev3, Irvine, CA) is recommended to deliver PED.

5 Alternative Practices and Procedures

Surgical approaches to treatment of wide-necked IAs include clipping, wrapping and bypass. Endovascular approaches to treatment of wide-necked IAs include parent vessel occlusion, placement of embolic coils, stent-assisted coiling, or placement of other materials in the IA fundus. In many cases surgical approaches are limited by IA size and/or location or high expected morbidity/mortality. Endovascular approaches are limited by inability to deploy devices due to IA geometry, inability to completely treat the IA, morbidity from overpacking the IA fundus, or lack of an appropriate parent artery into which to place currently available devices. If left untreated, IAs can rupture, which can cause death or significant permanent morbidity.

6 Marketing History

PED is CE marked and is currently approved for sale in 47 countries.

7 Potential Complications and Adverse Effects of the Device on Health

7.1 Observed Adverse Effects

PUFS (Pipeline for Uncoilable or Failed Aneurysms) was a prospective interventional cohort of 107 patients with large and giant IAs who received PED. Serious adverse events (SAEs) observed in PUFS and meeting the ISO14155 definition for SAE are listed in **Table 2**. Of the events listed in **Table 2**, 15 were judged to be probably or definitely related to PED. 24 of 44 events occurred prior to Day 30 of follow-up.

Table 2. Serious adverse events observed in PUFS clinical trial (n=107).

Event Type	N (%)
Neurologic Events	
Amaurosis fugax	5
Headache	5
Intracranial hemorrhage	5
Ischemic stroke	4
Carotid cavernous fistula	2
Carotid occlusion	1
Cilioretinal artery embolism	1
Diplopia	1
Possible intracranial hemorrhage	1
Non-Neurologic Events	
Non-neurologic bleeding	5
Cardiac arrhythmia	3
Dizziness/tinnitus	2
Colitis	1
Deep venous thrombosis	1
Lightheadedness/palpitations	1
Lung cancer	1
Pulmonary embolism	1
Rectovaginal fistula	1
Recurrent breast cancer	1
Pneumonia/urinary tract infection	1
Visual field worsened	1
Total	44

Adverse events that did not meet the definition for SAE are shown in **Table 3**. No patient required reoperation as a result of an adverse event. One patient underwent placement of additional PEDs at 2 weeks because the initial treatment was incomplete.

Table 3. Non-serious adverse events in PUFS (n=107).

Event	N	Event	N
Headache	34	Facial pain	1
Nausea	10	Femoral puncture site infection	1
Diplopia	6	Flashing lights in vision	1
Ptosis	4	Hair loss	1
Skin bruising	4	Hand itching	1
Non-neuro bleeding: Epistaxis	3	Headache and CN 3/6 neuropathy	1
Non-neuro bleeding: Groin hematoma	3	Headache due to trauma	1
Anemia	2	Hyperesthesia of trigeminal V1 distribution	1
Diplopia (CN6), ptosis (CN3)	2	Leg cellulitis	1
Dizziness	2	Nausea / loss of appetite	1
Fever	2	Nausea / vomiting	1
Floaters in vision	2	Non-neuro bleeding: GI bleed	1
Non-neuro bleeding: Hematuria	2	Non-neuro bleeding: Groin bleeding	1
Urinary tract infection	2	Non-neuro bleeding: Heavy menses due to ovarian cyst	1
VF worsened	2	Non-neuro bleeding: Scalp hematoma	1
Abducens palsy possibly worse	1	Non-neuro bleeding: Vitreal hemorrhage	1
Achiness	1	Non-neuro bleeding: groin bleeding	1
Acute sinusitis	1	Non-neuro bleeding: groin hematoma	1
Anxiety reaction	1	Non-neuro bleeding: vaginal spotting	1
Arterial line site swelling	1	Numbness in fingertips	1
Back pain	1	Poor eye movement on examination	1
Bilateral lower extremity edema	1	Possible CN 4 palsy	1
Blurry vision	1	Rash due to aspirin	1

Bronchitis	1		Sore throat	1
Bubbling sound	1		Subconjunctival hemorrhage	1
Constipation	1		Thigh pain	1
Corneal abrasion	1		UE vein thrombosis	1
Deep/superficial venous thrombosis	1		Upper respiratory infection	1
Eye floater	1		Vomiting	1
Eye pain	1		Worsened hemianopia	1
Facial anesthesia	1		**Total**	**126**

7.2 Potential Complications or Adverse Effects

Potential adverse effects from use of PED, some of which can be fatal, are listed in **Table 4**.

Table 4. Anticipated adverse events related to PED, angiography and use of aspirin/clopidogrel.

Anesthesia or contrast reaction
Bleeding, including intracerebral, retroperitoneal or other location
Blindness
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
Groin injury, including infection, bleeding, pain, vessel or nerve damage
Headache
Hydrocephalus
Infection
Ischemic stroke
Perforation or rupture of aneurysm sac or parent artery
Reaction to radiation exposure
Stenosis or thrombosis of parent artery within PED or a branch vessel
Transient ischemic attack (TIA)
Vasospasm

8 Summary of Preclinical Studies

8.1 Laboratory Studies

8.1.1 Biocompatibility Testing

Biocompatibility testing of Pipeline and the PED delivery system (**Table 5**) was performed according to ISO 10993-1, Good Laboratory Practice (GLP) Regulations, and 21CFR58. All testing passed.

Table 5. Biocompatibility testing for PED implant and delivery system.

Implant	**Delivery System**
Acute Systemic Toxicity	Acute Intracutaneous Reactivity
Lymph Node Sensitization	Acute Systemic Toxicity
Acute Intracutaneous Reactivity	Lymph Node Sensitization
Bacterial reverse mutation study	In Vitro Cytotoxicity
Cytotoxicity	In Vitro Haemolysis
Hemolysis	Plasma Recalcification Time
In-Vitro Chromosomal Aberration Study in Mammalian Cells	In Vivo Thrombogenicity
Mouse Peripheral Blood Micronucleus Study	Rabbit Pyrogen
ASTM Partial Thromboplastin Time	
C3a Complement Activation Assay	
SC5b-9 Complement Activation Assay	

8.1.2 Sterility

The PED delivery system is sterilized using ethylene oxide (EO). The EO cycle was validated to a sterility assurance level of 10^{-6} per ISO 11135. The System was tested and met specifications after two sterilization exposures.

8.1.3 Functional Testing

Functional testing of PED and the PED delivery system included relevant tests suggested in FDA guidance documents for intravascular stents and neurovascular embolization devices. Testing (**Table 6**) confirmed that PED and the PED delivery system met functional requirements for safe and effective use in humans.

Table 6. Functional testing of PED and PED delivery system.

Stent dimensional verification
Percentage surface area
Foreshortening
Post-deployment integrity
Radial strength
Tensile strength
Stress analysis
Accelerated durability testing
Radiopacity
Deliverability
Bond strength / joint integrity
Coating integrity
Corrosion resistance

8.2 Animal Studies

Animal studies included 2 short-term implantation studies, 2 long-term (6-month) studies and one very long-term (12 month) study. Acute studies showed that PED was easily placed in the target vasculature. 6-month animal studies showed that all surgically created aneurysms in both studies were occluded at 6 months. Histology showed excellent healing, with infiltration of the dome with fibrocytes and matrix. The degree of healing within the domes of aneurysms covered by PED was similar or better than those treated with coils when compared to prior studies. Moreover, PED treatment allowed the aneurysm cavity to shrink over time, likely because no devices were placed in the aneurysm fundus as a space-occupying device. Arterial injury scores were very low and there was no evidence of stenosis in the treated parent artery. All covered lumbar and vertebral arteries were open at all time points.

A 12-month study showed that side-branches (lumbar arteries) remained open at 6 and 12 months even when 2 or 3 PEDs were placed in the rabbit aorta, one inside the other.

Biocompatibility testing and animal studies established that PED and its delivery system were biocompatible, hemocompatible, non-toxic, non-mutagenic and highly effective in embolizing aneurysms while keeping side branches open.

8.3 Additional Studies

8.3.1 Shelf Life

Shelf life was validated using a combined real time and accelerated aging study of finished devices. Package integrity testing included pouch seal integrity, label integrity, dye penetration, pouch burst, and ship testing.

8.3.2 Magnetic Resonance Imaging (MRI) Compatibility

PED was shown to be MRI compatible in MRI systems operating at a field strength of up to 3.0 Tesla. At these strengths no deflection forces and minimal heating were observed. Imaging testing showed that MRI artifacts may interfere with radiological interpretation within 2-3 mm of the implant, but will be recognizable as artifacts. Further away, there will be no impact on radiological interpretation.

9 Summary of Primary Clinical Studies

Two formal studies have examined the safety and effectiveness of Pipeline Embolization Device: PITA (Pipeline for Intracranial Treatment of Aneurysms) and PUFS (Pipeline for Uncoilable or Failed Aneurysms) (see **Table 7**). In addition, compassionate or special access use of PED was performed in 28 patients in the US, >50 patients in Canada, and >180 patients in Argentina. Each clinical experience is described below.

Table 7. Summary of clinical studies.

Clinical Study	Study Design	Objective	Number of Sites	Number of Subjects (Include enrolled, evaluable and lost to follow-up, etc.)
PITA (pilot) Pipeline for Intracranial Treatment of Aneurysms	Single-arm multicenter interventional cohort	Evaluate the safety and effectiveness of PED	4	31
PUFS (pivotal) Pipeline for Uncoilable or Failed Aneurysms)	Single-arm, multicenter interventional cohort	Evaluate the safety and effectiveness of PED	10	108
US Compassionate Use	NA	Compassionate Use	7	28
Canada- Special Access	NA	Compassionate Use	4	>50
Argentina	NA	Compassionate Use	1	>180

9.1 Pivotal Study Design Characteristics

The clinical study that formed the basis for FDA's finding that the Pipeline™ Embolization Device is safe and effective for its intended use was the Pipeline for Uncoilable or Failed Aneurysms (PUFS) study.

PUFS was a multicenter prospective interventional cohort of 108 subjects with large and giant intracranial aneurysms (IAs) in the intracranial portion of the internal carotid artery (ICA) who underwent attempted treatment with PED. To qualify, an IA had to have maximum fundus diameter of at least 10 mm and neck at least 4 mm or no neck (fusiform IA). Patients were from 21- 75 years of age. Patients were excluded if there was recent intracranial hemorrhage or surgery, if the patient's neurologic condition was unstable, if there was irreversible bleeding disorder, if the patient could not tolerate antiplatelet agents, if the patient had major ipsilateral carotid stenosis, if the patient had other conditions that increased the risk of stroke (e.g., atrial fibrillation), or if stent was in place in the parent artery. Patients that had failed previous coiling were included. Patients were asked to take dual antiplatelet therapy prior to PED placement (aspirin 325 mg daily for 2 days, clopidogrel 75 mg daily for 7 days or a 600 mg dose 1 day prior to PED placement) and after PED placement (aspirin 325 mg daily for at least 6 months and clopidogrel 75 mg daily for at least 3 months).

9.1.1 Clinical Endpoints and Success/Failure Criteria

The **primary safety endpoint** of the study was the proportion of subjects with major ipsilateral stroke or neurologic death by 180 days after treatment. Major stroke was defined as a stroke resulting in an increase from baseline in NIH Stroke Scale by 4 or more points up at 7 days after stroke. All serious adverse events (SAEs) were judged by a clinical events committee (CEC). A thorough review of the published medical literature established that conventional surgical and endovascular approaches were associated with risks of stroke and death averaging 10-15% and as high as 30%. The trial was interpreted as a safety success if the Bayesian posterior probability that the primary safety endpoint rate was less than 20% was >0.975.

The **primary effectiveness endpoint** of the study was the proportion of subjects with complete occlusion of the IA at 180 days in the absence of use of other devices and in the absence of major (i.e., >50%) stenosis of the parent vessel. IA occlusion was judged by an independent core laboratory of 3 neuroradiologists not otherwise involved in the study. The trial was interpreted as an effectiveness success if the Bayesian posterior probability that the primary effectiveness endpoint rate exceeded 50% was >0.975. Historically, the late complete occlusion rate for large and giant IAs treated with conventional endovascular methods is low, probably <30%.

9.1.2 Pre-Specified Statistical Analysis Plan

A Bayesian approach to analysis was used with a non-informative prior distribution. Subjects without angiograms at 180 days were treated as effectiveness failures. The approach calculated the probability that the effectiveness rate exceeded 50% given study data and that the safety rate was less than 20% given study data. The study took a co-primary endpoint approach and was interpreted as a success if both posterior probabilities were >0.975. A pre-study computer simulation showed that 100 subjects had adequate statistical power for the co-primary endpoints.

9.1.3 External Evaluation Groups

All serious adverse events (SAEs) underwent review and adjudication by a clinical events committee (CEC) consisting of two interventional neuroradiologists and one neurosurgeon. Whether a subject met the primary safety endpoint was adjudicated by the CEC. All scheduled angiograms underwent review and adjudication by a core radiographic laboratory consisting of 3 neuroradiologists not otherwise involved in the study. Whether an IA met criteria for effectiveness success was judged solely by the core radiographic laboratory.

9.1.4 Study Design Discussion

PUFS is a single-arm clinical study. A randomized trial was not feasible because:

- The target IA population was likely to include many IAs that could be treated by PED but not by any particular single alternative treatment.

- Neurosurgery for IAs near the skull base is extremely difficult and available in a limited number of study centers. Moreover, neurosurgery for large and giant IAs was already known to be associated with high rates of morbidity and mortality.

- The current standard for treatment, coil embolization, was predicted to be infeasible in many subjects.

- Although intracranial stents are available through the HDE route, manufacturers of these stents have not brought definitive evidence of effectiveness to FDA, so these stents were deemed not relevant. Moreover, many IAs are not feasibly treated with stent-assisted coiling.

- Historical information was sufficient to show that the likelihood of long-term complete occlusion of the target IA with coils was low. PUFS proposed a threshold for interpretation of trial success that was significantly higher than success rates quoted in the published medical literature for the target IA population.

9.1.5 Clinical Inclusion and Exclusion Criteria

Enrollment in PUFS was limited to patients who met the criteria shown in **Table 8**. Patients had to have a single target IA in the internal carotid artery (ICA) that was both wide-necked (i.e., ≥4 mm) and large (≥10 mm and <25 mm) or giant (≥25 mm) in size.

Table 8. Eligibility criteria for PUFS.

Inclusion Criteria
a) Age 21 to 75 years, inclusive
b) Patient has a single target IA that:
1) Is located in the following regions of the internal carotid artery:
i. Petrous
ii. Cavernous
iii. Paraophthalmic (including paraclinoid, ophthalmic and hypophyseal segments)
2) Has a neck >4 mm or no discernible neck AND a size (maximum fundus diameter) >10 mm
3) Has a parent vessel with diameter 2.5 – 5.0 mm distal/proximal to the target IA
c) Subject has provided written informed consent using the IRB-approved consent form
d) Subject has the necessary mental capacity to participate and is willing and able to comply with protocol requirements
Exclusion Criteria
a) More than one IA requires treatment in the next 6 months
b) Subarachnoid hemorrhage in the past 60 days
c) Any intracranial hemorrhage in the last 42 days
d) Major surgery in the last 42 days
e) Unstable neurologic deficit (i.e., any worsening of clinical condition in the last 30 days)
f) History of irreversible bleeding disorder
g) Platelet count < 100 x 10^3 cells/mm^3 or known platelet dysfunction
h) Inability to tolerate, documented evidence of adverse reaction or contraindication to study medications
i) Stent in place at the target IA
j) Contraindication to CT scan or MRI
k) Known allergy to contrast used in angiography that cannot be medically controlled
l) Known severe allergy to platinum or cobalt/chromium alloys
m) Relative contraindication to angiography (e.g., serum creatinine > 2.5 mg/dL)
n) Woman of child-bearing potential who cannot provide a negative pregnancy test

o) Evidence of active infection at the time of treatment
p) Other known conditions of the heart, blood, brain or intracranial vessels that carry a high risk of neurologic events (e.g., severe heart failure, atrial fibrillation, known carotid stenosis)
q) Current use of cocaine or other illicit substance
r) Any comorbid disease or condition expected to compromise survival or ability to complete follow-up assessments to 180 days
s) Extracranial stenosis greater than 50% in the carotid artery Intracranial stenosis greater than 50% in the treated vessel

9.1.6 Summary of Treatment, Follow-up Schedule and Evaluations

Subjects underwent baseline assessment (including a detailed neuro-ophthalmologic examination) followed by an angiographic procedure during which PED alone was placed in the parent artery. Subjects were seen in clinic at 30, 180 days. At clinic visits, subjects underwent adverse event assessment and a detailed neurologic examination. Repeat angiography was performed at 180 days (primary endpoint timing). A repeat neuro-ophthalmologic examination was performed at 180 days. Subjects underwent repeat clinic visit and cerebral angiogram at 1, 3 and 5 years after PED placement. Subjects also had telephone-based visits at 90 days and 2 and 4 years.

All angiograms were read by an independent core laboratory and IA occlusion was judged according to the scale of Roy.[*] All serious adverse events were adjudicated by a clinical events committee (CEC).

9.1.7 Accountability of PMA Cohort

108 subjects were enrolled and treated in PUFS. Clinical follow-up was excellent, with only 3 study withdrawals or loss to follow-up by 180 days and one subject who refused to have clinic visits but maintained contact with the study site. Of 104 subjects who were theoretically available for 180-day follow-up, 180-day follow-up was complete in 100 (96.2%, **Table 9**).

Table 9. Patient follow-up in PUFS.

Subject Subset	Procedure	Day 30	Day 90	Day 180	1 Year
Theoretical	108	108	108	108	108
Deaths (cumulative)	0	3	3	3	3
Failures (cumulative)	1	1	1	1	1
Expected*		104	104	104	104
Actual	-	102	101	100	99
% follow-up	-	98.1%	97.1%	96.2%	95.2%

*Expected = theoretical – (deaths + failures)

9.2 Study Population Demographics and Baseline Parameters

9.2.1 Subject Characteristics

108 subjects were enrolled and treated, of whom 96 (89%) were female. Mean age was 57.0. Prior SAH was reported in 8 (7.4%) subjects, but no subject had recent SAH from the target IA and no subject was treated in the setting of IA rupture. Eight (7.4%) subjects had undergone prior interventions for the target IA. Forty-five subjects (41.7%) had cranial neuropathy at baseline. The most common IA locations were the cavernous

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

(45, 40.9%) and paraophthalmic (35, 31.8%) segments of the ICA. Mean IA size was 18.2 mm and mean neck size was 8.8 mm. 85 (78.7%) IAs were large (maximum fundus diameter [MFD] 10-25 mm) and 22 (20.4%) were giant (MFD ≥25 mm).

9.2.2 Procedure Characteristics

All subjects underwent PED placement under general anesthesia. PED was successfully placed in all cases but 1; in this 1 case, the IA could not be crossed with the micro-guidewire. One giant IA was treated with adjunctive coiling. Mean procedure time was 124 minutes (range 39-427). 364 PEDs were used in 107 subjects. 2 subjects underwent bilateral IA treatment. 341 PEDs were implanted into 107 target IAs (**Table 10**). The mean number of PEDs placed per IA was 3.1 (median 3, range 1-13, see **Table 11**).

Table 10. Characteristics of PED devices used in target IA.

PED length, mm	N Used
10	13
12	55
14	62
16	67
18	63
20	81
PED diameter, mm	**N Used**
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

Table 11. Number of PEDs placed per subject (n=107 pts).

# of PEDs placed	N (%)
# of PEDs placed	
1	2
2	34
3	50
4	12
≥5	9
Mean (range)	3.1 (1-15)

Eight PEDs were placed into the microcatheter but then removed for various reasons. In 4 cases, there was excessive resistance to passage of PED through the microcatheter. The device delivery success rate was 348/354 (98.3%). In 1 case a single PED was correctly placed into the distal parent artery but the physician lost access to the IA with the delivery system. The subject was successfully retreated 2 weeks later. One PED failure occurred, in which part of the delivery wire broke. The wire fragment was pulled into the proximal parent artery and “sealed” in place with 2 additional PEDs placed in a normal segment of the petrous ICA.

9.3 Safety and Effectiveness Results

9.3.1 Primary Safety Endpoint

The statistical hypothesis for the primary safety endpoint was met with a high degree of statistical significance.

The safety cohort in PUFS consisted of 107 subjects.[*] Six subjects (5.6%, 95% posterior credible interval CI 2.6 - 11.7%) were judged by the CEC to meet the primary safety endpoint. The posterior probability that the major safety endpoint rate was less than 20%, the predetermined safety success threshold, was 0.999979.[†] Four of the events occurred in the perioperative period before postoperative day 30, 1 occurred between day 30 and day 180 and 1 occurred at an unknown time. 3 events were ischemic, 2 were hemorrhagic and one was unknown. Listed below are the serious and non-serious adverse events.

9.3.2 Primary Effectiveness Endpoint

The statistical hypothesis for the primary effectiveness endpoint was met with a very high degree of statistical significance.

The PUFS effectiveness cohort consisted of 106 target IAs in 104 subjects.[‡] (Two subjects had contralateral qualifying IAs that were treated with PED.) Of the 106 target IAs, complete IA occlusion without major stenosis was seen in 78 (73.6%, 95% posterior credible interval 64.4-81.0%). The posterior probability that the effectiveness rate exceeded 50% was 0.999999.[§] Reasons for incomplete occlusion are shown in **Table 12**.

Table 12. Reason for not meeting primary effectiveness endpoint at 180 days.

Reason Why Non-Success	N
Residual neck	8
Residual aneurysm	6
Death	3
Spontaneous parent artery occlusion	3
Patient refused 180-day angiogram	2
Stenosis of parent artery >50%	2
Withdrew or lost to follow-up	2
Carotid-cavernous fistula	1
Coils used in fundus*	1
Total	**28**

*Coil use in fundus was disallowed in protocol. However, subject had complete IA occlusion without stenosis.

[*] One subject was excluded from the safety analysis because the physician could not pass the micro-guidewire could beyond the target IA and no attempt at treatment with Pipeline was performed.

[†] The primary statistical analysis was Bayesian. The frequentist analog, an exact binomial comparison of the observed 5.6% vs. a 20% threshold, yields a p-value of 0.00002.

[‡] Four subjects were excluded from the effectiveness cohort, 3 because of anatomic criteria and 1 because the investigator could not pass the micro-guidewire across the IA neck (and no attempt at PED placement was made).

[§] The primary analysis used was Bayesian. An analogous frequentist statistical test, an exact binomial comparison of the observed 73.6% vs. a 50% threshold, yields a p-value of 0.0000006.

9.3.3 Subgroup Analysis

Pre-specified subgroups for the primary safety and effectiveness endpoints are listed in **Table 13**. Subgroup analysis showed that no factor was statistically significantly predictive of increased or decreased success rates.

Table 13. Prespecified subgroups in PUFS.

IA maximum dimension ≥25 mm vs. <25 mm
IA neck size ≥6 mm vs. <6 mm
IA partial thrombosed at baseline or not
Current/former smoker vs. never smoker

9.3.4 Secondary Endpoints

The study's secondary endpoints were: 1) rate of complete IA occlusion at 1, 3 and 5 years of follow-up, 2) incidence of ipsilateral major stroke by 180 days, 3) change in modified Rankin scale (MRS) at 180 days, 4) change from baseline in neurologic signs/symptoms related to target IA, and 5) incidence of device-related adverse events at 180 days, 1, 3 and 5 years. Each is reviewed below.

Rate of complete IA occlusion at 1, 3, and 5 years of follow-up. One-year follow-up in PUFS is complete.[*] Of 104 subjects in the effectiveness cohort, 89 (85.6%) had a one-year angiogram and 15 did not. Among the 89 subjects (91 IAs) with angiograms at 1 year, complete occlusion was seen in 78 IAs (85.7%) and effectiveness success (complete IA occlusion without major stenosis) was seen in 75 (82.4%). Using a Bayesian approach to imputing outcomes amongst the 9 subjects who did not have angiogram at 1 year and taking into account known failures, the 1-year predicted complete occlusion rate was 80.7% (95% posterior credible interval 72.7-87.7%) and the 1-year predicted effectiveness rate was 78.0% (95% CI 69.5-85.3%). The Bayesian posterior probabilities that the 1-year complete occlusion and effectiveness rates exceeded 50% were >0.999999. To date, no IA that was occluded at 180 days has shown recurrence.

Incidence of ipsilateral major stroke by 180 days. The CEC judged that 6 of 107 (5.6%) had ipsilateral major stroke by 180 days.

Change in modified Rankin scale (MRS) at 180 days. **Table 14** shows the change in MRS at 180 days in all subjects in the safety cohort. MRS was improved at 180 days in 21 subjects (19.6%), the same in 70 (65.4%), worse in 10 (9.3%), and unevaluable in 6 (5.6%) cases. Causes for worsened MRS scores were: death (3 cases), headache (2), residual findings from stroke (2), diplopia (1) and "bubbling sound in ears" (1).

Table 14. Change in modified Rankin score at 180 days compared to baseline. Gray cells indicate worsening of MRS.

Freq		**Score at 180 days**							
		ND	**0**	**1**	**2**	**3**	**4**	**6**	**Total**
Score at Baseline	**ND**	0	1	0	0	0	0	1	2
	0	3*	**48**	5	1	0	0	1	58
	1	1	12	**20**	1	0	0	1	35
	2	1**	2	5	**1**	0	0	0	9
	3	0	0	1	1	**0**	0	0	2
	4	0	0	0	0	0	**1**	0	1
	Total	5	63	31	4	0	1	3	107

[*] 2-year follow-up began in November 2010.

*Patients withdrew from study
**Patient stopped participating prior to day 30 but still in contact with study site

Change from baseline in neurologic signs/symptoms related to target IA. 100 subjects were examined at baseline and 180 days of follow-up. 24 of 100 (24%) subjects had no signs/symptoms related to the target IA at either baseline or follow-up. 34 (34%) subjects had improved signs/symptoms, 9 (9%) had mixed changes, 19 (19%) had no change, and 6 (6%) worsened.

Device-related adverse events at 180 days. 21 adverse events (15 SAEs and 6 non-SAEs) were judged to be probably or definitely related to PED (**Table 15**). The rate of device-related AEs was 21/107 (19.6%). The rate of serious device-related events was 14% and the rate of non-serious device-related events was 5.6%.

Table 15. Adverse events rated as probably or definitely related to PED.

		Relatedness	
SAE	**Event**	**Probably**	**Definitely**
No	Headache	4	0
	Diplopia	1	0
	Nausea	1	0
Yes	Amaurosis fugax	5	0
	Carotid cavernous fistula	1	0
	Carotid occlusion	1	0
	Diplopia	0	1
	Headache	1	2
	Ischemic stroke	1	3
Total		**15**	**6**

9.4 Adverse Events

9.4.1 Serious Adverse Events

Table 16 shows serious adverse events in PUFS. 21 events occurred prior to Day 30 and 19 occurred after Day 30. 25 events were neurologic. 15 were rated as probably or definitely related to PED, 8 events were rated as probably or definitely related to the PED placement procedure, 10 were rated as probably or definitely related to use of antithrombotic agents, and 15 were rated as probably or definitely related to a pre-existing condition. **Table 17** shows relatedness of the SAE to the device and **Table 18** shows the distribution of events by timing.

Table 16. Serious Adverse Events in PUFS (n=107 subjects).

Event Type	N (%)
Neurologic Events	
Amaurosis fugax	5
Headache	5
Intracranial hemorrhage	5
Ischemic stroke	4
Carotid cavernous fistula	2
Carotid occlusion	1
Cilioretinal artery embolism	1
Diplopia	1
Possible intracranial hemorrhage	1

Non-Neurologic Events	
Non-neurologic bleeding	5
Cardiac arrhythmia	3
Dizziness/tinnitus	2
Colitis	1
Deep venous thrombosis	1
Lightheadedness/palpitations	1
Lung cancer	1
Pulmonary embolism	1
Rectovaginal fistula	1
Recurrent breast cancer	1
Pneumonia/urinary tract infection	1
Visual field worsened	1
Total	44

Table 17. Relatedness of serious adverse event to PED, PED placement procedure, use of antithrombotic medications and preexisting conditions as determined by clinical events committee (CEC).

Relatedness	PED	PED Placement Procedure	Antithrombotic Meds	Preexisting Condition
Not yet rated	4 (9.1%)	4 (9.1%)	4 (9.1%)	4 (9.1%)
Unrelated	14 (31.8%)	24 (54.5%)	28 (63.6%)	11 (25.0%)
Unlikely	2 (4.5%)	3 (6.8%)	1 (2.3%)	6 (13.6%)
Possibly	9 (20.5%)	5 (11.4%)	1 (2.3%)	8 (18.2%)
Probably	9 (20.5%)	2 (4.5%)	8 (18.2%)	11 (25.0%)
Definitely	6 (13.6%)	6 (13.6%)	2 (4.5%)	4 (9.1%)
Total	44 (100%)	44 (100%)	44 (100%)	44 (100%)

Table 18. Timing of serious adverse events.

Event started at or during interval before…	N (%)
Procedure	1 (2.3%)
Post-procedure /prior to discharge	15 (34.1%)
30 day follow-up	8 (18.2%)
90 day follow-up	5 (11.4%)
180 day follow-up	8 (18.2%)
1 year follow-up	7 (15.9 %)
Total	44 (100%)

9.4.2 Non-Serious Adverse Events

126 non-serious AEs occurred in PUFS; these are listed in **Table 19**. **Table 20**, **Table 21**, and **Table 22** show the number of non-serious AEs by follow-up interval, status and relatedness to device, procedure or underlying disease. Six events were probably or definitely related to PED, 15 were probably or definitely related to the PED placement procedure, and 18 were probably or definitely related to an underlying condition. Most events resolved completely. None of the events raised new issues regarding safety. No device changes were made as a result of adverse events in PUFS.

Table 19. Summary of non-serious adverse events.

Event	N	Event	N
Headache	34	Facial pain	1
Nausea	10	Femoral puncture site infection	1
Diplopia	6	Flashing lights in vision	1
Ptosis	4	Hair loss	1
Skin bruising	4	Hand itching	1
Non-neuro bleeding: Epistaxis	3	Headache and CN 3/6 neuropathy	1
Non-neuro bleeding: Groin hematoma	3	Headache due to trauma	1
Anemia	2	Hyperesthesia of trigeminal V1 distribution	1
Diplopia (CN6), ptosis (CN3)	2	Leg cellulitis	1
Dizziness	2	Nausea / loss of apetite	1
Fever	2	Nausea / vomiting	1
Floaters in vision	2	Non-neuro bleeding: GI bleed	1
Non-neuro bleeding: Hematuria	2	Non-neuro bleeding: Groin bleeding	1
Urinary tract infection	2	Non-neuro bleeding: Heavy menses due to ovarian cyst	1
VF worsened	2	Non-neuro bleeding: Scalp hematoma	1
Abducens palsy possibly worse	1	Non-neuro bleeding: Vitreal hemorrhage	1
Achiness	1	Non-neuro bleeding: groin bleeding	1
Acute sinusitis	1	Non-neuro bleeding: groin hematoma	1
Anxiety reaction	1	Non-neuro bleeding: vaginal spotting	1
Arterial line site swelling	1	Numbness in fingertips	1
Back pain	1	Poor eye movement on examination	1
Bilateral lower extremity edema	1	Possible CN 4 palsy	1
Blurry vision	1	Rash due to aspirin	1
Bronchitis	1	Sore throat	1
Bubbling sound	1	Subconjunctival hemorrhage	1
Constipation	1	Thigh pain	1
Corneal abrasion	1	UE vein thrombosis	1
Deep/superficial venous thrombosis	1	Upper respiratory infection	1
Eye floater	1	Vomiting	1
Eye pain	1	Worsened hemianopia	1
Facial anesthesia	1	**Total**	**126**

Table 20. Non-serious adverse events to date by interval.

Event started at or during interval before…	N (%)
Post-proc/prior to disc	52 (41.3%)
<30 days	42 (33.3%)
30-90 days	14 (11.1%)
90-180 days	14 (11.1%)
180 days – 1 year	4 (3.2%)
Total	126 (100%)

Table 21. Status of non-serious events to date.

Outcome	N
Resolved	94 (74.6%)
Ongoing but stable	24 (19.0%)
Not available	2 (1.6%)
Unknown	4 (3.2%)
Recovered with sequelae*	2 (1.6%)
Total	126 (100%)

*Example: Headache improved but not completely resolved.

Table 22. Level of relatedness to Pipeline device, placement procedure or pre-existing condition for non-serious adverse events to date.

	Relatedness to…		
Level of Relatedness	**PED**	**PED Placement Procedure**	**Preexisting Condition**
Not available	2 (1.6%)	1 (0.8%)	1 (0.8%)
Unrelated	71 (56.3%)	55 (44.4%)	80 (63.5%)
Unlikely	15 (11.9%)	13 (10.3%)	1 (0.8%)
Possibly	32 (25.4%)	41 (32.5%)	26 (20.6%)
Probably	6 (4.8%)	11 (8.7%)	12 (9.5%)
Definitely	0 (0%)	4 (3.2%)	6 (4.8%)
Total	126 (100%)	126 (100%)	126 (100%)

9.4.3 Additional Endpoints in PUFS

Additional endpoints in PUFS include those listed in **Table 23**. These additional endpoints were supportive of the primary and secondary endpoints in PUFS.

Table 23. Additional endpoints in PUFS.

Endpoint	**Result**
Technical success	100%
IA occlusion ranking at 180 days*	**Finding** / **N (%)**: Complete occlusion 81 (81.8%); Residual neck 8 (8.1%); Residual aneurysm 7 (7.1%); Indeterminate 3 (3.0%)
Complete occlusion rate including salvage treatment	73.6%
Incidence of neurologic death by 180 days	3/107 (2.8%)
Change in mean deviation index (MDI) of the visual field examination at 180 days	Change / N (%): Improved 19 (21.3%); Same 65 (73.0%); Worsened 5 (5.6%). In 4 of the 5 subjects who showed worsening of visual fields, test reliability was low, making interpretation of worsening difficult; in addition, some subjects had apparent worsening of pre-existing eye diseases (glaucoma, cataracts). In 1 case, worsened MDI was due to cilioretinal artery embolism.
Frequency of > 2 lines lost in visual acuity by Snellen chart	5/91 (5.5%)
Frequency of > 2 lines gained in visual acuity by Snellen chart	8/91 (8.8%)
Incidence of secondary treatments for the target IA	0 (0%)
Distal PED migration	0 (0%)
Stenosis in PED	2 (1.9%), 1 symptomatic

*Excludes 7 subjects in whom angiogram not done

9.5 Conclusions from the PUFS Study

Patients in PUFS had large or giant IAs of the ICA with wide necks. Many PUFS subjects were referred to treatment centers by neurosurgeons who could not offer any reasonable surgical treatment options. A review of published medical literature showed that long-term rate of complete IA occlusion with conventional treatments (coils, stent-assisted coiling, neurosurgical procedures) is low. In this difficult-to-treat patient population, the rate of complete IA occlusion without major stenosis after treatment with PED was high (73.6%, 95% posterior credible interval 64.4-81.0%). The safety profile of PED placement was good when taking into account the complexity of the target IA, with only 6 of 107 subjects (5.6%) having major stroke or neurologic death. Amongst patients with IA-related symptoms, symptomatic improvement was common, including some subjects with marked improvements in visual fields and visual acuity. Other clinical trial endpoints were supportive of the primary and secondary endpoints of the study.

10 Summary of Supplemental Clinical Information

10.1 PITA (Pipeline for Intracranial Treatment of Aneurysms)

PITA was a multicenter prospective interventional cohort of 31 subjects with small and large IAs that were either wide-necked (neck >4 mm or dome/neck ratio <2) or had failed previous attempts at treatment. Adjunctive coil placement was allowed. Clinical follow-up was performed 30 days and 180 days after PED placement. At 180 days, all subjects also underwent repeat angiography. Angiographic images were interpreted by a core radiology laboratory. The scale of Roy* was used to judge the level of occlusion as complete, residual neck and residual aneurysm. All subjects took dual antiplatelet therapy (aspirin and clopidogrel) preoperatively and for 3-6 months postoperatively.

31 subjects were treated, of whom 25 (81%) were female. Mean age was 54.6. Treated areas included the following areas of the ICA: paraophthalmic segment (15 subjects), cavernous (5), superior hypophyseal (4), posterior communicating (4), MCA proximal segment (1). Additional locations were vertebral artery (1) and vertebrobasilar junction (1). 12 of 31 (39%) had undergone previous treatment of the target IA. 71% of IAs had wide necks and slightly more than 1/3 were considered large (>10 mm maximum dimension). 47 PEDs were placed in 31 subjects. Embolic coils were used in 15/31 (48%) of cases. In one case, a Neuroform stent was also placed.

PED placement was successful in 46/47 (97.9%) of IAs. In one case, the device was delivered successfully to the target location but device placement was considered unsuccessful and the subject experienced a stroke after device removal. Two subjects (6.5%) experienced ipsilateral stroke soon after the placement procedure. Twenty-nine of 31 subjects without perioperative adverse events had identical neurologic status at the 180-day evaluation.

At 180 days, all subjects underwent repeat angiography. Of 30 cases, complete occlusion of the IA was seen in 28 (93.3%). Residual filling of the IA was seen in 2 (6.7%) cases. In post-study follow-up, 1 of 2 cases that were incompletely occluded at 180 days showed complete occlusion on repeat angiography at 1 year. Two-year post-study follow-up in all 30 cases has shown no cases of recanalization or evidence of late stenosis or late thrombosis. Physician satisfaction with device performance was very high.

10.2 Compassionate Use in the U.S.

PED has been used in 28 compassionate use cases in the US. Use of PED in the ICA in 12 lesions qualitatively similar to those enrolled in PUFS has shown a high rate of IA occlusion and low rate of stroke and death. Compassionate use of PED in very complex posterior circulation cases has also

* Stroke 2001;32:1998

shown excellent effectiveness and a good safety profile but this experience is still considered preliminary.

10.3 Special Access Use in Canada

PED has been used in >50 special access cases in Canada using the Special Access program. Experience in Canada in IAs of the ICA has been similar to that of PUFS; however, no formal prospective feedback was pursued.

10.4 Clinical Experience in Argentina

PED was used in >180 patients in Argentina under clinical investigation. Clinical experience in the first 53 cases (mean age 55.2 years, 48 women) has been published.[*] Treated IAs in these 53 were in both the anterior and posterior circulation and nearly half (48%) were large or giant. A total of 72 PEDs were used, with 1 PED in 44 IAs, 2 in 17 IAs and 3 in 2 IAs. Mean follow-up time was 5.9 months (range 1-22 months). Complete angiographic occlusion of the target lesion was seen in 93% of cases at 6 months. Amongst the 180 cases, 6-month follow-up showed 79% with complete occlusion. One-year follow-up showed 93% with complete occlusion. Fourteen patients have >2 years of follow-up. No IA recurrence has been seen.

11 Overall Conclusions from Clinical Data

Studies performed to date have shown that treatment of IAs with PED is very effective in completely occluding the target IA and carries a good safety profile. The pivotal (PUFS) study endpoints were met with a high degree of statistical significance and demonstrated that the benefits of PED treatment outweigh the risks. PITA showed that PED is effective both with and without use of adjunctive coiling. Use of PED in the compassionate use setting substantiated these clinical trial outcomes.

11.1 Risk/Benefit Analysis

The primary risks faced by patients undergoing reconstructive endovascular treatment of IA are ischemic or hemorrhagic stroke.

- **Ischemia** can occur due to coil prolapse into the parent artery or thrombosis or stenosis of the parent artery if a stent is placed. In PUFS, there was one case each (1/107, 0.9%) of parent artery thrombosis and parent artery stenosis causing stroke. In a recent large (n=284) cohort of patients undergoing Neuroform-assisted coiling of wide-necked IAs (of which only the minority were large or giant in size), there were 5 (1.8%) fatal perioperative infarctions and 4 (1.4%[†]) strokes due to in-stent stenosis or subacute stent thrombosis.[‡] Thus, the rate of ischemic or stenotic complications after PED placement appears similar to other approved intracranial endovascular implants.

- **Hemorrhagic risks** of endovascular IA treatment include IA perforation during the endovascular procedure and intracranial hemorrhage (ICH). In the Neuroform cohort described above, the rate of major stroke due to iatrogenic IA perforation was 2 in 284 (0.7%) and the rate of major stroke or death due to late intracranial hemorrhage was 4 in 284 (1.4%). The Neuroform cohort is relevant because patients in this study underwent intracranial artery device placement in the context of dual antiplatelet therapy for treatment of IA. In PUFS, 4 subjects (3.7%) had non-traumatic intracranial hemorrhage prior to

[*] Neurosurgery 2009;64:632-42.

[†] The percentages may be underestimates because follow-up was incomplete in this study.

[‡] JNIS 2009;10:1136.

postoperative day 30. One case was associated with use of tirofiban, a platelet inhibitor. One case was shown by autopsy to be distal to the treated IA and probably due to hypertensive hemorrhage. One case occurred in a subject with known coagulopathy who was treated with both dual antiplatelet therapy and warfarin, and had an elevated prothrombin time at the time of the bleeding event. The rate of hemorrhagic complications specifically associated with PED itself was low and most complications were related to use of dual antiplatelet therapy or additional medications given.

- Additional risks, especially in patients with large or giant IAs, include transient perioperative cranial neuropathies, possibly related to swelling at or near the thrombosing aneurysm, and ischemia due to low flow resulting from multiple coverage of a side branch with PED.

11.2 Effectiveness

The effectiveness of available treatments for large and giant IAs is known to be poor. In contrast, at 180-day angiography, 78 of 106 (73.6%) IAs in PUFS met the primary effectiveness endpoint (complete aneurysm occlusion without major stenosis of the parent artery). The high rate of complete occlusion observed in PUFS was supported by use of PED in PITA and other clinical settings (e.g., compassionate use). The effectiveness rate in PUFS met the pre-determined effectiveness threshold for the study, which was set substantially higher than historical rates for this difficult-to-treat patient population. Moreover, the effectiveness rate was high when taking into account known biases in the published medical literature, including: 1) common failure to report long-term occlusion rates, 2) unclear reporting of IA status, 3) high rates of loss to follow-up, 4) unconfirmed radiographic interpretation by study authors, and 5) unclear patient selection.

12 Conclusion

Clinical evidence from multiple sources demonstrates that the Pipeline™ Embolization Device (PED) is safe and effective when used for the treatment of large and giant IAs in the ICA and that the benefits outweigh the risks.