Sponsor Executive Summary

Pipeline Embolization Device
Executive Summary
P100018

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Executive Summary

1 Device Description

Pipeline™ Embolization Device (PED) is a braided, multi-alloy cylindrical mesh designed for the treatment of intracranial aneurysms (IA). PED is packaged on a simple guidewire system and is delivered into the parent artery of vessels affected by IA during an endovascular procedure. PED is available in fully expanded lengths of 10-20 mm and diameters of 2.5-5.0 mm.

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 Background

3.1 Definition, Epidemiology and Clinical Consequences

An aneurysm is an abnormal balloon-like bulging of an artery's wall. Intracranial aneurysms are those aneurysms occurring in brain arteries.

IAs are also commonly characterized by their shape and the size of the aneurysm neck. This PMA concerns large (maximum fundus diameter 10-25 mm) and giant (>25 mm) IAs and IAs that are wide-necked (neck ≥4 mm). Large and giant IAs are uncommon,[1-5] with an estimated incidence rate in the US of approximately 2,000 per year.

IAs have two major clinical consequences: rupture and mass effect. As the IA grows, its walls become weakened and the chance of rupture increases. IA rupture causes subarachnoid hemorrhage (SAH), a devastating injury with severe medical consequences. Approximately half of all patients with SAH die.[6] Of the survivors, another half are left functionally incapacitated.[7] While the rupture rate in small IAs is low, the rate in large and giant IAs is substantially higher.[8, 9] In some size subgroups, the 5-year rupture rate can be as high as 50%. In addition to rupture, large and giant IAs often impinge upon local nerves (so-called "mass effect"), causing blindness, double vision, facial pain and other major neurologic syndromes. Without treatment, mass effect from large and giant IAs typically worsens over time.

3.2 Available Treatments

Available treatments for unruptured large and giant IAs include deconstructive approaches, such as parent vessel occlusion or ligation, and reconstructive approaches such as surgical clipping and coil embolization. This PMA concerns reconstructive approaches only.

When IAs are large or giant, reconstructive treatment is often extremely difficult. Surgical morbidity and mortality rates in large and giant IAs remain very high, and many IAs cannot be treated surgically. Endovascular approaches to large/giant IA treatment consist primarily of placement of embolic coils into the fundus of the aneurysm. Unfortunately, the success rate of coil embolization for large and giant IAs has been shown in many studies to be very low. Moreover, regrowth of the IA after coil placement is common, especially in large/giant IAs with wide necks.

Intravascular stents that hold coils in place are available through the humanitarian device exemption (HDE) pathway. Unfortunately, manufacturers of these devices have not provided definitive information supporting the effectiveness of these stents.

3.3 Goals of Treatment

The primary goal of IA treatment is complete occlusion of the target IA. Complete occlusion of the IA isolates the IA from the parent artery circulation, thereby reducing exposure of the thin aneurysm walls to systemic blood pressure and decreasing the risk of rupture. Incomplete occlusion of the target IA leads to two consequences:

- **Incomplete occlusion increases risk of rebleeding**. Not surprisingly, incomplete occlusion of a target IA is associated with elevated risks of rebleeding. CARAT, a multicenter prospective and retrospective cohort of patients treated for IA rupture, confirmed that the more incomplete the occlusion of a target IA using coil embolization, the more likely the IA was to spontaneously rupture.[10] IAs that continued to fill showed a nearly 22-fold elevated risk of re-rupture.

- **Incomplete occlusion increases the risk of retreatment**. ISAT, a large randomized trial of surgical vs. endovascular treatment of ruptured IAs, showed that when an IA was incompletely occluded, the risk for retreatment of the target IA due to IA recurrence was 4- to 7-fold higher compared to IAs that were completely occluded. Retreatment implies that patients treated with embolic coils need to undergo repeated and prolonged monitoring to ensure that the target IA has been adequately treated.

Unfortunately, many published studies have shown that the larger an IA is, the less likely it can be completely occluded with embolic coils. Moreover, published literature has shown that the rate of perioperative adverse events in patients undergoing coiling of large/giant IAs is very high, with stroke rates of 5-10% and death rates of 5-10%.

In summary, **large and giant IAs remain an unmet medical need**. No therapy is available that can address the majority of large/giant IAs that provides a documented high rate of effectiveness and low rate of stroke/death.

4 PED Mechanism of Action

PED is designed to treat complex, wide-necked IAs by two mechanisms of action:

- **Flow disruption**. Placement of PED in the parent artery disrupts the pulsatile flow of blood from the parent artery into the IA fundus. Stasis of blood in the IA fundus leads to increased blood viscosity, which favors thrombosis. Formation of a blood clot relieves the aneurysm fundus walls from systemic blood pressure, minimizing the risk of spontaneous rupture.

- **Re-endothelialization**. PED forms a scaffold upon which endothelial cells can grow. Full coverage of the implant, including over the neck of the IA, seals the IA fundus from the parent artery, minimizing the risk of spontaneous rupture as well as recanalization. The PED mesh forms a distinct but smooth border between parent artery and aneurysm fundus.

Placing embolic coils into the fundus of an IA prevents the fundus from shrinking; worsening of mass effect after coil embolization is common. In contrast, PED is placed in the parent artery, not the aneurysm fundus. Clot that forms in the aneurysm fundus is reabsorbed by normal healing processes, potentially resulting in relief from mass effect.

5 Marketing History

As of December 2010, PED is approved for marketing in 51 countries worldwide. In commercial use outside of the US, the estimated rate of adverse events reported to the Sponsor was low (**Table 5-1**), especially given the broad indication in Europe (all intracranial aneurysms). There have been no new unanticipated adverse events and no recalls/field corrections.

Table 5-1. Adverse events reported to Sponsor since July 2009. Percent figures assume 1,600 patients treated.

Event Description	N (est %)
Anesthesia complication	1 (0.1%)
Delayed rupture	7 (0.4%)
Intraoperative hemorrhage	2* (0.1%)
Intraparenchymal hemorrhage	6 (0.4%)
Postoperative death, cause unknown	3 (0.2%)
Postoperative stroke	9 (0.6%)
Postoperative swelling	1 (0.1%)
Technical complication causing stroke	3 (0.2%)
Technical complication, no stroke	1 (0.1%)
Vasospasm	2** (0.1%)
Worsened mass effect	1 (0.1%)
Total	36 (2.3%)

*One patient treated insetting of SAH/acute aneurysm rupture.
**Both patients treated in setting of SAH/acute aneurysm rupture.

6 Summary of Preclinical Studies

PED has undergone a battery of pre-clinical tests. All biocompatibility and functional testing (**Table 12-1**) has passed.

Table 6-1. Biocompatibility testing for PED implant and delivery system.

Biocompatibility Testing according to ISO10993 and 21CFR58		Functional Testing
Implant	**Delivery System**	**Implant and Delivery System**
Acute Systemic Toxicity	Acute Intracutaneous Reactivity	Stent dimensional verification
Lymph Node Sensitization	Acute Systemic Toxicity	Percentage surface area
Acute Intracutaneous Reactivity	Lymph Node Sensitization	Foreshortening
Bacterial reverse mutation study	In Vitro Cytotoxicity	Post-deployment integrity
Cytotoxicity	In Vitro Haemolysis	Radial strength
Hemolysis	Plasma Recalcification Time	Tensile strength
In-Vitro Chromosomal Aberration	In Vivo Thrombogenicity	Stress analysis
Study in Mammalian Cells	Rabbit Pyrogen	Accelerated durability testing
Mouse Peripheral Blood		Radiopacity
Micronucleus Study		Deliverability
ASTM Partial Thromboplastin Time		Bond strength / joint integrity
C3a Complement Activation Assay		Coating integrity
SC5b-9 Complement Activation		Corrosion resistance
Assay		

PED has also undergone extensive animal testing. Acute animal studies showed that PED is easily placed in the target vasculature. Long-term studies in a well-accepted experimental aneurysm model have shown that PED treatment results in:

- A high rate of IA cure (i.e., complete occlusion)

- Very low injury scores
- IA shrinkage over time
- Preserved patency of covered side branches, even when side branches are covered with up to 3 PEDs. Branches remain patent due to flow demand.

7 Clinical Studies

Safety and effectiveness of PED were demonstrated in two clinical trials, summarized in **Table 7-1**. Each trial is summarized briefly below and described in more detail in further sections.

Table 7-1. Summary of clinical experience with Pipeline Embolization Device.

Clinical Experience	Study Design	Objective	Target aneurysms	Subjects Treated	Success Rate at 6 Mo	Stroke Rate at 6 Mo
PITA (Pipeline for Intracranial Treatment of Aneurysms) CE Mark Study	Multi-center, single-arm prospective cohort	Safety and effectiveness of PED	Difficult-to-treat wide-necked IAs	31	93.3%	6.5%
PUFS (Pipeline for Uncoilable or Failed Aneurysms) IDE Study	Multi-center, single-arm prospective cohort	Safety and effectiveness of PED	Large and giant wide-necked IAs	108	73.6%	5.6%

7.1 PITA

7.1.1 Design

PITA was a multicenter prospective interventional cohort of 31 subjects with small and large intracranial aneurysms 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[11] was used to judge the level of occlusion as complete, residual neck and residual aneurysm. As is standard in use of intracranial stents, all subjects took dual antiplatelet therapy (aspirin and clopidogrel) for 3-6 months after PED placement.

7.1.2 Results

31 subjects were treated, of whom 25 (81%) were female. Mean age was 54.6. Treated areas were primarily the internal carotid artery, with 1 case each in the vertebral artery and vertebrobasilar junction. 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. At 180 days, repeat angiography showed complete IA occlusion in 28 of 30 (93.3%). Residual filling of the aneurysm was seen in 2 (6.7%) cases. In post-study follow-up, 1 of 2 cases with residual filling at 180 days showed complete occlusion

on repeat angiography at 1 year. 2-year post-study follow-up in all 30 cases has shown no cases of recanalization or evidence of late stenosis or late thrombosis.

PITA showed a high aneurysm occlusion rate with use of PED with or without coils in subjects with wide-necked aneurysms or aneurysms that had failed previous treatments. The adverse event rate was low. Device performance was excellent. **CE mark (ability to market PED in Europe) was granted based on the PITA study.** PITA was published in the peer-reviewed medical literature.[12]

7.2 PUFS

7.2.1 Design

PUFS (Pipeline for Uncoilable or Failed Aneurysms) is the primary IDE study submitted by Chestnut Medical to support safety and effectiveness for its intended use. PUFS is a prospective, multi-center, single-arm interventional cohort. The study duration is 5 years. FDA agreed with Chestnut Medical that safety and effectiveness can be evaluated at the 180-day time point.

PUFS included patients with IAs of the internal carotid artery (ICA) that were both wide-necked (i.e., neck ≥4 mm) and either large (10-25 mm in largest dimension) or giant (>25 mm in largest dimension). PUFS excluded subjects with ruptured aneurysm, recent bleeding or stent in place. A subject could be included if prior non-stent treatment had failed.

Subjects underwent PED placement during an angiographic procedure in which PED alone was placed in the parent artery. Subjects were pre-treated with 325 mg aspirin for at least 2 days and 75 mg clopidogrel for at least 7 days (or a 600 mg loading dose of clopidogrel the day prior to the procedure). Intravenous heparin was used during the procedure. Subjects were asked to take dual antiplatelet therapy (aspirin 325 mg daily for at least 6 months and clopidogrel 75 mg daily for at least 3 months) after PED placement.

Subjects were seen in clinic at 30, 180 days and 1 year. At clinic visits, subjects underwent adverse event assessment and a detailed neurologic examination. Repeat angiography was performed at 180 days (primary endpoint) and 1 year. A neuro-opthalmologic examination, performed by an ophthalmologist prior to PED placement, was repeated at 180 days.

The **primary effectiveness endpoint** of the study was the proportion of subjects showing complete angiographic occlusion of the target IA without major (>50%) stenosis of the parent vessel at 180 days. IA occlusion was judged by an independent core laboratory.

The **primary safety endpoint** of PUFS was the proportion of subjects with major ipsilateral stroke or neurologic death by 180 days after treatment as judged by a clinical events committee. Major stroke was defined as increase from baseline in NIH Stroke Scale by 4 or more points up to 7 days after stroke.

As specified in the trial protocol, the study was to be interpreted as an effectiveness success if the effectiveness success rate was demonstrated to be statistically greater than 50% and the safety rate (stroke/death) was demonstrated to be statistically less than 20%. The threshold values for study success were based on a thorough literature review showing effectiveness rates for large/giant wide-necked IAs of <30% and unacceptably high stroke/death rates of 10-15%.

Key secondary endpoints included components of the primary safety and effectiveness endpoints, changes in neurologic status related to the target aneurysm, and device-related adverse events.

The study design was thought to be appropriate given the target IA population. A concurrent control group was not possible in the PUFS study because many subjects had IAs that could be treated with PED but could not be treated with standard endovascular therapy or surgery. Moreover, a review of published literature showed that there was substantial evidence confirming that the effectiveness of standard endovascular approaches to the treatment of large/giant IAs was very low.

7.2.2 Results

108 subjects were enrolled and treated. At 180 days, 100 subjects (96.2% of potentially available subjects) underwent evaluation. 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 108 subjects enrolled and treated, 96 (89%) were female and mean age was 57.0. Prior SAH was reported in 8 (7.4%) of subjects, but no subject had recent SAH from the target aneurysm and no subject was treated in the setting of aneurysm rupture. Eight (7.4%) subjects had undergone prior interventions for the target aneurysm. 45 (41.7%) had cranial neuropathy at baseline. Mean aneurysm size was 18.2 mm and mean neck size was 8.8 mm. 85 (78.7%) aneurysms were large (10-25 mm) and 22 (20.4%) were giant (≥25 mm).

All subjects underwent PED placement under general anesthesia. The aneurysm could not be crossed with the micro-guidewire in one case. In all other cases, PED was successfully placed. Only 1 aneurysm was treated with adjunctive coiling. Mean procedure time was 124 minutes (range 39-427). 341 PEDs were used in 107 target IAs. 2 subjects underwent additional treatment of a contralateral qualifying IA. The mean number of PEDs placed per aneurysm was 3.1 (median 3, range 1-13). The per-device delivery success rate was 349/357 (97.7%). 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 proximal ICA.

PUFS met its predetermined primary effectiveness endpoint. Of 106 target IAs in 104 subjects, complete IA occlusion with PED alone without major stenosis occurred in 78 (73.6%, 95% posterior credible interval 64.4-81.0%). The posterior probability that the effectiveness rate exceeded 50% was 0.999999.

The following preoperative characteristics were evaluated as **pre-determined subgroup analysis** for potential association with outcomes: IA size (large vs. giant), neck size (< 6 vs. ≥6 mm), partially thrombosed at baseline vs. not, and current/former smoker vs. never smoker. None of these predetermined subgroups were predictive of increased or decreased effectiveness.

PUFS met its predetermined safety endpoint. Of 107 subjects in the safety cohort, major ipsilateral stroke/neurologic death occurred in 6 (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.

Four major safety events occurred in the perioperative period (<30 days after PED placement), 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. Subgroup analysis

showed that the study's predetermined subgroups were not predictive of increased or decreased safety.

The study's secondary endpoints were supportive of the primary findings:

- **Rate of complete IA occlusion at 1, 3, and 5 years of follow-up.** PUFS is an ongoing study. One-year follow-up, completed in Fall 2010, showed a 1-year complete IA occlusion rate of 80.7%. Of 71 subjects with angiographic success at 180 days, 69 (97%) were also occluded at 1 year. To date, no IA that was occluded at 180 days has shown recurrence.

- **Incidence of ipsilateral major stroke by 180 days.** Six of 107 (5.6%) had ipsilateral major stroke by 180 days.

- **Change in modified Rankin scale (MRS) at 180 days**. 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.

- **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 aneurysm at either baseline or follow-up. 34 (34%) subjects had improved signs/symptoms, 19 (19%) had no change, 9 (9%) had mixed changes, and 6 (6%) worsened. Of subjects who improved, many had marked improvement in multiple modalities.

- **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. 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%.

21 serious adverse events occurred prior to Day 30 and 19 occurred after Day 30. 25 serious adverse 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. 3 subjects with SAEs died.

126 non-serious adverse events occurred. The most common events were headache and nausea. Most events resolved completely.

7.2.3 Conclusions of the PUFS Study

All subjects in PUFS had large or giant wide-necked IAs of the internal carotid artery. This is a difficult-to-treat aneurysm population with documented low rates of effectiveness and poor safety with available treatments. Many PUFS subjects were referred to treatment centers by neurosurgeons who could not offer any reasonable surgical treatment options.

In this difficult-to-treat subject population, PED's rate of effectiveness success (complete IA occlusion with PED alone without major stenosis) was very high (73.6%, 95% posterior credible interval 64.4-81.0%). The probability that the study met its predefined endpoint was 0.999999. PUFS also met its pre-defined safety endpoint (stroke/death rate of 5.6%, 95% posterior credible interval of 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. In subjects with mass effect related to the target IA, symptomatic improvement was common, including some remarkable improvements in visual fields and

visual acuity. Other clinical trial endpoints were supportive of the primary and secondary endpoints of the study.

8 Overall Conclusions

Large and giant IAs remain an **important unmet medical need**. Combined with the PITA study, PUFS study results show that **PED is a remarkable, breakthrough technology for the treatment of these previously untreatable large and giant IAs**. The benefits of PED for this difficult-to-treat patient population outweigh the risks.

9 Background Information

9.1 Intracranial Aneurysms

An aneurysm is an abnormal balloon-like bulging of an artery's wall. Intracranial aneurysms (IAs, also called cerebral or brain aneurysms) are those aneurysms occurring in brain arteries.

IAs are commonly characterized by their size and shape. This PMA concerns large (maximum fundus diameter 10-25 mm) and giant (>25 mm), and IAs that are wide-necked (neck ≥4 mm). Large and giant IAs are uncommon,[1-5] with an estimated incidence rate in the US of approximately 2,000 per year. An IA neck can involve part of the artery's wall, resulting in an aneurysm that is "saccular" (**Figure 9-1**) or it can involve the entire circumference of the parent artery, resulting in a "fusiform" aneurysm. Wide-necked IAs involve much of the artery wall. IA shape has a marked impact on available treatments (see **Section 9.6**).

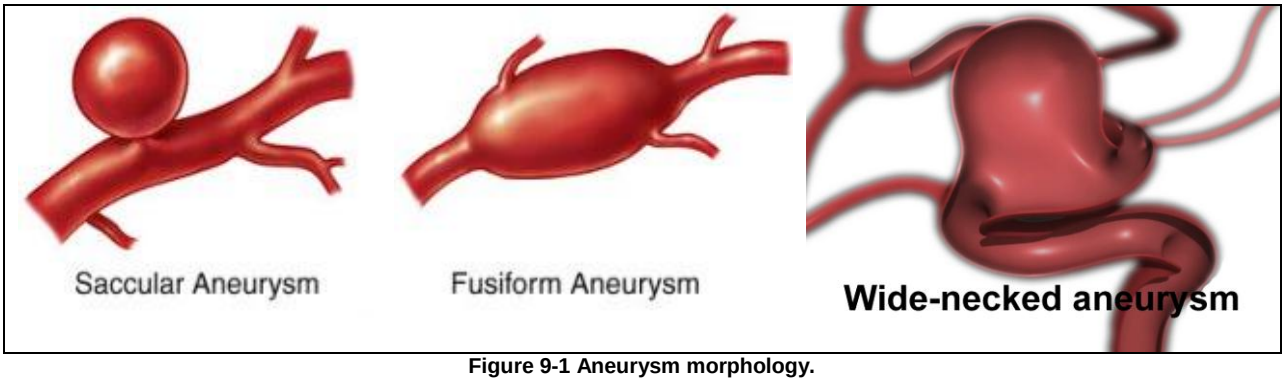


Figure 9-1 Aneurysm morphology.

9.2 Epidemiology

This PMA concerns large and giant IAs only. Large and giant IAs are uncommon,[1-5] with an age-adjusted incidence rate of 3.1 and 0.7 per 100,000.[1, 2] Roughly 1/3 of IAs are in the anterior circulation. Assuming a population of 304 million* persons at risk in the US and that 18% are in the ICA, the incidence of large and giant IAs in the internal carotid artery is approximately 2000/year (**Table 9-1**).

Table 9-1. Large/Giant aneurysm incidence calculation.

Aneurysm size	Rate	Proportion in ICA	US Annual Incidence*
Large (10-25 mm)	3.1/100,000	18%	1,696
Giant (>25 mm)	0.7/100,100	18%	383
Total			2,079

*Assuming US population of 304 million

* http://www.census.gov/popest/states/NST-ann-est.html, accessed October 12, 2009

9.3 Aneurysm Rupture

As an aneurysm bulges, its walls become weakened and its chances of rupture increase. IA rupture causes subarachnoid hemorrhage (SAH), a condition with severe medical consequences. The SAH case-fatality rate is 51%.[6] Of survivors, nearly half are left functionally incapacitated.[7] Those who survive often face a prolonged hospital course combined with severe residual neurologic abnormalities.

9.4 Aneurysm Size Predicts Rupture Risk

IA rupture is uncommon in small IAs. However, in large and giant IAs, the risk is substantially higher. For example, in the ISUIA study of unruptured aneurysms, large unruptured IAs had a 13% 6-year risk of rupture and giant IAs had a 27% 6-year risk of rupture (**Figure 9-2**).[8, 9] In some subgroups, the 5-year rupture rate was as high as 50%.

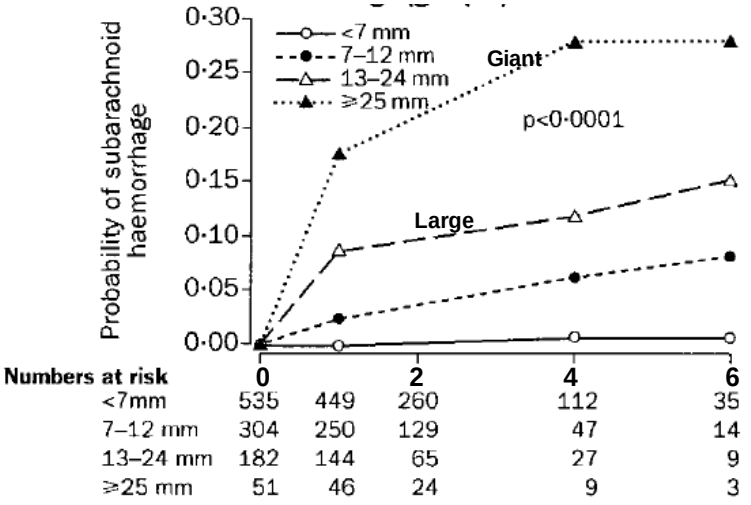


Figure 9-2. Risk of rupture in unruptured IAs by size.[9]

9.5 Aneurysms Exert Mass Effect

In addition to rupture, large and giant IAs often impinge upon local nerves, causing blindness, double vision, facial pain and other major neurologic syndromes. This is called "mass effect." Without treatment, mass effect from large and giant IAs typically worsens over time. Unruptured aneurysms can also be the source of embolic stroke.

9.6 Available Treatments

This PMA concerns the treatment of large and giant IAs only. Available treatments for unruptured large and giant IAs include "deconstructive" and "reconstructive" approaches, as described below.

9.6.1 IA Deconstruction

Deconstructive IA treatment means permanently removing or destroying the parent artery from which the IA originates. Deconstruction can be done surgically (i.e., ligation of the parent artery) or via an endovascular approach (placing coils or balloons in the parent artery with the intent of occluding the entire parent artery).

9.6.2 IA Reconstruction

Reconstructive IA treatment involves surgical or endovascular approaches to treating the IA without sacrificing the parent artery. The most common surgical reconstructive

approach is placing a clip directly on the IA neck. The most common endovascular approach involves placing embolization coils or embolic liquids into the aneurysm fundus, leaving the parent artery patent. PED is a new type of reconstructive treatment, increasing the available choices for parent artery reconstruction.

9.7 Limitation of Available Treatments

9.7.1 Limitations of IA Deconstruction

IA deconstruction requires adequate collateral circulation to the brain distal to the artery to be sacrificed. Without adequate collateral circulation, sacrifice of the parent artery will cause major stroke. Even when adequate collateral circulation is demonstrated (for example via transient occlusion of the carotid artery using a balloon), deconstruction can sometimes cause major stroke. Deconstructive therapy is available to only a minority of patients with IAs.

9.7.2 Limitations of IA Reconstruction

While it can be effective for small IAs, reconstructive IA treatment for large and giant IAs can be extremely difficult. Surgical clipping of large and giant IAs often requires complex multi-clip reconstruction of the parent vessel. Intra-aneurysmal thrombus or calcification of the wall of the aneurysm are common features of large and giant aneurysms and can further complicate the surgical therapy. Depending on the IA location, surgical clipping can involve dissections that are associated with very high perioperative morbidity.

Most large/giant IAs are wide-necked; in this situation, endovascular reconstruction using coils is commonly limited by lack of a suitable aneurysm neck to hold coils in place (**Figure 9-3**) and migration of coils into the parent artery occludes the parent artery occlusion and cause massive stroke. Intravascular stents, available through the humanitarian device exemption (HDE) pathway, can be placed into the parent artery of a wide-necked IA to hold coils in place. However, the effectiveness of this approach has not been demonstrated. Moreover, many IAs in the PUFS study were not treatable using these HDE-approved devices.

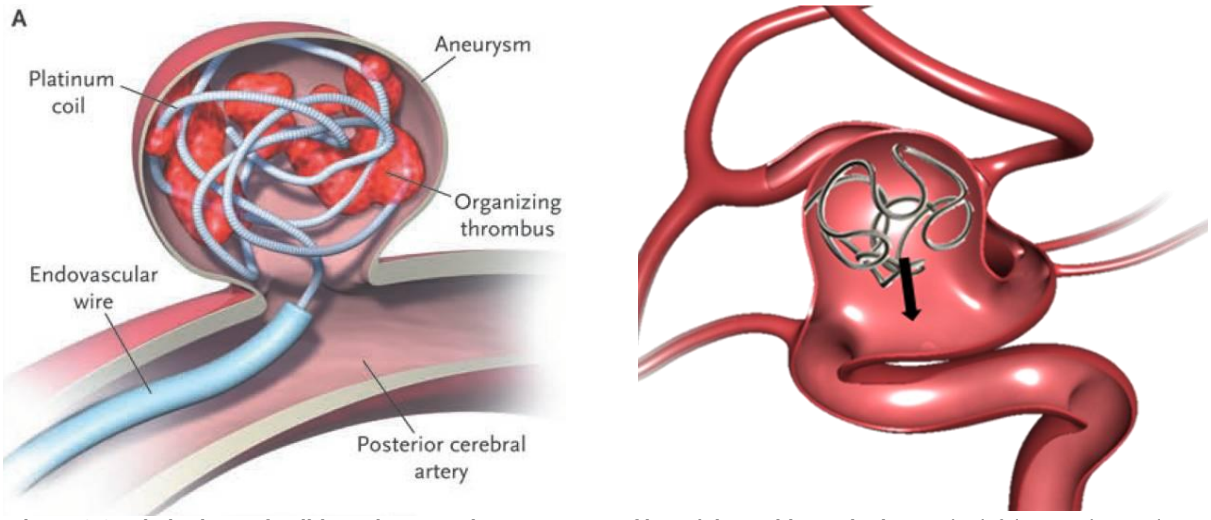


Figure 9-3. Limitations of coil-based approach to treatment of large/giant wide-necked IAs. The left image shows placement of coils into a small aneurysm using an endovascular approach. The right image shows the limitations of coil placement into large/giant wide-necked IAs: coils simply fall back into the parent artery (arrow), resulting in occlusion of the parent and stroke.

9.8 Incomplete Occlusion Associated with Elevated Risk of Re-bleeding

The goal of IA treatment is <u>complete occlusion of the aneurysm fundus</u>. Complete occlusion of the IA implies a permanent and complete separation of the IA from the parent artery circulation, reducing exposure of the thin IA walls to systemic blood pressure and decreasing the risk of rupture and recurrence/retreatment.

Not surprisingly, incomplete occlusion is associated with elevated risks of re-bleeding. A multicenter cohort study of patients treated for IA rupture confirmed that incomplete occlusion of the target IA results in an increased risk of IA re-rupture.[10] The more incomplete the occlusion, the higher the risk of rupture (**Figure 9-4**). IAs that continued to fill showed a nearly 22-fold elevated risk of re-rupture.

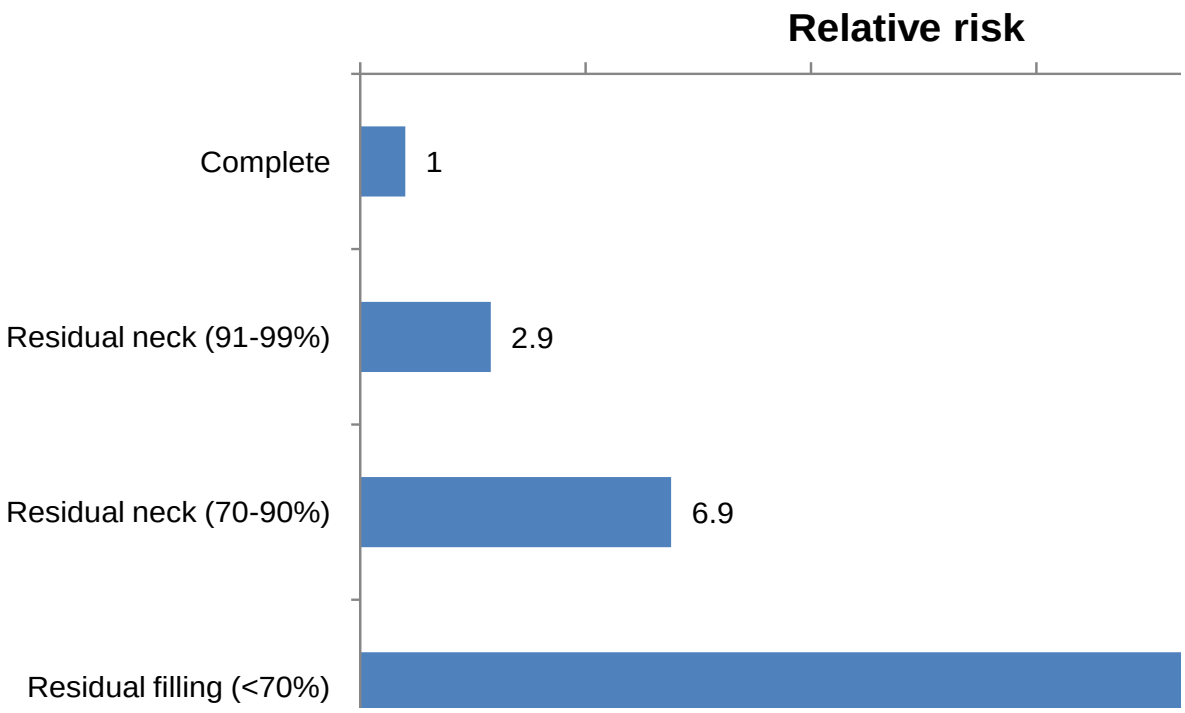


Figure 9-4. Re-rupture rate of coiled IAs by degree of initial occlusion.[10]

9.9 Incomplete Occlusion Increases Risk of Retreatment

Incomplete occlusion of an IA also increases the risk of retreatment. ISAT, a large randomized trial of surgical vs. endovascular treatment of ruptured IAs, showed that when an IA was incompletely occluded, the risk for retreatment of the target IA due to IA recurrence was 4- to 7-fold higher compared to IAs that were completely occluded (**Table 9-2**).[13] Retreatment implies that patients treated with embolic coils need to undergo repeated and prolonged monitoring to ensure that the target IA has been adequately treated.

Table 9-2. Risk of retreatment when aneurysm incompletely occluded.[13]

Occlusion grade	N (%) retreated	RR for retreatment
Complete	34/586 (5.8%)	-
Subtotal or neck	47/228 (20.6%)	4.1 (2.6-6.4)
Incomplete	13/69 (18.8%)	7.6 (3.3-17.5)

9.10 Complete Occlusion Rate Decreases with Increasing IA Size

Despite its limitations, coil embolization is the current standard for the treatment of wide-necked large and giant IAs. Unfortunately, the rate of complete IA occlusion for large and giant IAs is low, and the larger the IA, the more likely incomplete occlusion occurs. For example, in a very large series from University of California Los Angeles, 56% and 73% of early (1990-1995) and late (1996-2002) subjects with small-necked IAs had complete occlusion, respectively.[14] In contrast, complete occlusion occurred in only 40% of large (11-25 mm) aneurysms and 26% of giant (> 25 mm) aneurysms. Similar results have been observed in other studies (see, for example, **Figure 9-5**).

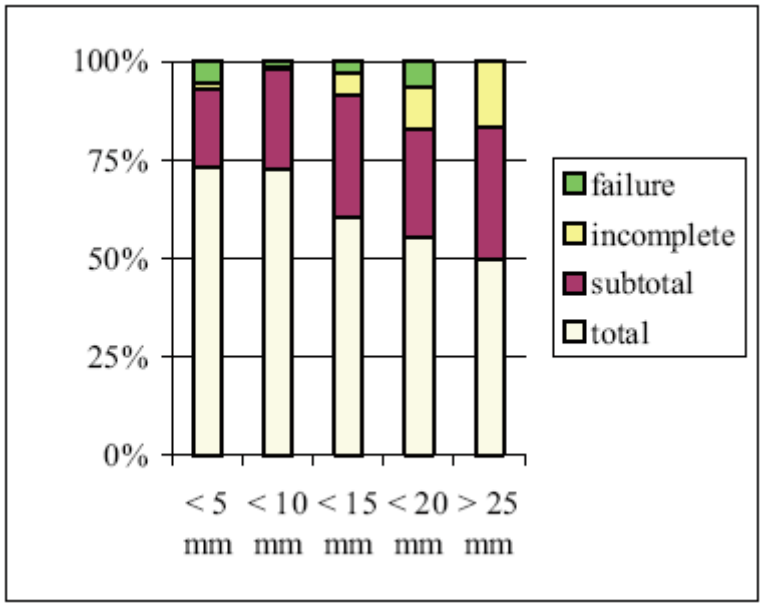


Figure 9-5. Post-procedure angiographic outcomes after IA treatment with coil embolization.[15]

The presence of a wide neck also predicts low rates of complete IA occlusion. In the UCLA series, 56% and 73% of early (1990-1995) and late (1996-2002) subjects with small-necked IAs had complete occlusion.[14] In contrast, only 46% (early) and 41% (late) of those with small aneurysms and wide necks had complete occlusion. A thorough literature review conducted prior to PUFS (see below) showed that complete occlusion of large and giant IAs is uncommon. **It is the low likelihood of complete angiographic occlusion of large/giant IAs that prompted the development of PED.**

9.11 Literature Review

As part of the PUFS investigational device exemption (IDE) study, Chestnut Medical performed a comprehensive literature search regarding surgical and endovascular treatment of large and giant IAs. 1,200 abstracts were reviewed and data were extracted from 250 full-text articles reporting relevant clinical experiences. The comprehensive literature search supported the overall design of

the PUFS study. The following conclusions were drawn regarding the treatment of large and giant IAs:

- **Complete aneurysm occlusion after neurosurgery** for large and giant IAs is rarely documented and the reported success rates are low.

- **Stroke after aneurysm surgery was common**. Of 89 reported articles, 18 cohorts were identified. Most cohorts reviewed were a mixture of giant, large and small aneurysms. Stroke or intracranial hemorrhage after aneurysm surgery varied across studies. 4 cohorts reported 0 strokes; the remaining 14 cohorts reported rates from 4-25%.

- **Death after aneurysm surgery** ranged from 0-14%. Review articles on surgery for giant IAs have noted death rates as high as 25%[16] and combined morbidity/mortality rates as high as 45%.[17]

- **Complete aneurysm occlusion after endovascular treatment** of large and giant IAs is uncommon. Studies commonly documented rates <30%.

- **Stroke after coil embolization, with or without stents** occurred in 2-10% of subjects in 77 published cohorts. Of those cohorts that distinguished stroke rates amongst IAs of different sizes, **stroke was more common among patients with large or giant IAs**.

- **Death after reconstructive IA treatment** varied from 0 to 13.8%**. Cohorts with a high fraction of giant IAs reported the highest death rates**.

The literature review concluded that:

- The long-term safety and effectiveness of surgical and endovascular approaches to IA treatment decreases the larger the IA size.

- The long-term effectiveness of surgical and endovascular approaches to large and giant IA treatment is low, probably <30%. Effectiveness was defined as documented complete occlusion of the aneurysm.

- The stroke and death rate from commonly used surgical and endovascular approaches to large and giant IA treatment showed a combined major stroke/death rate of at least 10-15%.

9.12 Rationale for PED

PED was designed to address the limitations of prior treatments for large/giant IAs. **Table 9-3** shows how PED addresses the major deficiencies of current treatments for large and giant IAs.

Table 9-3. Summary of how PED addresses deficits of current approaches to large and giant IA treatment.

Problem	PED addresses problem by…
Surgery	
Complex dissection required to access target IA	Endovascular procedure, no dissection required
Prolonged recovery	Endovascular procedure, rapid recovery
Coil Embolization	
Target IA cannot hold coils in place	PED stays in place by anchoring to normal vessel proximally and distally.
Coils in target IA represent permanent mass in aneurysm fundus, potentially worsening mass effect of target IA	With PED, coil placement in the IA fundus is not necessary. PED is placed in the parent artery, not IA fundus. The fundus shrinks after PED placement, potentially relieving mass effect symptoms
Coils may migrate and compact into the IA fundus, allowing the IA to reopen, often requiring retreatment and increasing the risk for spontaneous rupture	PED reconstructs the vessel, eliminating need for coils and reducing chance of recurrence
Intracranial Stents	
Require coils for treatment	Coils not required with PED use but can be used if necessary
Buckle or kink when placed in tortuous anatomy	PED design avoids avoid buckling/kinking when placed in tortuous artery

10 Device Description

10.1 Implant Description

PED consists of a braided, multi-alloy mesh cylinder-shaped implant combined with a simple guidewire-based delivery system. The PED is provided sterile (EtO) with the implant compressed inside an introducer sheath (**Figure 10-1**, upper). The implant is manufactured from [redacted] alloy wires (**Figure 10-1**, lower). [redacted] is radiopaque and both [redacted] and [redacted] are known to be biologically inert, making them ideal metals for a permanent endovascular implant. Moreover, [redacted] has a long history of usage as a neurological embolization material in the form of detachable coils.

[redacted]

Figure 10-1. Pipeline Embolization Device (PED). Upper figure shows device constrained in introducer sheath. Lower figure shows PED implant subassembly, which is trimmed during manufacturing to the appropriate length (10-20 mm).

The braided configuration of PED results in approximately [redacted] metal coverage of the arterial wall [redacted] free area). The system is designed to be introduced into commercially available 3F neurovascular microcatheters (with an ID of [redacted]) for delivery to the target vessel adjacent to the intracranial aneurysm. By virtue of its woven mesh construction, PED is designed to conform precisely to the walls of highly tortuous arteries such as those found in the intracranial circulation. PED is manufactured in lengths from 10-20 mm and fully expanded diameters of 2.5 to 5.0 mm.

10.2 Delivery System Description

The PED delivery system is a 175 cm micro-guidewire-based technology. The core wire is 304SS with a [redacted]. The [redacted] coils [redacted], the [redacted]l marker a [redacted]y, and the [redacted] joints are a [redacted].

The tip is designed to be soft and flexible, to allow placement into distal neurovasculature with minimal trauma to vessels. The [redacted] until the operator deploys PED. Rotating the proximal delivery wire [redacted] of PED, allowing it to spontaneously expand into the parent artery. Other than being held in place [redacted]. A [redacted] 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.

The PED delivery system is manufactured by [redacted] the components into place with the [redacted] marker position [redacted].

10.3 Device Mechanism of Action

PED placement is intended to treat IAs by two mechanisms of action:

- **Flow disruption**. Placement of PED in the parent artery disrupts the pulsatile flow of blood from the parent artery into the IA fundus. Stasis of blood in the IA fundus leads to increased blood viscosity, which favors thrombosis. Formation of a blood clot relieves the aneurysm fundus walls from systemic blood pressure, minimizing the risk of spontaneous rupture.

- **Re-endothelialization**. PED forms a scaffold upon which endothelial cells can grow. Full coverage of the implant, including over the neck of the IA, seals the IA fundus from the parent artery, minimizing the risk of spontaneous rupture as well as recanalization. The PED mesh forms a distinct but smooth border between parent artery and aneurysm fundus.

Placing embolic coils into the fundus of an IA prevents the fundus from shrinking; worsening of mass effect after coil embolization is common. In contrast, PED is placed in the parent artery, not the aneurysm fundus. Clot that forms in the aneurysm fundus is reabsorbed by normal healing processes, potentially resulting in relief from mass effect.

11 Procedure Description

PED is placed into the brain artery during an endovascular procedure. The femoral artery is cannulated using standard techniques. A guide sheath is placed into the aorta. A guide catheter is placed through the guide sheath into the proximal brain artery. A microcatheter is placed through the guide catheter into the parent artery just distal to the target IA. The PED delivery system is introduced into the proximal end of the microcatheter and the protective sheath is removed and discarded. PED on its delivery wire is passed through the microcatheter into the parent artery just distal to the IA. The PED delivery wire is then advanced and the microcatheter simultaneously retracted, exposing the distal end of PED. The delivery wire is rotated clockwise to release the distal end from the [redacted]. The remaining portion of PED is then exposed to deploy the proximal end. If placement of a second PED is required, the microcatheter is passed through the previously placed PED and the delivery process repeated.

Principle actions involved in deploying PED are shown in **Figure 11-1**. Draft instructions for use are provided in **Appendix 1**.

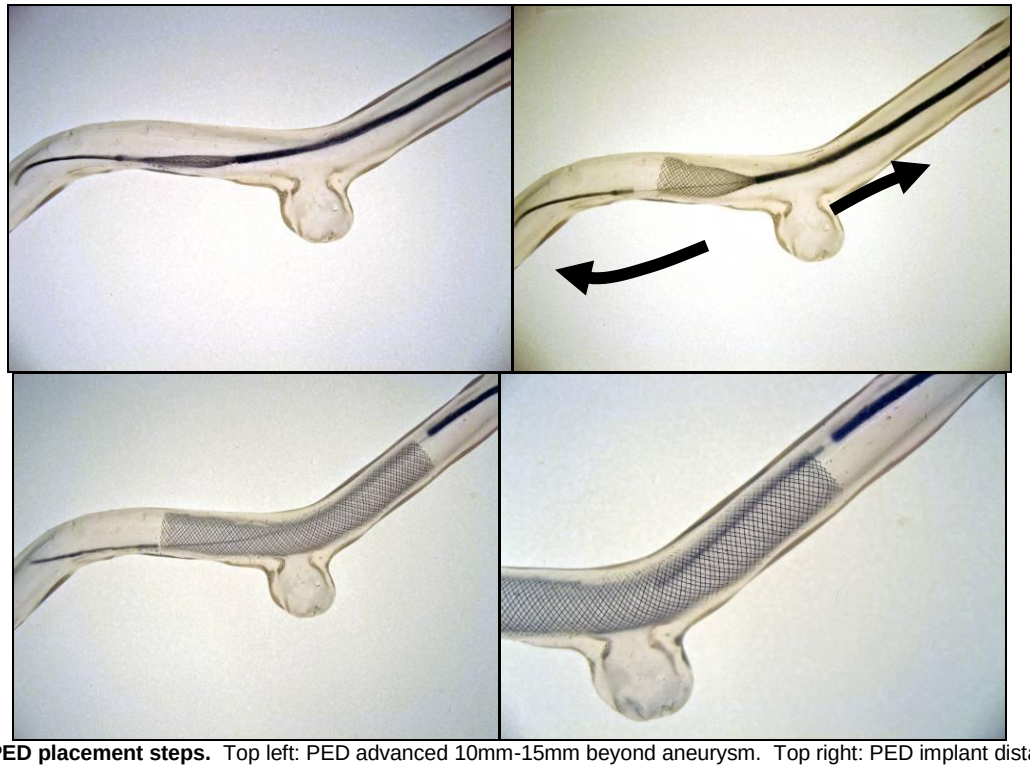


Figure 11-1. PED placement steps. Top left: PED advanced 10mm-15mm beyond aneurysm. Top right: PED implant distal end expanded. Bottom left: PED implant fully deployed across the aneurysm. Bottom right: PED delivery system withdrawal.

12 Summary of Preclinical Studies

Biocompatibility testing of Pipeline and the PED delivery system, summarized in **Table 12-1** was performed according to ISO 10993-1 and 21CFR58. All testing passed.

Table 12-1. 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	

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 12-2**) confirmed that PED and the PED delivery system met functional requirements for safe and effective use in humans. Additional functional studies included shelf-life and package validation, and MRI compatibility testing.

Table 12-2. 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

Animal studies included 3 short-term implantation studies, 2 long-term (6-month) studies and one long-term (12 month) study (**Table 12-3**).

Table 12-3. Animal study summary.

Study Location	Study Type	Study Model / Results
Mayo Clinic	Acute	Rabbits with elastase-induced surgical aneurysms. PED easily placed in parent artery across aneurysms.
LyChron	Acute	Pigs without aneurysms. PED compatible with microcatheter, easily delivered into target vessel, sufficient radiopacity, expanded well and anchored. Covered side branches patent.
Mayo Clinic	Acute	Rabbits with elastase-induced surgical aneurysms. PED implants easily placed into parent artery across aneurysm neck. PED sufficiently radiopaque, compatible with microcatheter, detached well, expanded well. No acute migration. Side branches patent acutely.
Mayo Clinic	Chronic (2 studies)	1-, 3- and 6-month sacrifice of rabbits with elastase-induced surgical aneurysms treated with single PED. Low artery injury scores histologically, all treated aneurysms occluded with good healing. No evidence of migration or stenosis in parent vessel. All covered side branches patent.
Mayo Clinic	Chronic	6- and 12-month sacrifice of rabbits without aneurysms treated with 1, 2 or 3 PEDs one inside the other, all positioned in the abdominal aorta covering lumbar arteries. At sacrifice, all covered lumbar arteries patent angiographically and histologically. Histology consistent with smooth, thin layer of neo-intimal growth and re-endothelialization. Injury scores very low.

Acute studies showed that PED was easily placed in the target vasculature, was compatible with microcatheters, had sufficient radiopacity, and did not show migration.

Long-term studies showed that all surgically created aneurysms in both studies were occluded at 6 months. These studies have been published in the medical literature.[18, 19] Histology showed excellent healing of the aneurysms, 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. 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 long-term study of side branches showed that side branches (lumbar arteries) remained open at 6 and 12 months even when 2 and 3 PEDs were placed one inside the other. Arteries probably remain open due to demand gradients.

13 Marketing History

PED has been commercially available outside the US since June 2008. Formal launch of PED outside of the US began in September 2009. Product launch was controlled, with appropriate physician training and proctoring. PED is currently available in 51 countries worldwide and more than 1,600 patients have been treated worldwide to date. In Europe and other locations, PED's indication includes treatment of any intracranial aneurysm (i.e., is not restricted to a particular anatomic location in the brain).

Between July 2009 and mid-January 2011, 3,452 PED devices have been provided to physicians outside of the US. Adverse events reported to Chestnut/ev3 are summarized in **Table 13-1**. On occasion, physicians have used PED in subjects with SAH from acute aneurysm rupture. The estimated event rates are low, especially given the broad indication for PED in Europe. There were no new unanticipated adverse events. There have been no recalls and no changes to the labelled indication.

Table 13-1. Adverse events reported to Sponsor since July 2009. Percent figures assume 1,600 patients treated.

Event Description	N (est %)
Anesthesia complication	1 (0.1%)
Delayed rupture	7 (0.4%)
Intraoperative hemorrhage	2* (0.1%)
Intraparenchymal hemorrhage	6 (0.4%)
Postoperative death, cause unknown	3 (0.2%)
Postoperative stroke	9 (0.6%)
Postoperative swelling	1 (0.1%)
Technical complication causing stroke	3 (0.2%)
Technical complication, no stroke	1 (0.1%)
Vasospasm	2** (0.1%)
Worsened mass effect	1 (0.1%)
Total	36 (2.3%)

*One patient treated insetting of SAH/acute aneurysm rupture.
**Both patients treated in setting of SAH/acute aneurysm rupture.

14 US Regulatory History

The main study in which PED has been used in the US is PUFS (see **Section 17**). **Table 14-1** summarizes regulatory events in the PUFS IDE study as well as the modular PMA application. In June 2010, FDA noted that this PMA would undergo expedited review. Chestnut Medical has passed a quality system and manufacturing FDA audit as well as a clinical "BIMO" audit. In addition, two PUFS sites in the US underwent and passed a BIMO audit. Throughout these inspections there were no observations.

Table 14-1. Timeline of regulatory events.

Event	Date Submitted	Date Approved
PUFS IDE study	[redacted]	
PMA Module 1 (pre-clinical) approval		
PMA Module 2 (manufacturing) approval		
PMA Module 3 (clinical)		

*Conditional approval, full approval in May 2009

PUFS enrollment is complete. However, a small number of sites are enrolling subjects into PUFS-CA, a continued access* study nearly identical to PUFS. This pathway allows physicians to have continued access to an unapproved medical device during the time period in which FDA is evaluating the device for approval. PUFS-CA was approved by FDA on January 10, 2010. To date, 20 subjects have been enrolled in PUFS-CA with no occurrence of stroke.

15 Summary of Clinical Studies

Table 15-1 lists the clinical experiences submitted in support of PED for the treatment of large and giant IAs. PITA, described in Section 16, was a multicenter prospective study of patients with untreatable or recurrent aneurysms not suitable for treatment with coils. PUFS, described in **Section 17**, is a multicenter IDE study of PED in the treatment of wide-necked large and giant IAs of the internal carotid artery. Compassionate use of PED in the US is described in **Section 18**. All studies and clinical uses involved patients with difficult-to-treat IAs and showed a high rate of complete occlusion of the target aneurysm with a low rate of stroke.

Table 15-1. Summary of clinical studies supporting PED.

Study / Cross-Reference	Setting	Design/Setting	Patients	Results
PITA Section 16 *(CE Mark study)*	Europe and South America	Multicenter prospective single-arm study (n=31)	Wide necked IAs unsuitable for treatment with coils	93% complete occlusion @180 days 6.5% perioperative stroke
PUFS Section 17 *(IDE study)*	US, Europe, Middle East	Multicenter prospective single-arm study (n=108)	Large and giant, wide-necked IAs of the internal carotid artery	74% complete occlusion @180 days 5.6% stroke @180 days
Comp Use Section 18	US	Case series under compassionate use (n=28)	Individual patients with untreatable IAs not suitable for clinical trials	High rate of angiographic cure, low rate of stroke/death

16 PITA

16.1 Design and Methods

PITA was a multicenter prospective interventional cohort of 31 patients with small and large intracranial aneurysms that were either wide-necked (neck >4 mm or dome/neck ratio <2) or had failed previous attempts at treatment. PITA was conducted in four centers in Europe and South America. Patients were treated with PED with or without adjunctive placement of coils. 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[11] was used to judge the level of occlusion as complete, residual neck and residual aneurysm. All patients took dual antiplatelet therapy (aspirin and clopidogrel) for 3-6 months after PED placement.

PITA was conducted under compliance to ISO14155 and all study data were monitored.

* For a description of continued access, see http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080260.htm.

16.2 Patient and Aneurysm Characteristics

31 subjects were treated, of whom 25 (81%) were female. Mean age was 54.6. Treated areas included the following areas of the internal carotid artery (ICA): paraophthalmic segment (15 patients), 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 in maximum dimension).

16.3 Procedure Outcomes

47 PEDs were placed in 31 patients. Embolic coils were used in 15/31 (48%) of cases. In one case, a Neuroform stent was also placed. 46 of 47 (97.9%) PED devices were placed successfully.

16.4 Effectiveness

At 180 days, 30 of 31 subjects underwent repeat angiography.[*] Of 30 cases, complete occlusion of the aneurysm was observed by the core laboratory in 28 (93.3%). Residual filling of the aneurysm was seen in 2 (6.7%) cases, both of whom had pre-existing neurovascular stents at the site of IA treatment.

16.5 Safety Outcomes

Two subjects (6.5%) experienced ipsilateral stroke soon after the placement procedure. One patient had a basal ganglion infarct resulting in right-sided hemiparesis with motor aphasia immediately upon awakening. One patient had slow flow in the ICA immediately following PED placement. Angioplasty of the PED and supraclinoid carotid artery was performed, resulting in iatrogenic rupture of the supraclinoid artery; the patient underwent carotid ligation. CT scan performed 3 days later showed a left hemispheric stroke. The remaining 29 of 31 subjects without perioperative adverse events had no change in neurologic status from the baseline to 180-day evaluation.

16.6 Post-Study Follow-Up

PITA was a 6-month study. However, PITA patients have returned to clinic for extended clinical follow-up. In this “post-study” follow-up, all 28 patients with complete occlusion at 6 months were also completely occluded at approximately 2 years of follow-up. Of the 2 IAs that were not completely occluded at 6 months in PITA, one was completely occluded at late (2-year) follow-up. There have been no cases of late recanalization, stenosis or thrombosis.

16.7 Conclusions from PITA

PITA showed that treatment of difficult-to-treat IAs with PED was safe and effective, with a high rate of angiographic cure. **PITA study data were sufficient for CE marking, allowing legal marketing of the device in Europe.** PITA was published in the peer-reviewed medical literature.[12]

[*] One subject had intraoperative iatrogenic rupture of the ICA and subsequent surgery; this subject did not undergo follow-up angiography.

17 PUFS

PUFS is the primary IDE study submitted in support of this PMA application.

17.1 Study Overview

PUFS (Pipeline for Uncoilable or Failed Aneurysms) is a multicenter, single-arm interventional clinical trial. PUFS was executed under investigational device exemption (IDE) approval granted by US FDA.

17.2 Physician Participants

PUFS investigators were interventional neuroradiologists or neurosurgeons. Investigators were trained in placement of PED using a benchtop model and underwent proctoring by PED-experienced physicians.

17.3 Trial Design and Justification

PUFS was a single-arm, prospective interventional cohort. A randomized trial was discussed at length with FDA but rejected as infeasible for a number of reasons:

- The target IA population was likely to include many IAs that could be treated by PED but not by any particular single alternative treatment.
- The current standard for treatment, coil embolization, was predicted to be infeasible in many subjects.
- 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. Several subjects were referred to PUFS by prominent neurosurgeons who had no reasonable treatment alternative to offer.
- Although intracranial stents are available through the HDE route, manufacturers of these stents have brought no definitive evidence of effectiveness to FDA, so these stents were deemed not relevant. Moreover, many IAs in PUFS were not treatable with stent-assisted coiling.
- The likelihood of long-term success with coil embolization (with or without stenting) in large/giant IAs was demonstrated by review of the published medical literature to be poor. As noted above, many PUFS IAs were predicted to be “uncoilable.”
- 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.

17.4 Study Protocol

17.4.1 Target Population

Eligible patients had IAs of the internal carotid artery (ICA) that were both wide-necked (i.e., neck ≥4 mm) and either large (≥10 mm and <25 mm) or giant (≥25 mm) in size. Eligibility criteria are shown in **Table 17-1**.

Table 17-1. Study inclusion and exclusion criteria.

Inclusion Criteria	Exclusion 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	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 [redacted] 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 t) Intracranial stenosis greater than 50% in the treated vessel

17.4.2 PED Placement

Prior to PED placement, subjects took oral aspirin (325 mg daily for 2 days) and clopidogrel (75 mg daily for 7 days or single 600 mg dose 1 day prior to placement procedure). Placement of PED was done under general anesthesia in a neuroradiology suite. Intravenous heparin was administered after placement of the microcatheter and prior to PED placement with the goal of increasing activated clotting times (ACT) to at least twice normal.

17.4.3 Post-Placement Medical Regimen

Postoperatively, subjects were required to take 325 mg aspirin daily for at least 6 months and 75 mg clopidogrel daily for at least 3 months, after which use of these agents was at the investigator's discretion.

17.4.4 Assessments and Follow-Up Schedule

All patients in PUFS underwent the following assessments.

- **Baseline**. At baseline, patients underwent medical history and neurologic examination. The neurologic examination focused on cranial nerves II-VI, as these nerves are most likely to be affected by IAs of the ICA. Investigators ranked neurologic function using the NIH Stroke Scale (NIHSS) and the Modified Rankin Scale (MRS). NIHSS is a commonly accepted measure of severity of stroke; scores range from 0 (no neurologic abnormalities) to 42 (severe

neurologic deficit).[20] NIHSS was re-assessed at any time during study follow-up if a stroke occurred. MRS is a validated scale of global neurologic function ranging from 0 (no symptoms) to 6 (dead).[21] In order to better understand response to treatment, and under the expectation that cranial neuropathies affecting eye function would be common and improvement in eye dysfunction resulting from reduced mass effect would occur after PED placement, subjects were also asked to undergo examination by a neuro-ophthalmologist prior to PED placement and 180 days after PED placement. This examination consisted of the following assessments:

  - Fundus photograph (baseline only).
  - Detailed cranial nerve (CN) exam.
  - Visual acuity using a Snellen chart.
  - Visual field (VF) assessment using automated static perimetry.

- **Procedure**. PED was placed during an angiographic procedure performed in the angiography suite. Just prior to PED placement, patients underwent angiogram to assess the dimensions of the target IA. Immediately after PED placement, angiography was repeated to obtain immediate post-placement views of the IA and PED. Various aspects of the procedure were recorded (e.g., procedure time, use of heparin, etc.).

- **Prior to discharge**. Patients underwent repeat neurologic examination by the investigator prior to hospital discharge to document any changes in neurologic status and/or adverse events.

- **Clinic visits**. Subjects had clinic visits at 30 days, 180 days and 1 year.[*] At clinic visits, patients underwent focused medical history assessment, detailed neurologic examination, and MRS score assessment. Patients were also assessed for the occurrence of adverse events. Repeat catheter angiography of the treated vessel was performed at 180 days (primary endpoint) and at 1 year.

- **Phone calls**. Sites called study subjects at 90 days after PED placement.[†] The primary purpose of phone call was to assess medical status and the occurrence of adverse events.

Although the study includes very late follow-up visits (3 and 5 years), FDA agreed that the study's primary endpoints could be evaluated at the 180-day visit.

17.4.5 Radiographic Imaging

Because the primary effectiveness endpoint of PUFS, described in a section below, was radiographic, investigators were asked to provide the following angiographic images:

- Pre-placement: digital subtraction angiogram (DSA) images in the AP, lateral and working views, and 3D reconstructions. 3D reconstructions allow improved visualization of the complexity of the target IAs compared to standard 2D views.

[*] PUFS is a 5-year study, and clinic visits at 3 and 5 years will begin in 2011.

[†] Phone calls are also required at 2 and 4 years after PED placement.

- Immediately post-placement: DSA and plain fluoroscopic images in AP, lateral and working views. The post-placement plain fluoroscopic view was used as a comparator against which to judge device migration at 180 days. (Device migration has been seen with other intracranial stents.[*])

Late follow-up (180 days, and 1, 3 and 5 years after placement): DSA and plain fluoroscopic images in the AP, lateral and working views.

17.4.6 Core Radiology Laboratory Assessments

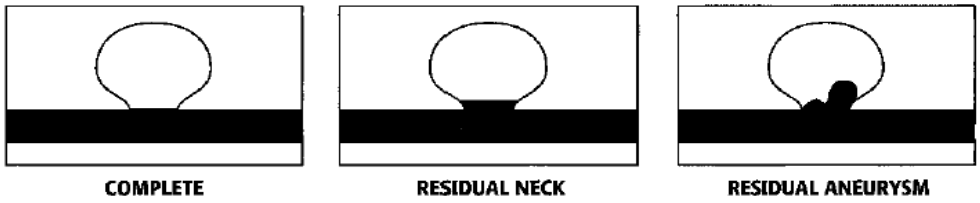
A core radiology laboratory, consisting of 3 experienced neuro-interventionalists, viewed all angiographic images submitted by investigators and adjudicated the radiographic change in IA status. Core laboratory assessments included:

Occlusion: Degree of angiographic occlusion of the target IA according to the scale of Roy (see **Figure 17-1**).[11] This rating system is commonly used in the medical literature to assess the success of IA treatment.

Stenosis: Degree of narrowing of the parent artery in follow-up compared to baseline. Stenosis was judged according to the method of Samuels[28], which was used in the WASID study.[29]

Migration: Whether device migration occurred, comparing immediate post-placement views with identical angiographic views taken later. Device migration was defined as a change in location of a PED device of 5 or more mm compared to the immediate post-placement location.

Figure 17-1. Criteria of Roy[11] for judging IA endosaccular embolization success.



Complete = complete occlusion, no flow of contrast seen in the sac
Residual Neck = partial occlusion, some flow, or eddying flow, in the sac
Residual Aneurysm = incomplete occlusion, apparent flow into the sac

All core radiology laboratory assessments were independent of the Sponsor and each rater was unaware of the other raters' ratings.

17.4.7 Clinical Events Committee

All reported adverse events meeting the ISO14155 definition for serious adverse event (SAE)[†] were reviewed by the Clinical Events Committee, consisting of an interventional

[*] Device migration refers to movement of an implant after deployment, and has been reported with with Neuroform[22-24] and Enterprise[25-27] intravascular stents. Both of these devices are manufactured from laser-cut nitinol hypotubes and have persistent radial force post deployment that can cause a "watermelon seed" movement when deployed in vessels of different calibers. In contrast, PED is a [redacted], which can taper and accommodate varying parent vessel diameters resulting in a more stable implant. Endothelialization of the implant, which, in animal studies occurs in weeks to months, results in a device incorporated into the wall of the parent vessel, thus preventing device migration.

[†] ISO14155:2003 defines a serious adverse event as any adverse event that:

neurologist, an interventional neuroradiologist and a neurologic surgeon. The CEC came to consensus on each event and the CEC's adjudication as to whether the event met the definition for the study's primary safety endpoint was used in the primary safety endpoint analysis.

17.5 Primary Endpoints

The **primary effectiveness endpoint** of the study was complete angiographic occlusion of the target IA at 180 days with PED alone in the absence of >50% stenosis or the use of other devices (e.g., coils) in the target aneurysm. IA occlusion and parent artery stenosis were judged by the core radiology laboratory. In case of disagreement between the 3 core laboratory radiologists, a "2 out of 3" approach was used.

The **primary safety endpoint** is the occurrence of major ipsilateral stroke or neurologic death by 180 days after treatment. Major stroke was defined as a stroke present after 7 days that increases the NIH Stroke Scale score by at least 4 points. Whether an adverse event met the definition for the primary safety endpoint was adjudicated by the CEC.

17.5.1 Justification for Primary Endpoints

Effectiveness. Prior studies have shown that incomplete IA occlusion increases the risk of rupture and retreatment. Therefore, PUFS was designed with a "high bar" for effectiveness, namely complete occlusion of the target IA.

Safety. The primary risks of either surgery or endovascular approaches to IA treatment are stroke resulting from ischemia or stenosis and intracranial bleeding resulting from aneurysm rupture or procedure-related perforation. Therefore, PUFS counted any major ipsilateral stroke or neurologic death occurring within 180 days of device placement as meeting the primary safety endpoint. When comparing stroke rates, it should be noted that **most published studies report only perioperative strokes**.

17.5.2 Study Success Criteria

A Bayesian approach to statistical analysis and interpretation of clinical trial success was used for primary endpoints. As documented in the study protocol, the study was to be interpreted as a success if the following two conditions were met:

$$\Pr(p_E > 0.50 \mid \text{Trial Data}) > 0.975$$

AND

$$\Pr(p_S < 0.20 \mid \text{Trial Data}) > 0.975$$

That is, the posterior probability that the effectiveness rate (p_E) exceeds 50% given trial data is at least 0.975 and the posterior probability that the safety rate (p_S) is less than 20% is at least 0.975. A non-informative beta(1,1) prior distribution was used for both calculations. The 0.975 probability values are analogous to one-sided p-values of 0.025.

Justification for effectiveness success threshold. At the time of IDE submission, an initial literature review showed that the effectiveness of coil embolization, the current

---

1. Led to a death
2. Led to a serious deterioration in the health of the subject that
   a. resulted in a life-threatening illness or injury
   b. resulted in a permanent impairment of a body structure or a body function
   c. required in-patient hospitalization or prolongation of existing hospitalization
   d. resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function
3. Led to fetal distress, fetal death or a congenital abnormality or birth defect.

treatment standard for large/giant IAs, was poor, with long-term effectiveness rates substantially less than 50%. FDA asked for a complete summary of the published literature on this topic. In January 2009 Chestnut submitted a comprehensive review of the effectiveness and safety of surgical and endovascular approaches to large and giant aneurysm treatment. This review, which summarized 250 published clinical cohorts, concluded that the long-term complete occlusion rate for large and giant IAs treated with surgical or endovascular approaches was <30%. For this reason, a new technology with a 6-month complete occlusion rate statistically exceeding 50% represents a significant advance for this patient population.

Justification for safety success threshold. The sample comprehensive literature review submitted in January 2009 also examined the safety of surgical and endovascular approaches to IA treatment. The review showed that the risk of stroke from large/giant IA treatment was 10-15% and the risk of perioperative neurologic death was in the same range. It should be noted that **most studies reported only perioperative outcomes**; very few reported morbidity and mortality out to 6 months after treatment. FDA agreed that a procedure with an associated long-term stroke/neurologic death rate having an upper confidence limit of <20% would represent a treatment that, in the setting of a high complete occlusion rate, would be seen as having a positive benefit-risk balance for the target patient population.

17.5.3 Power Analysis

Chestnut submitted a detailed power analysis to FDA prior to study initiation. The analysis showed that a sample size of 100 subjects had a high chance of showing study success given then-current knowledge of safety and effectiveness. **It should be noted that a sample of 100 subjects represents a substantial proportion of the estimated target population for the device.**

17.5.4 Interim Analysis

The statistical analysis plan included a description of Bayesian interim analysis aimed at early cessation of enrollment in the setting of a high predicted probability of eventual trial success. Aspects of the interim analysis will not be described, since study enrollment was completed before the first interim analysis could be done.

17.6 Subgroup Analyses

The study protocol included subgroup analyses of the primary effectiveness and safety endpoints for the following subgroups:

- 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

These subgroups were selected because they were known to be predictive of long-term success in patients treated with coil embolization. Fisher's exact test was used to compare proportions reaching the primary effectiveness or safety endpoints for each subgroup. Adjustment for multiplicity was performed using the Holm step-down procedure.[30]

17.7 Secondary Endpoints

PUFS secondary endpoints are listed in **Table 17-2**. These endpoints focused on effectiveness at later time points, components of the primary safety endpoint, and change in neurologic signs or symptoms related to the target IA at 180 days.

Table 17-2. Secondary endpoints.

1. Complete occlusion of the target IA at 1, 3 and 5 years
2. Ipsilateral stroke at 180 days
3. Change in Modified Rankin Scale $\geq$ 2 points at 180 days
4. Change from baseline in neurologic signs/symptoms related to target IA at 180 days
5. Device-related adverse events at 180 days, 1, 3 and 5 years

17.8 Additional Endpoints

Additional study endpoints are listed in **Table 17-3**. Additional endpoints focused on technical aspects of the procedure (technical success), a more detailed assessment of aneurysm occlusion rankings, a component of the primary safety endpoint (neurologic death) and eye function.

Table 17-3. Additional endpoints.

Endpoint	Comment
Technical success, defined as the proportion of patients in whom at least one attempt was made to pass the access catheter distal to the target IA in whom the final locations of the PEDs placed are all within 5 mm of the desired location.	Judged by investigator
IA occlusion ranking at all post-procedure timepoints	Judged by core laboratory using scale of Roy
Complete IA occlusion at 180 days, including salvage treatments, if provided	Judged by core laboratory
Incidence of **neurologic death** by 180 days	Adjudicated by clinical events committee
Change in **mean deviation index** (MDI) of the Humphrey Visual Field Assessment from baseline to 180 days after the index treatment	Measured by study ophthalmologist
Frequency of **worsened eye alignment** by clinical examination	Measured by study ophthalmologist
Frequency of $\geq$ **2 lines lost** in visual acuity by Snellen chart	Measured by study ophthalmologist
Frequency of $\geq$ **2 lines gained** in visual acuity by Snellen chart	Measured by study ophthalmologist
Incidence of **secondary treatments for the target IA**	
Distal PED migration, defined as distal movement of one or more PEDs of more than 5 mm in its parent artery location when comparing the 180-day angiogram with the post-placement angiogram.	Judged by core laboratory
Proportion of PED subjects in whom more than **mild stenosis at the PED occurs**.	Judged by core laboratory using methods adopted from WASID

17.9 Protocol Deviations

Deviations from the protocol were captured continuously throughout the enrollment and follow-up periods. Deviations were characterized as major or minor (**Table 17-4**).

Table 17-4. Definition of protocol deviation types.

Deviation	Definition

Type	
Major deviation	Any deviation from subject inclusion and exclusion criteria, subject informed consent procedures or unauthorized device use.
Minor deviation	Deviation from a protocol requirement such as incomplete/inadequate subject testing procedures, follow-ups performed outside specified time windows, etc.

17.10 Results

17.10.1 Study Enrollment

111 patients were enrolled in PUFS between November 2008 and July 2009. **Table 17-5** shows the number of study patients by site. 79 patients were enrolled in the US and 32 outside of the US. Extensive analyses requested by FDA comparing US vs. OUS (outside of US) subjects showed no systematic differences. Three patients, who were enrolled into the study but were withdrawn prior to treatment, were eliminated from all analyses and not considered further.

Table 17-5. PUFS enrollment by clinical site.

Site ID	N Subjects Enrolled
01	3
02	5
04	30
05	21
08	7
09	4
10	14
12	18
13	2
15	7
Total	111

17.10.2 Patient Characteristics

17.10.2.1 Baseline Characteristics – Medical History

Baseline characteristics of the 108 subjects who underwent a PED placement procedure are shown in **Table 17-6**. The preponderance of women in PUFS was not surprising, as female gender is a strong risk factor for IAs.[9] There were no statistically significant differences in age, IA neck and IA size across study sites. Medications at baseline were varied and were almost entirely for the treatment of diseases other than IA (not shown). Similarly, baseline medical conditions were varied (not shown) and were unrelated to the target IA. Hypertension was very common, consistent with it being a known risk factor for IA. Eight subjects had undergone previous treatment for the target IA, of which 6 had undergone coil embolization.[*]

[*] Note: coils in place in the target IA was not an exclusion criterion.

Table 17-6. Baseline characteristics (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	
SAH	8 (7.4%)
Stroke	7 (6.5%)
Coronary artery disease	6 (5.6%)
Hypertension	60 (55.6%)
Diabetes	7 (6.5%)
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%)

17.10.2.2 Baseline Characteristics – Physical Examination

Physical examinations by both the study investigator and the participating ophthalmologist were performed in all subjects prior to the procedure (**Table 17-7**). Cranial neuropathies relevant to IAs in the ICA (i.e., cranial nerves II through VI) were common, occurring in 45/108 (41.7%) subjects.

Table 17-7. Baseline characteristics of PUFS subjects (n=108).

Characteristic	Mean (SD, Range) or N (%)
Body mass index, mean (range), n=105	27.3 (5.2, 17.6-44.0)
Blood pressure, n=107	
Systolic, mean (range)	130.3 (17.0, 99-180)
Diastolic, mean (range)	78.0 (9.8, 52-109)
NIH Stroke Scale	
0	78 (72.2%)
1	21 (19.4%)
2	3 (2.8%)
5**	1(0.9%)
6**	1(0.9%)
10**	1 (0.9%)
Not done	3 (2.8%)
Modified Rankin Score	
0	60 (55.6%)
1	34 (31.5%)
2	9 (8.3%)
3	2 (1.9%)
4	1 (0.9%)
Not done	2 (1.9%)
Cranial neuropathy	
CN 2	20 (18.5%)
CN 3	20 (18.5%)
CN 4	3 (2.8%)
CN 5	7 (6.5%)
CN 6	21 (19.4%)

**Subjects had previously documented stroke. In one case ([redacted]), stroke was due to emboli from the target IA.

17.10.2.3 Aneurysm Characteristics

PUFS included only IAs of the ICA that were at least 10 mm in size and had a wide neck (i.e., neck ≥4 mm). All IAs met size and location criteria (**Table 17-8**) except for three.[*] Mean aneurysm size was 18.2 mm. 80% of IAs were large, 19% were giant and 1% were small.[†] Mean neck size was 8.8 mm and mean dome was 14.6 mm. There was no variation in aneurysm size or neck length across study sites (ANOVA p-values of 0.7641 and 0.8480, respectively).

Although it was not formally assessed, it should be noted that investigators excluded no subjects from participation in PUFS because the IA was too large or too difficult to treat or because the vascular anatomy was too tortuous.

Table 17-8. Target IA characteristics (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%)

*This small aneurysm was excluded from the effectiveness analysis.
**This non-qualifying aneurysm was excluded from effectiveness analysis.

17.10.3 Procedure Characteristics

All subjects received both aspirin and clopidogrel preoperatively. These agents were administered according to the protocol-required dosing regimen in 103 and 98 subjects, respectively.

All subjects underwent PED placement under general anesthesia and heparin was used in all cases. Procedures lasted from 39 to 427 minutes (mean 124 minutes, **Table 17-9**), which is typical for endovascular procedures for IA treatment. Longer procedure times were primarily due to complex maneuvers required to catheterize the parent artery distal to the target IA, which is necessary for PED placement. Fluoroscopy time averaged 48.4 minutes (range 8 – 205.6). Although a direct comparison to coil embolization is not possible, investigators noted that procedure/fluoroscopy times with PED were shorter

[*] One IA was cervical, not intracranial; one was in the posterior communicating segment of the IA and had a stent in place, and one was too small.

[†] Small aneurysm was excluded from effectiveness analysis.

than what they would typically expect in those cases in which IAs could potentially be treated with coils.

Table 17-9. 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)

*Fluoroscopic equipment at one site did not measure fluoroscopy time.

17.10.3.1 PED Use

One or more PEDs was successfully placed in 107 of 108 (99.0%) of study subjects. In one subject [redacted]), 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 only.

In the 107 subjects in whom PED was placed, 341 PEDs were placed in the target IA (**Table 17-10**). Two subjects underwent treatment of both the target IA and a contralateral qualifying IA. Thus the total number of PEDs implanted was 349. PEDs of all currently manufactured lengths were used (**Table 17-11**). On average, 3.1 PEDs were used per IA (median 3, range 1-13, see **Table 17-12**).

Table 17-10. PED placement by target and device disposition.

	Disposition			
Aneurysm treated	Implanted	Inserted into Microcatheter Then Removed*	Opened Not Used*	Total
Target aneurysm	341	8	7	356
Contralateral aneurysm	8	0	0	8
Total	349	8	7	364

Table 17-11. Characteristics of PED devices used in target aneurysm.*

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

* Note that Chestnut currently manufactures PEDs with lengths of 10, 12, 14, 16, 18, and 20 mm and diameters of 2.5, 2.75, 3.0, 3.25, 3.5, 3.75, 4.0, 4.25, 4.5, 4.75 and 5.0 mm, comprising a total of 66 different configurations.

Table 17-12. Number of PEDs placed per subject (n=107 pts).

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

Eight PEDs (2.2%) were inserted into the microcatheter and subsequently removed for various reasons, primarily excessive resistance. No subject had an adverse event directly related to removal of the PED from the microcatheter and all went on to successful PED placement.

17.10.3.2 Device Failures

Of 357 devices placed into the delivery catheter and/or inserted into the parent artery, 1 (0.3%) broke. In this subject [redacted]), the tip of the deliver wire distal to the protective coil broke just after delivery of the last device; the wire fragment could not be removed. An additional PED was used to trap the fragment in place between PED and the artery wall. The subject did not have an adverse event attributable to the wire fragment.

17.10.4 Clinical Follow-Up

Subject flow in PUFS is described graphically in **Figure 17-2**. Subject loss to follow-up and withdrawal were minimal:

- One subject [redacted]) refused to attend the 30-day visit and subsequently withdrew from the study. She had normal neurologic status at last contact.
- One subject [redacted]) stopped actively participating in the study at approximately day 30. She had two "house calls" from a study site physician in her home town in rural Northern Wisconsin, primarily to assess safety outcomes.
- One subject [redacted]) became lost to follow-up after the Day 90 phone call.
- One subject [redacted] refused to participate further in the study after the 90-day phone call and did not undergo 180-day angiogram. The subject was readmitted to the hospital at approximately 1 year after PED placement with headache. Angiogram showed new contralateral (right-sided) IAs. The target (left-sided) IA was completely occluded.
- One subject ([redacted]) withdrew from the study after the 180-day angiogram.

One subject's (P15-004-HAMMA) parent artery could not be catheterized distal to the target IA; this subject did not undergo PED placement but rather underwent repacking of the IA with coils. Three subjects died during the first month after the procedure (see **Section 17.10.6**).

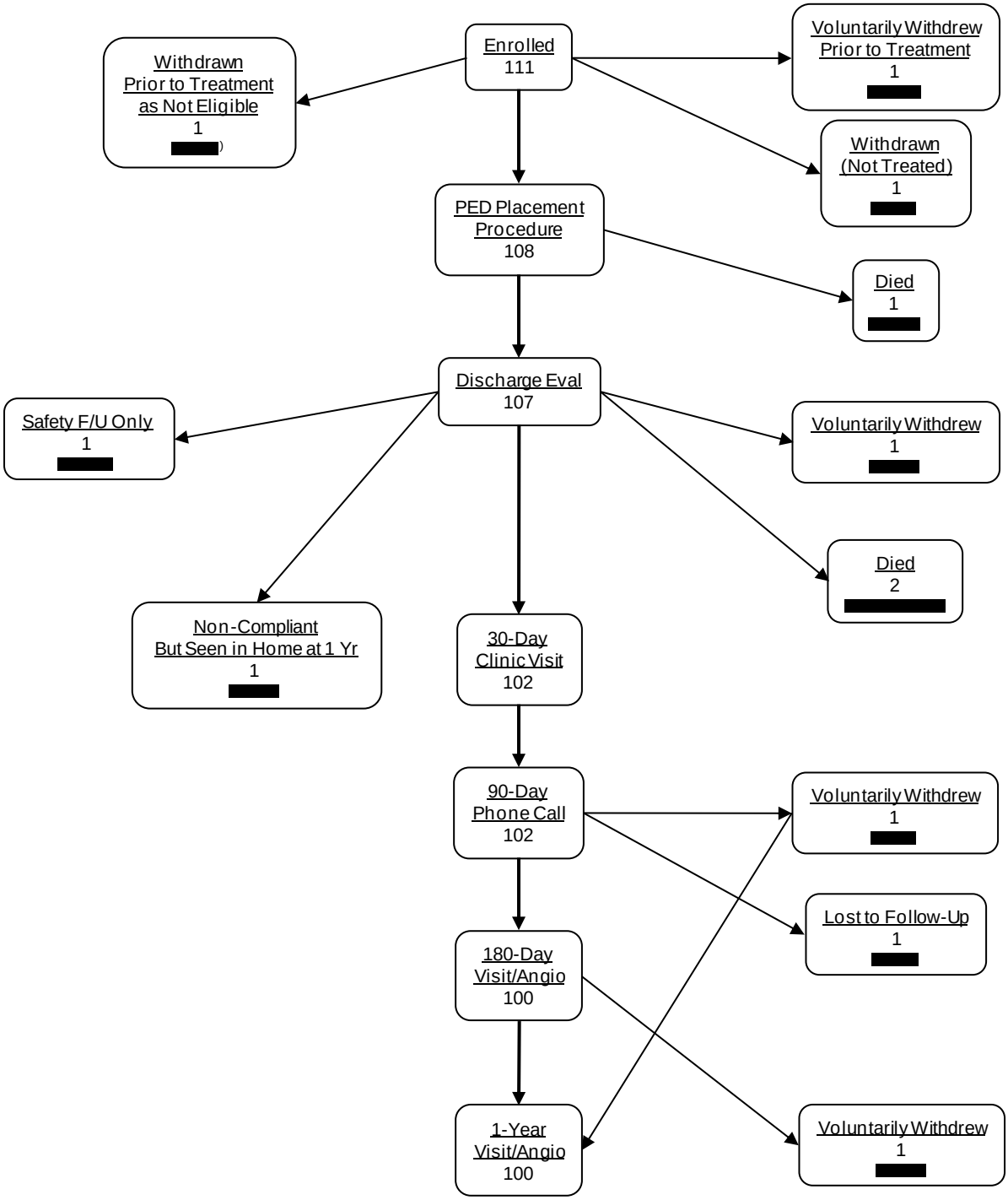


Figure 17-2. Subject flow in PUFS. Values in parentheses are subject name codes.

Table 17-13 shows a summary of follow-up accounting. At Day 180, 96.2% of potentially available subjects had follow-up. At 1 year, one subject had withdrawn from the study, resulting in a follow-up rate of 95.2%. Of the 107 subjects enrolled and treated with PED, medical outcomes at 180 days are unknown or unclear in only 3 cases and the last contact with these subjects suggested that they had not experienced any adverse events.

Table 17-13. Subject 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)

17.10.5 Primary Effectiveness Endpoint Analysis

17.10.5.1 Effectiveness Analysis Cohort

108 subjects underwent attempted PED placement. Of these 108 subjects, 4 were excluded from the effectiveness cohort: 3 were excluded because they were determined not to meet IA eligibility criteria[*] and 1 was excluded because the micro-guidewire could not be passed into the parent artery distal to the target IA and no PED placement attempt was made. Two subjects had contralateral qualifying IAs that were treated with PED, resulting in an effectiveness cohort of 106 IAs.

Of 104 subjects (106 IAs) in the effectiveness cohort, 180-day catheter angiograms were performed in 97 (93.3%) subjects. Angiograms were not performed in 3 subjects because of subject death, in 3 subjects due to study withdrawal, and in 1 subject due to study non-participation/non-compliance. Of the 99 subjects in the effectiveness cohort who were still participating in the study at 180 days, 180-day angiography was performed in 97 (98.0%).

17.10.5.2 Primary Effectiveness Endpoint Rate

Effectiveness success (i.e., complete IA occlusion at 180 days with PED alone in the absence of major stenosis) occurred in 78 of 106 IAs (73.6%). The 95% posterior credible interval for the effectiveness success rate was 64.4-81.0%. The posterior probability that the primary effectiveness endpoint exceeded 50%, the pre-determined success threshold, was 0.999999.[†] This probability value exceeds the pre-determined success probability of 0.975 and is therefore considered statistically significant.

There was no significant site $\times$ treatment effect for the primary effectiveness endpoint across site (exact chi-squared p-value 0.8287). Interrater reliability of core laboratory assessments of IA occlusion was excellent with kappa values of 0.7732, 0.6038 and 0.8019, respectively, amongst the 3 core laboratory radiologists.

Three typical examples of complete IA occlusion are shown in **Figure 17-3.**

[*] In 2 cases, the aneurysm location was incorrect (one of these had a pre-existing Neuroform stent), and in 1 case the aneurysm size was too small.

[†] 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.

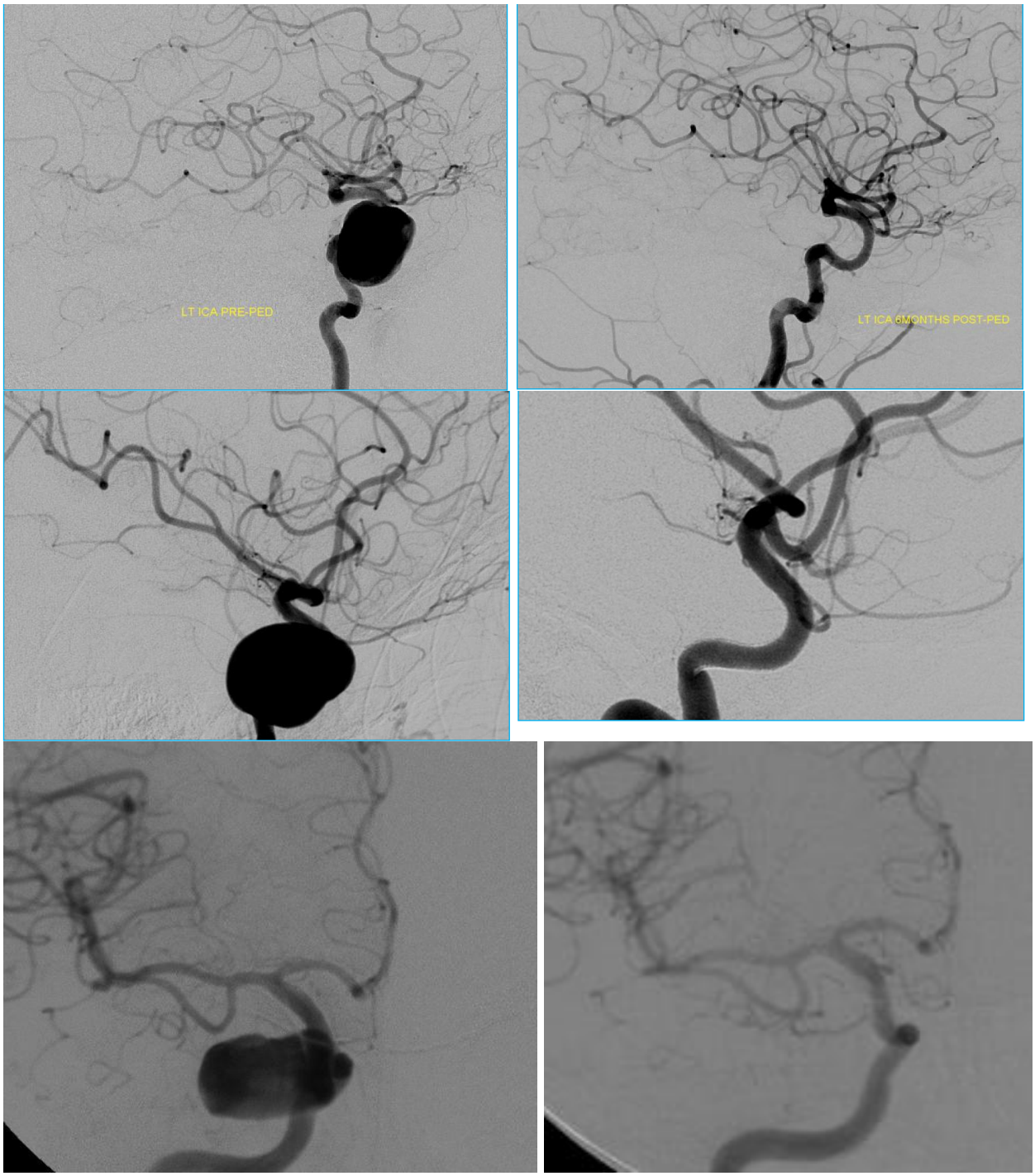


Figure 17-3. Representative complete IA occlusions in PUFS. Shown are subjects [redacted], and [redacted]. Each set of images shows pre-Pipeline angiogram on the left in either the AP or lateral views and the 180-day angiogram on the right in the same view. The parent artery is perfectly reconstructed at 180 days.

17.10.5.3 Reasons for Effectiveness Non-Successes

28 subjects in the effectiveness cohort did not meet the criteria for effectiveness success at 180 days (**Table 17-14**). In 8 cases with "residual neck," there was often a tiny amount of contrast in the aneurysm. In standard practice and in the published literature, these tiny residuals would likely be called "completely occluded." In 2 cases, the IA was completely occluded but the parent artery showed >50% stenosis, which

does not meet the study's definition of effectiveness success. In 1 case, the target IA was completely occluded at 180 days but coils had been placed in the target IA fundus, which does not meet the study's definition of effectiveness success.[*]

Table 17-14. Reasons for primary effectiveness endpoint non-success.

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

17.10.5.4 Stenosis of the Parent Artery

Stenosis of the parent artery is reported in this section because the absence of major stenosis was part of the study's primary effectiveness endpoint definition. Two subjects had stenosis at 180-day angiography (2/107, 1.9%). One case was symptomatic (see **Section 17.10.10.1**) and one case was not associated with symptoms.

17.10.6 Primary Safety Endpoint Analysis

17.10.6.1 Safety Analysis Cohort

Of 108 subjects enrolled and treated in PUFS, one subject [redacted]) was excluded from the safety analysis because the physician could not pass the micro-guidewire could beyond the target aneurysm. PED placement was abandoned (no PED package was opened during the case), the subject was treated with further coil packing, and was followed for safety purposes only. The patient experienced a coil-related serious adverse event.[†] Therefore the safety cohort consists of 107 subjects.

17.10.6.2 Primary Safety Endpoint Rate

The primary safety endpoint (ipsilateral major stroke or neurologic death 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 exceeds the pre-study probability threshold of 0.975 and is therefore considered statistically significant.[‡]

Each event is described in detail in **Appendix 2**. Four of the events occurred in the perioperative period before postoperative day (POD) 30, 1 occurred between POD 30

[*] It should be noted that concomitant use of coils with PED can be a successful treatment strategy, as shown in the PITA study; however, the intent of PUFS was to examine use of PED alone.

[†] The patient's target IA had been previously treated with coils and had recurred. Because the investigator could not place PED, he decided to fill the IA with more coils. Bioactive polymer-loaded Cerecyte coils (Micrus, San Jose, CA) were placed into the IA. Postoperatively, the patient developed fever and confusion. CT scan showed hydrocephalus unchanged from preoperative scans. The patient's confusion responded to lumbar puncture.

[‡] The primary analysis used 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.

and POD 180 and 1 occurred at an unknown time. 3 events were ischemic, 2 were hemorrhagic and one was unknown.

Extenuating circumstances were common in subjects meeting the primary safety endpoint:

- 1 subject was non-compliant with the study and the required antiplatelet regimen.
- 1 subject with stroke due to stenosis of the parent artery had a contralateral IA that was treated with stent-assisted coiling. This contralateral artery also showed stenosis.
- 1 subject received concomitant tirofiban (Aggrastat, a glycoprotein IIb/IIIa inhibitor) postoperatively, which was probably directly related to the hemorrhage.
- 1 subject had multiple risk factors for intracranial hemorrhage, including: a) hypertension with recent change in medication, b) history of subarachnoid hemorrhage in same location 1 year earlier due to head trauma, c) use of aspirin and clopidogrel as required by the protocol, d) alcohol use,[31] and e) recent initiation of a selective serotonin reuptake inhibitor (sertraline HCl), which has been shown to reduce platelet serotonin content and increase bleeding time.[32, 33]
- 1 subject had an extensive history of cardiac disease, with known dilated cardiomyopathy, a history of cardiac arrhythmia treated with an automated implantable cardiodefibrillator (AICD) and multiple medications for ventricular arrhythmia. At the time of presentation, the subject's death appeared typical for sudden cardiac death and treating physicians had not ordered head CT nor a neurologist evaluation. Autopsy was refused. The event was initially judged by the CEC to be non-neurologic, but the CEC revised its rating at a subsequent CEC meeting.

17.10.7 Subgroup Analysis

Pre-specified subgroup analysis for the primary effectiveness and safety endpoints, with groupings as listed in **Section 17.6**, were evaluated. No subgroup analysis (**Table 17-15**, **Table 17-16**) showed significant differences in the proportion of subjects meeting the primary effectiveness or safety endpoint by subgroup.

Table 17-15. Subgroup analysis for effectiveness.

Subgroup	N/N (%)	P-Value*
IA size, mm		
≥25	15/22 (68.2%)	0.5891
<25	63/84 (75.0%)	
IA neck size, mm		
≥6	60/85 (70.6%)	0.2677
<6	18/21 (85.7%)	
Smoker		
Current or former smoker	45/61 (73.8%)	1.0
Non-smoker	33/45 (73.3%)	
Target IA partially thrombosed		
Yes	11/16 (68.8%)	0.7588
No	67/90 (74.4%)	

*Fisher's exact test.

Table 17-16. Subgroup analysis for safety.

Subgroup	N/N (%)	P-Value
IA size, mm		
≥25	0/22 (0%)	0.3419
<25	6/85 (7.1%)	
IA neck size, mm		
≥6	5/85 (5.9%)	1.0
<6	1/22 (4.5%)	
Smoker		
Current or former smoker	2/62 (3.2%)	0.2363
Non-smoker	4/45 (8.9%)	
Target IA partially thrombosed		
Yes	0/17 (0%)	0.5866
No	6/90 (6.7%)	

17.10.8 Secondary Endpoints Analysis

The study's secondary endpoints, listed in **Section 17.7**, are summarized below.

IA Occlusion at 1, 3 and 5 years of Follow-Up. Complete occlusion of the target IA was the major component of the primary endpoint. As a secondary endpoint, we examined occlusion at later time points. Since study enrollment began in November 2008, only 1-year angiograms have been performed.*

Of 104 subjects in the effectiveness cohort, 89 (85.6%) had a one-year angiogram and 15 did not. Reasons why 15 subjects did not have angiogram at 1 year are shown in **Table 17-17**. 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%). Of the 71 subjects with complete occlusion at 180 days and who also had an angiogram at 1 year, 1-year angiography showed continued complete occlusion in 69 (97%). 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. It should be recalled that FDA has agreed that the primary effectiveness endpoint for PED could be evaluated at 180 days.

* 2-year follow-up began in November 2010. The first 3-year angiogram is due in November 2011.

Table 17-17. Subjects in effectiveness cohort who did not have 1-year angiogram (n=15).

Angiogram at 180 days	1 Year Status	N
Yes	Carotid occlusion at 180 days	2
	Insurance issue*	2
	Subject refused*	4
	Withdrew*	1
	Total	**9**
No	Postoperative death	3
	Poor follow-up	1
	Loss to follow-up	1
	Withdrawal	1
	Total	**6**

*7 subjects who withdrew, whose insurance refused to pay for 1-year angiogram, or who refused 1-year angiogram all had complete occlusion at 180-day angiogram.

Incidence of ipsilateral major stroke by 180 days. Six of 107 subjects (5.6%, 95% CI 2.6 – 11.7%) had major ipsilateral stroke, as adjudicated by the CEC.

Change in modified Rankin scale (MRS) at 180 days. At 180 days, MRS, a general measure of neurologic function, was available in 101 subjects. It was unavailable in 3 subjects due to study withdrawal (though all 3 subjects were known to be doing well at last follow-up). An MRS of 6 was assigned for any subject who was dead at 180 days.

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. 94 (87.9%) subjects had an MRS of 1 or less at 180 days. Causes for worsened MRS scores were: death (3 cases), headache (2), residual findings from stroke (2), diplopia (1) and "bubbling sound in ears" (1). Three of these cases were rated as probably or definitely PED-related.

Table 17-18. Change in modified Rankin scale at 180 days compared to baseline. Shaded cells show subjects who worsened. Bolded values show subjects who were the same at baseline and follow-up

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

*Subjects withdrew from study
**Subject stopped participating prior to day 30 (ZARPE) but still in contact with study site

Change from baseline in neurologic signs/symptoms related to target IA. Analysis of change from baseline in neurologic signs/symptoms related to the target IA involved 100 of the 108 subjects undergoing attempted PED placement. 8 subjects were excluded from the analysis of change in neurologic status, 3 because of death, 3 because of voluntary withdrawal, 1 because she was not treated with PED (safety follow-up only), and 1 because the 180-day eye examination was incomplete. 24 subjects (24%) had normal neurologic examinations at baseline and follow-up and had no symptoms related to the target IA (**Table 17-19**). Of the remaining 76, who had neurologic signs or symptoms related to the target IA, 31 (41%) showed improvement at 180 days compared to baseline, 3 (4%) improved due to unrelated reasons and 5 (7%) were possibly improved, 9 (12%) showed mixed findings (i.e., some aspects improved,

some worsened), 19 (25%) showed no change, 8 (11%) were worse (in 2 cases unrelated to treatment of the target IA), and 1 (1%) showed unclear changes.

Table 17-19. Summary of changes in neurologic status.

Overall Change	N
Normal at baseline and follow-up, no symptoms	24 (24%)
Improved	31 (31%)
Improved, but improvement unlikely related to treatment of target IA	3 (3%)
Possibly improved	5 (5%)
Mixed	9 (9%)
No change	19 (19%)
Unclear	1 (1%)
Worse	6 (6%)
Worse but probably unrelated to treatment of target IA	2 (2%)
Total	100 (100%)

When interpreting changes in neurologic function, the following should be kept in mind: the likelihood that a subject with cranial nerve palsies due to mass effect improves after PED placement and involution of the IA may be affected by the duration of symptoms prior to PED. Subjects with long-standing neuropathies may have irreversible damage such that relief of mass effect may not result in improvement in function. The duration of specific symptoms or neurologic findings was not documented in PUFS. However, several subjects had long-standing neuropathy.

Device-related adverse events at 180 days. 21 events (15 SAEs and 6 non-SAEs) were judged to be probably or definitely related to PED (**Table 17-20**). 18 events occurred prior to Day 180, 3 occurred between Day 180 and Day 365 and no events have occurred after day 365.

Table 17-20. Adverse events rated as probably or definitely related to PED.

		Days from Procedure to AE		
SAE	**Event Description**	**<180**	**180-365**	**>365**
No	Diplopia	1	0	0
	Headache	4	0	0
	Nausea	1	0	0
Yes	Amaurosis fugax	3	2	0
	Carotid cavernous fistula	1	0	0
	Carotid occlusion	0	1	0
	Diplopia	1	0	0
	Headache	3	0	0
	Ischemic stroke	4	0	0
Total		18	3	0

17.10.9 Additional Endpoints

The PUFS protocol specified the additional endpoints. Results, summarized in **Table 17-21**, were highly supportive of the study's primary and secondary endpoints.

Table 17-21. Additional endpoints in PUFS.

Endpoint	Result
Technical success	100%
IA occlusion ranking at 180 days	Complete occlusion: 81 (81.8%) Residual neck: 8 (8.1%) Residual aneurysm: 7 (7.1%) Cannot determine: 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 worsened eye alignment by clinical examination by the ophthalmologist	Not analyzed
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%), of which 1 symptomatic

17.10.10 Adverse Events

Sections above reported on 1) SAEs meeting the primary safety endpoint definition (major ipsilateral stroke or neurologic death) and 2) AEs that were device-related (a secondary endpoint). The section below summarizes all events occurring to date.

17.10.10.1 Serious Adverse Events

An adverse event was considered a serious adverse event (SAE) if it met the ISO14155 definition for SAE. All SAEs were reviewed by the clinical events committee (CEC). In total, 44 SAEs occurred in PUFS (**Table 17-22**). The most common neurologic events were amaurosis fugax, severe headache, and stroke resulting from intracranial hemorrhage or ischemia. The most common non-neurologic events were non-neurologic bleeding and cardiac arrhythmia. 15 events were judged as probably or definitely related to PED, 8 were judged as probably or definitely related to the placement procedure, 10 events were judged as probably or definitely related to the use of antithrombotic medications and 15 were judged as probably or definitely related to a pre-existing condition (**Table 17-23**). **Table 17-24** shows the timing of SAEs relative to key time points in the study.

Table 17-22. Summary of SAEs to date.

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 17-23. Relatedness of SAE to PED, PED placement procedure, use of antithrombotic medications and preexisting conditions as determined by CEC. 4 events have not yet been rated by the CEC.

Relatedness per CEC	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 17-24. 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%)

Two additional SAEs occurred in one subject who did not undergo PED treatment. Subject [redacted] did not undergo PED treatment because the parent artery could not be catheterized distal to the target IA. SAEs occurring in this subject are not relevant to the PED experience since she was not treated with PED. Instead she underwent additional coil packing of her IA. Post-coiling, the subject experienced postoperative confusion and fever. CT scan showed no persistent IA-related hydrocephalus. Confusion and fever resolved after lumbar puncture. The subject was rehospitalized on postoperative day 129 for a hypertensive crisis.

17.10.10.2 Non-Serious Adverse Events

In total, 126 non-serious AEs have occurred to date in PUFS. Non-serious adverse events are shown in **Table 17-25**. **Table 17-26**, **Table 17-27** and **Table 17-28** show breakdowns 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.

Table 17-25. Summary of non-serious adverse events to date.

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 17-26. 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 17-27. 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 17-28. 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%)

Summary of serious and non-serious adverse events. The SAE rate after PED placement was low given the complexity of cases. SAEs occurred primarily in the peri-procedural setting. AEs were uncommon between Day 180 and 1 Year and were typically unrelated to PED.

17.10.11 Protocol Deviations

Table 17-29 summarizes protocol deviations in PUFS. Only 8 deviations were considered major in that they involved a deviation from study eligibility criteria. The remaining minor deviations were either medically required, were considered standard institutional procedures, or involved minor details of assessments. Deviations had no impact on the scientific validity of the study and did not violate patient protection measures..

Table 17-29. Summary of protocol deviations.

Deviation Class	Deviation	N
Major Deviations		
Not meet eligibility criteria (major deviations)	Increased risk of stroke	1
	Nontarget IA treated	3
	Not irreversible coagulopathy	1
	SAH	1
	Stent in place	1
	Wrong location	1
Minor Deviations		
Required test not done	1-year angiogram refused	1
	Blood test not done	6
	Eye exam not done	1
	Fundus photo not taken	1
	MRS not done	6
	NIHSS not done	4
	Neuro exam not done	2
	Refused angiogram	1
Required med not given/stopped early	Aspirin dose lowered	13
	Aspirin stopped	6
	Clopidogrel dose lowered	2
	Clopidogrel stopped	3
	Heparin bolus not in range	35
	Preop aspirin incorrect	6
	Preop clopidogrel incorrect	10
	Preop clopidogrel/aspirin incorrect	1
	Ticlopidine substituted for clopidogrel	2
Test/visit outside of window		49
Test not done acc to protocol	Coordination not done/incomplete	2
	DTR not done or incomplete	11
	Eye alignment not done	7
	Fundus photo not taken	5
	Gait not assessed	1
	Other reflexes not done/incomplete	30
	Part of eye exam not done	58
	Part of phys exam not done	2
	Pupil function incomplete	2
	Sensory not done or incomplete	39
	Strength exam not done due to AE	1
	VA not done/incomplete	34
	VF not done/incomplete	13
Missed visit		8
Other type of deviation	Coils used	1
	Crossover procedure on table	1
	Nontarget IA treated	1
Total		373

*VA = visual acuity; VF = visual fields; N/A = not applicable; IA = intracranial aneurysm

17.11 Discussion

PUFS is a multicenter international clinical trial of PED for the treatment of large or giant IAs that were either untreatable by coils alone, failed prior coil treatment, or had a very low expected rate of complete occlusion based on information published in the medical literature. Large and giant IAs are an important clinical problem in that patients with large and giant IAs face a high risk of

spontaneous, potentially fatal IA rupture and many patients with large and giant IAs have debilitating neurologic symptoms due to mass effect from the IA.

17.11.1 Clinical Trial Design

PUFS was a single arm clinical trial. Because no single technology could address large/giant IAs potentially treatable by PED, no feasible control group was possible in PUFS. For this reason, effectiveness rates were compared to historical information based on a thorough literature review. This literature review established that:

- The effectiveness of available treatments, when they could be applied, was documented to be poor, with success rates not higher than 30%.
- The safety of available treatments was also poor, with documented stroke rates of 10-15% and death rates of 5-10%.

17.11.2 Study Conduct and Follow-Up

Patient follow-up in PUFS was excellent and much better than most published studies. 99 of 100 patients still participating in the study at 180 days underwent study-related angiograms. Only 3 of 107 (2.8%) treated patients either withdrew or were lost to follow-up. It should be noted that many patients were referred by their neurosurgeons to participating study centers in distant locations, requiring substantial patient travel for follow-up visits. Major protocol deviations were few in number and did not affect the scientific validity of the study.

17.11.3 Primary Effectiveness Endpoint Discussion

PUFS showed that PED is a highly effective treatment for large and giant IAs of the ICA. The posterior probability that the study's effectiveness rate exceeds 50%, the study's pre-set threshold for success, was 0.999999.[*] The observed effectiveness success rate was 73.6% (95% posterior credible interval 64.4%-81.0%). Therefore, the trial met its predetermined threshold for effectiveness success.

180-day complete occlusion of the target IA without major stenosis was selected as the primary effectiveness endpoint because incomplete occlusion of an IA is increases the risk of IA rupture.[9] A pre-study review of the literature showed that conventional endovascular treatment of large and giant IAs is associated with very low rates of long-term complete IA occlusion. An exhaustive review of the published literature conducted during the beginning of the study confirmed that success rates with currently available technologies are very poor. To ensure that PUFS results were definitive, the protocol specified a 50% comparator for effectiveness success. PUFS results were highly statistically significant, and the observed success rate (74%) was much higher than the trial's pre-defined success criterion. Therefore, **PED therefore represents a breakthrough medical advance for this unmet medical need.**

Strength of evidence. The observed effectiveness success rate in PUFS was remarkable when taking into account the following potential strong biases present in the medical literature:

- **Lack of core laboratory**. The vast majority of studies in the published literature reporting angiographic occlusion of coiled IAs did not use a core laboratory for interpretation of radiographic images. Instead, occlusion is self-adjudicated by

[*] The primary analysis of PUFS was Bayesian. A frequentist evaluation of the observed success rate compared to a 50% threshold yields a p-value of 0.0000006.

study authors. Pierot et al[34] showed that self-reporting of IA occlusion rates can lead to a nearly 40% overestimation of the true portion of completely occluded aneurysms (**Figure 17-4**). In contrast, in PUFS a core laboratory of independent neuroradiologists judged target IA occlusion. Inter-rater agreement regarding IA occlusion in PUFS was excellent.

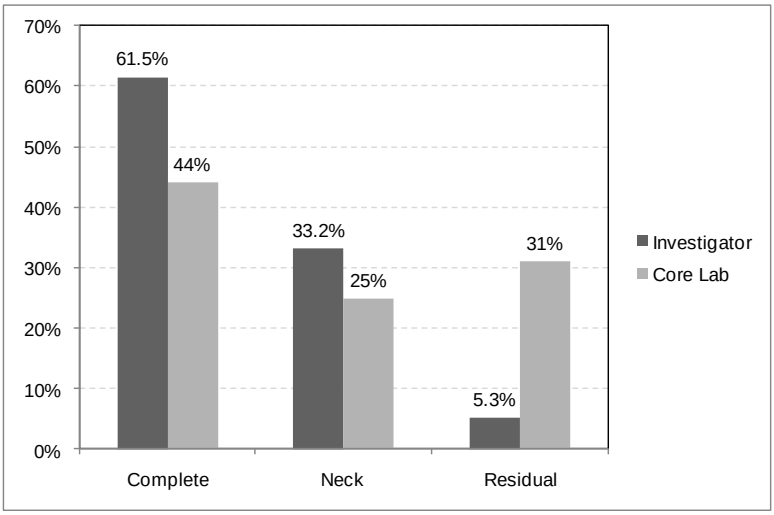


Figure 17-4. Comparison of readings by investigators and core lab for complete occlusion after coiling an aneurysm (Matrix registry[34]).

- **Unclearly defined endpoints**. PUFS used a simple, binary, easily interpreted effectiveness endpoint: complete IA occlusion without major stenosis. This is in marked contrast to published studies, which often report outcomes using terms such "aneurysm stability" or "progressive thrombosis," terms which are typically not defined and highly subjective.

- **High loss to follow-up**. Many studies in the published literature ignore any patient who fails to return to clinic for angiographic follow-up, thus introducing a potential bias. It is possible that patients who fail to have follow-up are more likely to be effectiveness failures; thus, those who do return for follow-up may represent a biased sample of all patients, resulting in overestimation of the true effectiveness rate. In contrast, PUFS determined the number of angiographic successes among all patients in whom PED placement was attempted; if the patient did not return for follow-up, the patient was not dropped from the denominator but was instead was treated as an effectiveness failure. Moreover, the rate of angiographic follow-up in PUFS was very high compared to most published articles.

- **Unknown degree of selection bias.** Studies in the published literature report outcomes for those patients who were selected for treatment in question. However, many patients may not be eligible for a particular treatment. For example, subjects who fail balloon test occlusion are not candidates for parent vessel occlusion. Studies in the medical literature typically do not report outcomes for patients in whom the treatment in question was not provided or was deemed inappropriate. This is in marked contrast to PUFS, in which no IA was "rejected" because the IA's geometry was too complex. (Indeed, many PUFS IAs

were very complex, and many PUFS subjects were referred from highly specialized tertiary care centers who had nothing to offer the patient.)

- **Occlusion assessment difficult with coils in place**. Many published studies report treatment of IAs with coil embolization. Angiographic interpretation of IA occlusion is often difficult due to the presence of a dense coil mass in the IA fundus. Even when imaging is perfectly orthogonal to the coil mass, the radiopaque coil mass itself can obscure the IA neck, making the evaluation of IA occlusion nearly impossible. Moreover, the coil mass can completely obscure residual contrast in the IA fundus. In contrast, while PED is radiopaque it remains in the parent vessel and not inside the aneurysm and thus allows sensitive and accurate evaluation of the aneurysm at follow up. It is highly likely that small residual necks are easier to detect with PED than with coil embolization.

Given these considerations, the complete IA occlusion rate with other technologies reported in the published medical literature is highly likely to be strongly biased upwards. The true, underlying IA occlusion rates after treatment of large/giant IAs with coils, stent-assisted coiling, or neurosurgery may be far less than 30%. In comparison to this value, the effectiveness success rate seen in PUFS was very high.

Twenty-eight IAs did not meet the study's pre-defined effectiveness endpoint. Of these cases, 2 particular situations deserve special attention:

- **Adjunctive use of coils**. In 1 subject ([redacted]), adjunctive coils were used, which enabled the physician to finish the case with PED. The 180-day angiographic result was excellent, with complete occlusion of the target IA and no stenosis. In this case coils were loosely placed in the aneurysm to provide a "backstop" and thus allow passage of the microcatheter to the distal parent artery, which is a prerequisite for PED deployment. The case was considered a non-success because the study protocol required use of only PED. However, combining coil treatment with PED is a reasonable strategy in certain clinical situations and was performed in the PITA study with a high success rate.

- **Residual necks were small**. In 8 cases, the core laboratory judged the IA to have "residual neck" at 180 days, i.e., tiny filling of the IA at the neck of the aneurysm. If such IAs were treated with coils and had similar residual contrast filling of the IA neck, it is highly likely that the residual neck would not be detected due to the coil mass obscuring the visualization of contrast. The amount of contrast in the residual neck was often tiny compared to the pre-treatment size of the IA. Moreover, in some studies, this amount of contrast is considered a success. In PUFS, patients with residual aneurysmal filling may undergo progressive thrombosis and show complete IA occlusion at later time points (this occurred in 3 subjects from 180-day to 1-year angiography).

PUFS provides very strong evidence to support a high effectiveness success rate for PED in the treatment of large and giant IAs of the ICA.

17.11.3.1 Stenosis

Stenosis of the parent artery after implantation of an intravascular metallic implant is not unexpected. In PUFS stenosis was rare, occurring in only 2 cases (1.9%). In one case, stenosis was symptomatic, resulting in major stroke. In the other case, no symptoms occurred and stenosis was improved at 1 year compared to 180 days. Stenosis after PED appears to occur at a rate similar to that after placement of other neurovascular devices. For example, Fiorella et al reported stenosis at late (3-12 month follow-up) angiogram in 9 of 156 patients (5.8%) undergoing Neuroform stent-assisted coil

embolization, of which 2 were symptomatic.[35] It should be noted that IAs in PUFS were substantially larger and more complex than those cases reported in the literature in which Neuroform was used.

17.11.3.2 Aneurysm Recurrence

Aneurysm recurrence after coil embolization is an extremely common problem. Recurrence is especially common in large and giant IAs, since the neck of the treated IA is not sufficiently protected from parent artery circulation and continues to expand. For example, in Hauck et al,[36] of the 15 patients with giant IAs undergoing coil embolization, 12 required retreatment. In Jahromi et al[37], of the 20 patients with giant IAs who underwent coil embolization (with or without stent), the mean number of treatments was 1.95, indicating that most patients were retreated.

In marked contrast, recurrence has not been observed in PUFS. The PUFS experience is backed up by experience in other PED cohorts (e.g., PITA) and commercial use of PED, in which aneurysm recurrence has not been seen to date in >1,600 cases performed worldwide.

17.11.3.3 PED Effectiveness Summary

PUFS provides very strong evidence that PED provides a high rate of complete IA occlusion without stenosis. PUFS confirms that PED is an important and highly effective new treatment for large and giant IAs. PED is a breakthrough medical technology for this unmet medical need.

17.11.4 Primary Safety Endpoint Discussion

PUFS provides strong evidence of adequate safety for PED in the target patient population. The primary safety endpoint in PUFS, the proportion of patients who had major ipsilateral stroke or neurologic death by 180 days after treatment, occurred in 6 of 107 (5.6%, 95% CI 2.6 – 11.7%) patients. **The primary safety endpoint met the pre-defined threshold for safety success in that the Bayesian posterior probability that the stroke/death rate after PED is <20% was 0.999979, which exceeds the pre-trial statistical threshold of 0.975.**[*]

The threshold against which safety success was judged was based on the same comprehensive literature review on the endovascular and surgical treatment of large and giant aneurysms. The literature review showed that the stroke rate for endovascular or surgical treatment of large and giant IAs is in the range of 5-20% and the death rate can be as high as 20%. In the most recently reported multicenter cohort of treatment of giant IAs, among the 20 patients treated with endovascular coiling with or without stent assist, 5 of 20 (25%) had major morbidity and 6 of 20 (30%) died.[37] In another recently published cohort,[38] 216 IAs (181 unruptured) underwent stent-assisted coiling. In this group, the permanent neurologic morbidity rate was 7.4% and 6.0% died. Mean IA size among stented IAs in this study was 9.3 mm, roughly half that of the current study. Recently published reviews of surgical treatment of large and giant IAs confirm that perioperative morbidity and mortality remains high despite advances in surgical techniques. Because treatment of giant IAs is so difficult, many PUFS cases were referred to PUFS study centers by neurosurgeons who had nothing else to offer such patients.

Of the 6 events meeting the primary safety endpoint, 3 were ischemic, 2 were hemorrhagic and one was unknown. Extenuating circumstances were common in patients meeting the primary safety endpoint.

[*] A frequentist calculation shows a p-value of 0.00002 compared to a fixed value of 20%.

Strength of evidence. Several aspects of PUFS strengthen the evidence it brings regarding the safety of PED treatment:

- In PUFS, the patient follow-up rate was very high and the withdrawal rate was very low. This is in marked contrast to the published medical literature in which long-term follow-up is typically quite poor.

- In PUFS, safety was judged on an intent-to-treat perspective. In contrast, studies in the published medical literature typically report safety outcomes only among those patients available for follow-up. A patient who is unavailable for follow-up, possibly due to an adverse event, is typically not reported in the medical literature.

- In PUFS, safety was judged out to 180 days after PED placement in PUFS. In contrast, the studies in the published literature often reported only perioperative safety outcomes. Patients with events occurring after the perioperative period would typically not be reported or described.

- In PUFS, medical records for each patient were reviewed for the occurrence of adverse events by medical monitors. In contrast, data monitoring is almost never done in articles published in the medical literature.

- In PUFS, all serious adverse events (SAEs) were adjudicated by an independent clinical events committee (CEC). Rarely are safety events reviewed externally in studies published in the medical literature.

- The primary safety endpoint was defined prior to study initiation and used a well-known metric (increase in NIH Stroke Scale). In contrast, the definition of what constitutes stroke in reports in the literature is typically not provided.

17.11.4.1 Comparison to Approved Devices

Three devices have been approved by FDA via the Humanitarian Device Exemption (HDE) pathway for use in wide-necked aneurysms: Neuroform Stent, Enterprise Stent and Onyx HD-500. A comparison of safety information presented by sponsors of these devices to that in PUFS is relevant for the following reasons:

- The target IA population treated in PUFS overlaps substantially with the set of patients for whom these devices are indicated (see below).

- HDE approval of a medical device requires that the manufacturer submit evidence to support safety and probable benefit. The regulatory definition of reasonable assurance regarding safety outcomes is identical between an HDE-approved product and a PMA-approved product.

Table 17-30 compares indication statements and study characteristics of PED vs. the 3 HDE-approved devices. Several aspects of this comparison support reasonable assurance of safety for PED:

- The sample size in PUFS was larger than the other 3 studies.

- Mean IA size and neck size in PUFS were larger (sometimes substantially so) than the other 3 studies.

- PUFS included fusiform IAs, which cannot be treated with Onyx and were therefore specifically excluded from the Onyx study.

- The stroke/death rates observed in PUFS were similar or lower than those observed in the other 3 studies, even when ignoring the increased complexity of PUFS IAs compared to those of the other studies.

Table 17-30. Summary comparison of PED with studies performed in relationship to 3 HDE-approved devices for treatment of wide-necked IAs.

Device	Indication	Mean IA Size, mm	Mean IA Neck, mm	Sample Size	Stroke / Death Rate
Pipeline	Large or giant wide-necked intracranial aneurysms in the paraclinoid, paraophthalmic, hypophyseal, cavernous and petrous segments of the internal carotid artery.	18.2	8.8	108	5.6% major, 2.8% minor / 2.8%
Neuroform	Wide neck, intracranial, saccular aneurysms arising from a parent vessel with a diameter of >2mm and <4.5mm that are not amenable to treatment with surgical clipping. Wide neck aneurysms are defined as having a neck of >4mm or a dome-to-neck ratio of <2.	7.4	4.9	29	10.3% / 3.4%
Enterprise	Wide-neck, intracranial, saccular or fusiform aneurysms arising from a parent vessel with a diameter of ≥3 mm and ≤4 mm. Wide-neck is defined as having a neck width >4mm or a dome-to-neck ratio ≤2.	8.6	5.3	30	10.7% / 3.6%
Onyx	Intracranial, saccular, sidewall aneurysms that present with a wide neck (≥4 mm) or with a dome-to-neck ratio ≤2 that are not amenable to treatment with surgical clipping.	15.8	7.0	66	22.7% / 4.5%

In comparison to information brought by manufacturers of other approved devices for the endovascular treatment of wide-necked IAs, information in support of PED:

- Is based on larger sample sizes
- Is based on treatment of more complex IAs
- Shows similar or better safety profiles

17.11.4.2 Summary Regarding Primary Safety Endpoint in PUFS

In summary, PUFS provides strong evidence that the safety profile of PED treatment of patients with large or giant IAs is good and the benefits strongly outweighed the risks. Moreover, the degree of assurance provided by study data is sufficient to support regulatory approval and is at least as great, if not greater, than that provided by other approved devices.

17.11.5 Secondary Endpoints Discussion

Secondary endpoints in PUFS were highly supportive of the study's main results.

- The **incidence of ipsilateral major stroke by 180 days** was low at 6/107 (5.6%).
- **Changes in modified Rankin scale (MRS) at 180 days** were supportive of an excellent safety profile.

- **Changes from baseline in neurologic signs/symptoms related to target IA** were strongly supportive of effectiveness findings. At baseline, 76 patients had neurologic signs or symptoms that were related to the target aneurysm. Among these 76, 31 (41%) had improvement in one or more signs/symptoms without worsening of other signs/symptoms. Objectively documented decrease in mass effect was seen in a large number of patients. Resolution of mass effect even occurred in some subjects with long-standing neurologic damage.

- **Independent ophthalmology examination**. An important strength of PUFS was the participation of independent ophthalmologists and neuro-ophthalmologist who examined study patients at baseline prior to PED placement and again at 180 days. Examination by an ophthalmologist is highly relevant to PUFS since IAs of the ICA can exert mass effect on local cranial nerves, primarily the optic, oculomotor and abducens nerves. Exams specific for visual and oculomotor function were performed by the ophthalmologist and were supportive of improvements in eye function related to reduced cranial neuropathy. Visual field examinations also helped to substantiate that coverage of the ophthalmic artery by PED resulted in a very low rate of retinal ischemia (1 patient, 0.9%).

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

17.11.6 Additional Endpoints Discussion

PUFS pre-specified several additional endpoints. Each endpoint was intended to be supportive of the primary and secondary endpoints of the study. In each case, positive outcomes were observed that supported the study's main goals.

18 Compassionate and Emergency Use Cases

Concomitant with PUFS, PED was used on a compassionate use basis in 28 cases in the US.

18.1 US Compassionate/Emergency Use Cases

As of February 2010, PED was used in 28 compassionate use cases in the US. These cases were characterized by complex lesions or emergency uses of PED for iatrogenic aneurysms. Patients typically did not meet criteria for enrolling clinical trials. Most cases were referred to physicians by neurosurgeons and interventional neuroradiologists who believed they had nothing else to offer the patient. The majority of cases had excellent outcomes, often with marked improvement in symptoms related to the target IA. Several of these cases were published as case reports in the medical literature.[39-42] In several cases, adverse events were related to the procedure, not to PED. In summary, compassionate use cases in the ICA were highly supportive of results in PUFS, and PED shows excellent promise for use in the posterior circulation.

19 Training Program

Chestnut has proposed a physician training program consisting of the following two mandatory parts:

1. **Centralized, multidisciplinary training course**. Physician users will attend a 1-day "off-site", centralized course with presentations on PED placement and techniques provided by both sponsor staff and one or more physicians experienced in PED placement. Trainees will practice PED placement using the same benchtop model as was used to train investigators in PUFS. The model has large/giant aneurysms and can be quite challenging.

2. **Proctoring**. Physicians will undergo proctoring of the first 5 clinical cases by a physician with expertise in PED placement.

20 Overall Conclusions

Two multicenter studies conducted and reported herein were performed in support of PED for the treatment of IAs.

- PITA was a multicenter study in Europe and Argentina of difficult-to-treat or failed wide-necked IAs of varying sizes in which PED was used with or without adjunctive coils. The 180-day aneurysm occlusion rate was 93% and the stroke rate was 6.3%.

- PUFS was a multicenter study in the US, Europe and Turkey of PED use alone for the treatment of wide-necked or fusiform large and giant IAs of the internal carotid artery. The target IA population in PUFS is commonly acknowledged to be either untreatable with current methods or have a very low rate of success with a high rate of procedure-related morbidity and mortality. Several PUFS cases had already failed coil treatment. PUFS showed that the PED effectiveness success rate at 180 days was 74% and the 180-day major ipsilateral stroke/neurologic death rate was 5.6%. In PUFS, the primary effectiveness and safety endpoints met their predetermined thresholds for success with very high degrees of statistical certainty. Moreover, careful neurologic assessments showed that many PUFS patients with severe baseline symptoms due to mass effect from the target IA showed marked improvements at 180 days.

The PITA and PUFS studies provide strong evidence of safety and effectiveness to support the use of PED in the treatment of patients with IAs. Results from use of PED in compassionate and special access cases in the US, Canada and Argentina[*] were highly supportive of results seen in PITA and PUFS.

The degree of effectiveness success for the PUFS target population provides strong evidence that PED is a breakthrough medical innovation. The level of evidence for safety met the study's pre-determined goals and appeared to meet or exceed that of other devices approved via the HDE route. Overall, the risks of PED use in the intended patient population appear to be strongly outweighed by the benefits. In conclusion, the PUFS study constitutes valid scientific evidence (21 CFR 860.7) and provides reasonable assurance that the device is safe and effective for its intended use (21 CFR 814.20).

[*] Use of PED in Canada and Argentina is described in more detail in the Pipeline Embolization Device PMA.

APPENDICES

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Appendix 1. Labeling and Instructions for Use

Labeling and draft instructions for use are provided on following pages. There are no written patient instructions.

ev3
THE ENDOVASCULAR COMPANY
www.ev3.net

Contents
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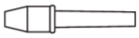
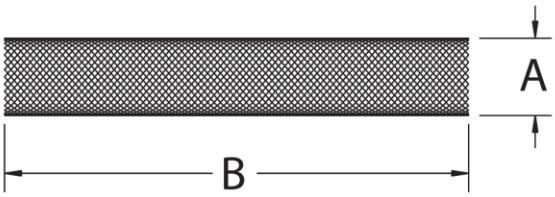


Pipeline™ Embolization Device

Pipeline™ 栓塞器械
Pipeline™-emboliseringsanordning
Pipeline™ embolisatiehulpmiddel
Pipeline™ -embolisaatiolaite
Dispositif d'embolisation Pipeline™
Pipeline™-Embolisationsvorrichtung
Συσκευήεμβολισμού Pipeline™
Dispositivo per embolizzazione Pipeline™
Pipeline™ emboliseringsanordning
Urządzenie Pipeline™ do embolizacji
Dispositivo de Embolização Pipeline™
Приспособление для эмболизации Pipeline™
Dispositivo de embolización Pipeline™
Pipeline™ emboliseringsanordning
Pipeline™ Embolizasyon Cihazı



US and Foreign Patents: Pending

A	
B	

Manufactured by:
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LBL-0014.F

Chestnut Medical

Chestnut Medical Technologies, Inc.
173 Jefferson Drive, Menlo Park, CA 94025
Phone: (650) 566-0057 Fax: (650) 566-0072

Instruction for Use (IFU)
Pipeline™ Embolization Device

	For Single Use Only (Do not Re-use)		Caution: Federal law (USA) restricts this device to sale by or on the order of a (licensed healthcare practitioner).
	Sterile -Ethylene Oxide		Non-pyrogenic Store in a cool, dry place
	Read Instructions Prior to Use	 	

Caution: Do not use product if the sterile package is damaged.

Device Description

The Pipeline™ Embolization Device (PED) consists of a flexible mesh-like device designed for placement in a parent vessel across the neck of an aneurysm.

The PED is packaged in a delivery system (an introducer and a flexible tapered delivery wire) and is designed to be **only** introduced into a microcatheter of 0.027 inch (0.69 mm) inside diameter. Marksman Catheter (ev3, Inc.) is recommended.

A platinum coil at the distal end of the delivery wire provides fluoroscopic visibility. A retaining mechanism at the proximal end of this platinum coil facilitates insertion of the PED through the lumen of a microcatheter. A platinum marker is located on the delivery wire proximally to the PED. This marker provides fluoroscopic visibility of the proximal location of the PED prior to deployment.

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~~, paraopthalmic, hypophyseal, cavernous and petrous segments~~ regions of the internal carotid artery.

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.

Potential Complications

Potential complications, some of which could be fatal, include, but are not limited to the following:

Adverse reaction to antiplatelet/anticoagulation agents or contrast media, intracerebral, bleeding, coma, device fracture, device migration or misplacement, dissection of the parent artery, embolism, groin injury, headache, hemorrhage, hydrocephalus, infection, intracerebral bleeding, ischemia, mass effect, neurological deficits, parent artery stenosis, perforator occlusion, post-procedure bleeding, ruptured or perforated aneurysm, seizure, stroke, thromboembolism, transient ischemic attack (TIA), vasospasm, vessel occlusion, vessel perforation and vision impairment.

Compatibility

PED is compatible with a 0.027" (0.69mm) inside diameter microcatheter. Marksman Catheter (ev3, Inc.) is recommended. The unconstrained diameter of PED is 0.25mm greater than the labeled diameter on the packaging. Do not use PED in vessel diameters that are larger than the labeled diameter.

Magnetic Resonance Imaging

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

- Static magnetic field of 3 Tesla or less.
- Spatial gradient field of 720 Gauss/cm or less
- Maximum whole-body-averaged specific absorption rate (SAR) of 4.0 W/kg for 15 minutes of scanning.

In non-clinical testing, the PED produced a temperature rise of less than 0.6°C at a maximum whole body averaged specific absorption rate (SAR) of 4.0 W/kg for 15 minutes of MR scanning in a 3 Tesla MR system.

The PED may create local field inhomogeneity and susceptibility artifacts which may degrade the diagnostic quality of the MRI images. Based on the non-clinical testing of the 5.0 mm device using standard views, the worst case maximum artifact was < 3mm when subjected to 3.0 Tesla. Local field artifact from the PED may decrease the accuracy of MR angiogram in assessing vessel luminal patency.

MR image quality may be compromised if the area is in the exact same area or relatively close to the position of the PED. Therefore, it may be necessary to optimize MR imaging parameters for the presence of this metallic implant.

Packaging and Storage

Store in a cool, dry place.

Directions for Use

1. Using standard interventional radiographic technique, place the microcatheter tip at least 20mm past the distal edge of the aneurysm. Gently retract the microcatheter to reduce slack in the microcatheter prior to inserting PED.

2. Choose a PED with labeled diameter that approximates the target vessel diameter.

3. Choose a PED with labeled length that is at least 6 mm longer than the aneurysm neck.

4. Remove packaging hoop from the pouch and detach wire from the white rubber wire-holder.

5. Carefully remove delivery wire and introducer sheath out of the packaging coil.

6. Insert introducer sheath into the rotating hemostatic valve at the catheter hub.

7. Secure introducer sheath to the hub by locking down the rotating hemostatic valve tightly.

8. Advance the PED into the microcatheter by pushing the delivery wire until the tip of the delivery wire aligns with the tip of the microcatheter.

Caution: Do not torque or pull back on delivery wire during insertion.

9. Once the tip of delivery system and microcatheter are aligned, verify that the PED is in the desired location. Distal end of PED should be placed at least 2-3 mm past the distal edge of the aneurysm.

10. Unsheath the PED by slowly retract the microcatheter while maintaining the position of the PED until the tip of the microcatheter is proximal to the distal end of the PED

11. Push the delivery wire to continue to expose the PED. After about 10mm of PED is exposed the distal end may detach from the delivery wire. Detachment can be facilitated by slowly rotating the delivery wire in the clockwise direction.

Warning: Never rotate the delivery wire more than 10 full turns. If PED does not open after 10 turns, remove the entire system (microcatheter and PED delivery system together).

12. After the distal end of PED has successfully expanded, deploy the remainder of PED by alternately advancing the delivery core wire and allowing the microcatheter to retract slightly.

Caution: Under fluoroscopy, carefully monitor the tip of the core wire during PED deployment. The core wire can be rotated and maneuvered as needed after the distal end of the PED has detached.

13. After the entire PED is deployed, advance the microcatheter through the PED. When the microcatheter tip is distal to the PED, retract while gently rotating the delivery core wire **clockwise** to prevent entanglement with the deployed PED and the microcatheter tip.

14. Carefully inspect the deployed PED under fluoroscopy to confirm that it is completely apposed to the vessel wall and not kinked. If the device is not fully opposed or is kinked, consider using an angioplasty balloon to fully open it.

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.

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.

Questions and Answers

Q If excessive friction is experienced during the insertion of delivery system at anytime during the delivery of PED, what should I do?
A Carefully remove the entire system simultaneously (microcatheter and delivery system).

Q Can I retrieve the PED if the distal end of the PED has expanded at an undesirable location?
A Yes. A partially deployed PED can be retrieved. Carefully pull back the delivery core wire until the PED is secured at the tip of the microcatheter. Then, if there is no resistance, simultaneously remove the entire system (microcatheter and delivery system).

Q Can I retrieve a fully deployed PED?
A Once fully deployed, the PED cannot be removed. A second PED can be deployed if needed.

Q Can I place a second PED inside another PED?
A Yes. A second PED can be placed inside another PED. After placing the first PED, advance the microcatheter over the delivery wire while keeping the delivery core wire across the PED. Position the microcatheter at the desired location and retrieve the delivery wire. Select a new appropriate PED and deploy it as normal.

Caution: Placement of multiple PEDs may increase the risk of ischemic complications.

Q Is it possible to place embolization coils inside an aneurysm after PED is deployed?
A Because a microcatheter cannot pass through the struts of the PED, the aneurysm should either be coiled prior to PED placement, or a microcatheter can be “jailed” in the aneurysm using PED. Coils can then be delivered after PED is deployed in a “parallel” technique.

Q If there is a difference between the proximal and distal diameter, which PED diameter do I choose?
A Choose a PED that matches larger (typically proximal) vessel diameter to ensure proper anchoring.

Appendix 2. Description of Primary Safety Endpoint Events

This section provides narrative description of PUFS subjects meeting the primary safety endpoint of the study.

[redacted]. 72-year-old man with a left-sided ophthalmic segment aneurysm that had failed prior surgical treatment. He underwent uneventful placement of 3 PEDs. About 8 hours after the procedure, he experienced a sudden change in his neurologic status. CT scan was negative. Emergency angiography showed acute occlusion of the left internal carotid artery at the location of the PED. The subject underwent thrombolysis and mechanical thrombectomy, with successful restoration of left internal carotid artery flow. He awoke with a severe ipsilateral stroke (NIHSS 11).

[redacted] 57-year-old woman from rural northern Wisconsin with a right-sided 15.7 mm cavernous segment IA. She had a history of frontal stroke from a previously treated aneurysm distal to the ICA terminus. The subject did not attend the 30-day visit due to death of her husband. She agreed to a home visit by a study investigator from the study site. Just prior to visit, the subject was seen in a local ER for questionable increase in confusion. Physical examination by the ER doctor and the study investigator showed no change. Based on phone calls with the subject's daughter, the study investigator suspected antiplatelet medication non-compliance. The subject refused to attend the 180-day scheduled angiogram and instead went on a cruise with her daughter in Florida. She had a CT angiogram performed at a local hospital approximately 10 months after PED placement, which showed occlusion of the carotid artery and new encephalomalacia in the ipsilateral posterior parietal lobe. The subject agreed to yet another home visit by a study investigator, which took place on February 3, 2010. This exam showed that the NIH Stroke Scale had increased to 6 from a baseline of 5. In adjudicating the event, the CEC believed that scoring of the examinations was incorrect and judged the NIHSS change score to be 4 points, i.e., a major stroke.

[redacted]. 66-year-old man with a left-sided 20.2 mm paraophthalmic segment IA. He had a history of non-ischemic dilated cardiomyopathy treated with biventricular automated implantable cardiodefibrillator (AICD) placement, hypertension, hypercholesterolemia, and obstructive sleep apnea. Medications included lisinopril, furosemide, potassium, simvastatin, digoxin, milrinone, carvedilol, pantoprazole. A note obtained from the treating cardiologist also showed prior treatment with mexilitine (Class Ib antiarrhythmic) as well as a history of non-sustained ventricular tachycardia, paroxysmal atrial fibrillation and a history of diaphragmatic pacer stimulation. The subject underwent uneventful PED placement. CT angiogram on POD 1 showed progressive thrombosis of the IA. Headaches had resolved and vision was improving. On POD 3 he was found by his wife unresponsive in the bathroom. 911 was called and paramedics found the subject to be in ventricular fibrillation. Electrocardiogram in the ER showed a paced rhythm but there was no blood pressure. Echocardiogram showed diffuse hypokinesis. Blood testing showed severe acidosis consistent with cardiac arrest. He was admitted to the cardiac ICU but died soon thereafter. At no point during the subject's brief hospital stay was he admitted to neurology or a neurologist consulted. Head CT was not done. Autopsy was refused. The CEC originally interpreted this event as sudden cardiac death. On re-review of the event approximately 1 year later, the CEC decided to adjudicate this event as neurologic death of unknown cause.

[redacted]. 63-year-old woman with a left-sided carotid ophthalmic aneurysm. She had a history of hypertension, alcohol use, and motor vehicle accident while drunk approximately 12 months prior to PED placement a right frontal contusion and subarachnoid hemorrhage. The target aneurysm was found incidentally during treatment of her closed head injury. She underwent successful PED placement on January 30, 2009. CT angiogram on POD 1 showed complete occlusion of the aneurysm. She was discharged home shortly thereafter. On POD 3 she saw her primary care physician who diagnosed acute sinusitis and anxiety. Benicar (olmesartan, an angiotensin receptor blocker) was stopped and Coreg (carvedilol) started. She also started taking Zoloft (sertraline HCl) for depression and Levaquin (levofloxacin). On POD 14 she experienced sudden onset of severe headache and was found dead at her home later that day. Autopsy demonstrated an intraparenchymal hemorrhage in the left frontal lobe.

There was no peri-aneurysmal or cisternal subarachnoid hemorrhage. The carotid artery, Pipeline device and aneurysm were all intact. The findings were characteristic of a hypertensive hemorrhage, unrelated to PED. Histopathology of the aneurysm showed no evidence of rupture or tear. PED was in place, with organizing intra-aneurysmal thrombus as expected.

[redacted]. 63-year-old woman with left-sided 13 mm supraclinoid aneurysm. She was treated with 3 PEDs. At the 30-day visit, the subject was well. On POD 62 the subject had dysphasia and right hemiparesis. The subject arrived to hospital about 15 hours after event onset. NIH Stroke Scale was 10. MRI showed watershed distribution of ischemic changes. Angiogram showed high-grade stenosis throughout the PED construct. The IA itself was completely occluded (i.e., successfully treated). PTA was performed inside PED with improvement of flow. Of interest, the subject had undergone previous stent-assisted coiling of a contralateral IA. Angiography of the contralateral lesion also showed stenosis, suggesting that the subject was predisposed to intimal hyperplasia with intra-arterial implants.

[redacted] 51-year-old woman with a complex, 22.5 mm left-sided cavernous segment ICA aneurysm. 15 PEDs were placed due to the long and complex nature of this lesion. Procedure time was more than twice the mean procedure time for PUFS cases (295 minutes vs. 124 minutes). The subject had mild dysphasia and disorientation postoperatively. MR showed 1 or 2 suspicious acute ischemic lesions. On the suspicion of ischemia of the ipsilateral ICA resulting from vasospasm, the investigator administered IV tirofiban (Aggrastat, a glycoprotein IIb/IIIa inhibitor). The next morning, the subject became confused. Repeat MR showed a left frontal cortex hematoma distal to the ICA terminus. NIH Stroke Scale score was 4. Aspirin was stopped and clopidogrel was held for 2 days. Tirofiban was suspected as the cause of frontal hematoma. The subject was discharged on POD 14. At the 30-day visit, the subject was noted to be asymptomatic, completely recovered, with a normal neurologic examination and an MRS of zero.

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