FDA Executive Summary

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Neurologic Devices Panel

P100018

Chestnut Medical

Pipeline™ Embolization Device

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ABBREVIATONS USED

ACT	Activated Clotting Time
AE	Adverse Event
CEC	Clinical Events Committee
EVRT	ENERI Vascular Reconstruction Trial
IA	Intracranial aneurysm
COCOA	Complete Occlusion of Coilable Aneurysms
MRI	Magnetic Resonance Imaging
mRS	Modified Rankin Score
OUS	Outside of the United States
PED	Pipeline embolization device
POD	Post-operative Day
PITA	Pipeline™ for Intracranial Treatment of Aneurysms
PMA	Premarket Approval
PUFS	Pipeline™ for Uncoilable or Failed Aneurysms
SAE	Serious Adverse Event
US	United States

BACKGROUND INFORMATION

1. Introduction

This is FDA's Executive Summary of premarket approval application P100018 from Chestnut Medical Technologies for the Pipeline™ Embolization Device (PED) for the treatment of wide-neck large or giant intracranial aneurysms. This summary includes a brief review of the clinical issues in the treatment of large and giant aneurysms, a brief description of the device, a review of pre-clinical studies and a summary of the pivotal study along with additional clinical data submitted. The sponsor bases the request for approval on the pivotal clinical study: "Pipeline™ for Uncoilable or Failed Aneurysms", "PUFS". The additional clinical data submitted provides supplemental safety data. The data presented in this summary also incorporates information provided by Chestnut in a 90-day Update received on July 30, 2010 pursuant to 21 CFR 814.20[e] and data submitted in response to FDA deficiencies received on October 22, 2010.

Clinical Background

Rupture of an intracranial aneurysm and the resulting subarachnoid hemorrhage carry an initial mortality as high as 60% with a high risk of significant disability in those who survive the initial event. The treatment of intracranial aneurysms (IAs) may be surgical, most often isolating the aneurysm from the parent artery by "clipping", or by endovascular intervention using implanted coils with or without the use of a supporting stent and/or the use of remodeling balloon inflation. The choice of treatment approach depends on aneurysm location, aneurysm size and physician or patient preference.

Although some small unruptured aneurysms may not merit intervention, the risk of rupture increases with size and may be as high as 25-30% over 5 years for aneurysms 25 mm or greater in diameter[1]. Therefore most unruptured aneurysms 10 mm or larger in size and essentially all ruptured aneurysms are generally considered for treatment[2]. The goal of both surgical and endovascular treatment is complete occlusion of the dome and neck of the aneurysm since any residual neck or evidence of blood flow into the dome of the aneurysm is associated with an increased risk of aneurysm recurrence and potential rupture. Successful treatment is generally measured by the extent of occlusion of the IA on follow-up angiography using a scale with three categories: complete occlusion, residual neck or residual aneurysm[3].

Aneurysms with a diameter of 10 – 25 mm in any plane are generally considered "large" and those over 25 mm are considered "giant"[4]. A neck of 4 mm or more is considered "wide". Some aneurysms have no discernible neck. Treatment of this subgroup of IAs is especially problematic. The surgical approach to these aneurysms can be challenging but may be the approriate choice for some subjects[5, 6]. However surgical treatment may be associated with a morbidity of approximately 30% and a mortality of approximately 20%, significantly higher compared to that for IAs that do not have these size characteristics [7, 8].

The role of endovascular techniques in the treatment of ruptured or unruptured intracranial aneurysms is supported by a number of studies, most notably the International Subarachnoid

Aneurysm Treatment (ISAT) trial, a large randomized trial of surgical vs. endovascular treatment of ruptured IAs[9]. The ISAT study 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[10]. CARAT, a multicenter prospective and retrospective cohort of treated IA subjects, also showed that the more incomplete the occlusion of a target IA using coil embolization, the more likely the IA was to spontaneously rupture[11]. Unfortunately the rate of incomplete initial endovascular treatment is highest for large and giant aneurysms, especially those with a wide or no discernible neck[4, 12]. Even when early results with the use of coils are encouraging, there is a tendency for a significant proportion of large and giant aneurysms to recur over time[13, 14]. It is therefore not surprising that the recurrence rate is highest for the large or giant wide-necked aneurysms[15]. Although actual rebleeding is relatively uncommon in studies of both surgical and endovascular treatment of intracranial aneurysms, the presence of a residual neck or evidence of flow within the dome of the aneurysm are viewed as carrying a significant risk of rebleeding and therefore the need for retreatment[15, 16].

Although early results from ISAT tended to favor endovascular treatment it is unclear whether this will be sustained with extended follow-up[15, 17]. Detection of aneurysm recurrence may be delayed to 1 to 2 years after initial treatment. In the ISAT study the mean interval to retreatment after initial endovascular treatment was 24 months for those that were completely occluded initially, 17 months for those with minor filling or residual neck and 12 months for those with persistent filling of the dome of the aneurysm[15]. Raymond et al. found a strong correlation of initial incomplete treatment, initial aneurysm dome or neck size and rupture status on the subsequent risk of recurrence and the need for retreatment. They also found that only 46.9% of recurrences were detected at 6 months after treatment. There were continuing recurrences detected at least to about 3 years when 96.9% of recurrences were detected[16].

Incomplete treatment after the endovascular use of coils for these aneurysms, especially those that are large or giant with a wide or no discernible neck may be due to difficulties achieving the desired packing volume within the dome of the aneurysm and/or to gradual compaction of the coils over time[6, 18, 19]. There is also a tendency of coils to not be retained within the aneurysm dome and/or to protrude into the parent artery lumen. The use of stents to retain the coils within the aneurysm is a more recent approach to the endovascular treatment of IAs. However this technique also appears to have a more limited success rate with large and giant aneurysms[20-22].

With placement of a stent within an intracranial artery there is also a risk of acute thrombosis of the stent as well as a risk of longer term stenosis or occlusion. This is most commonly seen when stents are used in the intracranial circulation for atherosclerotic disease. The risk of delayed stenosis when stents are used in otherwise normal arteries, such as for stent assisted coiling of intracranial aneurysms, is less well studied. In a study of the use of the Neuroform® stent for assisted coiling of intracranial aneurysms the incidence of in stent stenosis was 5.8%[23].

2. Device Description

The Pipeline Embolization Device™ (PED) is a permanent implant that is deployed using commercially available 3F (0.027 in ID) microcatheters. The PED is mounted on a 304 stainless steel (304SS) guidewire in an introducer sheath **(Figure 2-1)**. The PED is provided sterile. The

PED device has been used with the Renegade™ HiFlo Catheter (K00177) or the firm's own design Marksman™ Catheter (K091559). These catheters are indicated for use for the introduction of interventional devices and infusion of diagnostic or therapeutic agents into the neuro, peripheral, and coronary vasculature.

The PED implant is woven from Platinum/8% Tungsten and 35NLT (cobalt chromium nickel) alloy wires into a cylindrical shape. The deployed device resembles a stent; however, the walls of the device have nominally 30-35% metal coverage of the arterial wall surface area instead of the 10-15% coverage of a typical neurological stent such as the Neuroform® Stent or the Cordis Enterprise™ Stent. PED is available in diameters from 2.5 to 5.0 mm and lengths from 10 to 35 mm. Table 1 shows the sizes of the PED implants available at the time of the clinical studies. As indicated in the table, the expanded or un-constrained diameter is 0.25 mm larger, which ensures that the device contacts the arterial wall and prevents migration. Radial wall pressures were in the 1-7 mmHg range for the entire device at the labeled diameters. At the time of investigation, the PED implant was available in labelled diameters from 2.5 to 5.0 mm (2.75 mm to 5.25 mm when self-expanded) and lengths from 10 to 20 mm. The sponsor has submitted supplements that have been approved for lengths of 25, 30 and 35mm.

The delivery guidewire is 175cm long. A protective coil was designed to hold the collapsed PED in place inside the introducer sheath. The protective coil is not attached to the PED. It merely constrains it from expanding. To initiate deployment of the implant, the operator rotates the proximal end of the guidewire to remove/unscrew the coil constraining the implant. To finish the deployment, the physician then advances the wire and simultaneously retracts the microcatheter until the implant fully expands in the parent artery. Once fully deployed, the implant may not be retrieved or moved. The implant can be retrieved be retracting it back into the catheter if it is not fully deployed.

[redacted]

3. Proposed Indications for Use:

The sponsor proposes the following indication for use for the PED:

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.

The panel will be asked to discuss whether the data from the clinical trial support the safety and effectiveness of the PED for the proposed indication for use, including whether the terminology for the target anatomic region of the internal carotid artery adequately describes the region studied.

4. Regulatory History

The PMA has been submitted in modules. The pivotal clinical study submitted in the PMA was conducted under [redacted] (PUFS study). The device has also been studied under IDE [redacted] (COCOA study and compassionate use). The Pipeline™ Embolization Device (PED) has been approved for use in Canada and has received the CE mark in Europe.

5. Pre-clinical Studies

The following pre-clinical testing was reported in support of this PMA. The testing was reported in IDE [redacted], K091559 Marksman™ Catheter, and in module 1 of this submission.

Material Characterization

Material tests demonstrated that the PED implant has the mechanical integrity, corrosion resistance, and mechanical and physical properties appropriate for use in the neurovasculature as a flow-disruption/implant device. Specifically, studies support an implant life of ≥ 10 years, surface area coverage of 27.11 – 30.75%, and magnetic resonance imaging (MRI) compatibility at 1.5 and 3.0 T with artifact limited to within 2-3 mm of the device.

Benchtop delivery and deployment testing adequately demonstrated that the implant was mechanically strong and flexible enough to be readily deployed in humans.

Animal tests

Animal studies included 2 short term acute implantation studies (rabbit, pig models), 1 long term (6 months rabbits), and one very long term (12 month, rabbits) study. Acute studies showed that PED could be placed in the target vasculature. The six-month animal studies showed that all surgically created aneurysms in both studies were occluded at 6 months. Histology showed excellent healing, with infiltration of the dome with fibrocytes and matrix. The degree of healing within the domes of aneurysms covered by PED was similar to those treated with coils when compared to prior studies. The PED treatment allowed the aneurysm to shrink over time. Arterial injury scores were low and there was no evidence of stenosis in the treated parent artery. To assess the effect of the approximately 30% wall coverage, the PED was also placed in the lumbar aorta. All covered lumbar and vertebral arteries were open at all time points. A 6 and 12-month rabbit study showed that side-branches of the aorta (lumbar arteries) remained open when their ostia were covered by one, two telescoped or three telescoped PEDs.

Biocompatibility and Sterility tests

Biocompatibility tests demonstrated the PED implant was biocompatible, hemocompatible, non-toxic, and non-mutagenic. Similarly, testing demonstrated good biocompatibility for the PED

delivery system. Testing of the sterility and packaging for the device and delivery system were adequate. Testing of sterility and packaging supports a 3 year shelf-life.

Microcatheter Use

The PED was designed to be placed through any 0.027" microcatheter, such as the Renegade™ Hi-Flo (Boston Scientific) or Mass Transit (Cordis Neurovascular). All initial cases in PUFS were performed using Renegade™ Hi-Flo catheter. In February 2009, approximately 3 months after enrollment began, the Marksman™ Catheter was approved for use in the PUFS IDE study. Marksman™ Catheter was developed to address some of the deliverability difficulties with the use of the Renegade™ Hi-Flo. The Marksman™ Catheter received 510(k) marketing clearance in September 2009 and CE Mark approval in August 2009.

6. Pipeline™ for Uncoilable or Failed Aneurysms, "PUFS" Clinical Study

The primary support for reasonable assurance of safety and effectiveness of the PED device comes from the Pipeline™ for Uncoilable or Failed Aneurysms or "PUFS" study. The PUFS study is being conducted in the United States under an approved investigational device exemption (IDE) application [redacted] and in Hungary and Turkey.

6.1. Eligibility criteria

6.1.1. Inclusion criteria

a) Age 21 to 75 years, inclusive
b) Subject 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

6.1.2. Exclusion Criteria

a) More than one IA requires treatment in the next 6 months
b) Subarachnoid hemorrhage in the past 60 days
c) Any intracranial hemorrhage in the last 42 days
d) Major surgery in the last 42 days

e) Unstable neurologic deficit (i.e. any worsening of clinical condition in the last 30 days)
f) History of irreversible bleeding disorder
g) Platelet count <100 X 10^3 cells/mm^3 or known platelet dysfunction
h) Inability to tolerate, documented evidence of adverse reaction or contraindication to study medications
i) Stent in place at the target IA
j) Contraindication to CT scan or MRI
k) Known allergy to contrast used in angiography that cannot be medically controlled
l) Known severe allergy to platinum or cobalt/chromium alloys
m) Relative contraindication to angiography (i.e. 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 (i.e., severe heart failure, atrial fibrillation, known carotid stenosis
q) Current use of cocaine or other illicit substance
r) Any comorbid disease or condition expected to compromise survival or ability to complete follow-up assessments to 180 days
s) Extracranial stenosis greater than 50% in the carotid artery. Intracranial stenosis greater than 50% in the treated vessel

6.2 Study Objectives and Outcome Measures

The stated overall objective of the study was "to determine the safety and effectiveness of PED placement in the endovascular treatment of large or giant wide-necked intracranial aneurysms (IAs) in the petrous, cavernous or paraophthalmic (hypophyseal, ophthalmic, or paraclinoid) segments of the internal carotid artery".

6.2.1 Primary effectiveness endpoint

The study's primary effectiveness endpoint, called "PED treatment success," was the proportion of subjects who showed complete occlusion of the target IA and ≤50% stenosis of the parent artery at the target IA location, as judged by the independent radiology committee on 180-day angiography in whom an alternative treatment on the target IA had not been performed. The Raymond scale was used to categorize the degree of aneurysm occlusion, i.e. complete occlusion, residual neck or residual aneurysm.

6.2.2 Primary safety endpoint

The study's primary safety endpoint was the proportion of subjects who experienced either death due to neurologic reasons or major ipsilateral stroke by 180 days after the last IA treatment procedure (Table 2). All safety endpoints were adjudicated by an independent clinical events committee (CEC).

6.2.3 Secondary endpoints

- Rate of complete IA occlusion at 1, 3 and 5 years of follow-up
- Incidence of ipsilateral major stroke by 180 days
- Change in modified Rankin scale (mRS) at 180 days. The proportion of subjects with a change > 2 at the 180-day visit compared to baseline was determined. The modified Rankin Scale was judged by the investigator.
- Change from baseline in neurologic signs/symptoms related to target IA at 180 days
- Incidence of device-related adverse events at 180 days, 1, 3 and 5 years

For the purposes of this study protocol, stroke was defined as follows:

A focal neurological deficit of presumed vascular origin persisting more than 24 hours AND a neuro-imaging study or other quantitative study that does not indicate a different etiology. The 24-hour criterion is excluded if the subject undergoes cerebrovascular surgery or dies during the first 24 hours. The definition includes subjects presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral infarction. The definition also includes sudden loss or worsening of visual acuity due to retinal artery occlusion or retinal emboli. The definition excludes slowly progressive cranial nerve palsies or progressive visual field deficits due to continued aneurysm growth. The definition also excludes stroke events in cases of blood disorders such as leukemia or external events such as trauma.

Stroke was categorized as ipsilateral or contralateral and periprocedural (less than or equal to 30 days) or late (greater than 30-days from the procedure). Stroke severity was graded by the Investigator as major or minor:

> **Major Stroke:** A stroke, which is present after seven days and increases the NIH Stroke Scale of the subject by ≥ 4.
>
> **Minor Stroke:** A stroke, which resolves completely within seven days OR increases the NIH Stroke Scale of the subject by ≤3.

The grading system that was used by the sponsor for assessment of the degree of parent artery stenosis included four categories 0 through 3 for 0 – 25%, >25 – 50%, >50 – 75% and >75 – 100% respectively.

A clinical events committee adjudicated adverse events as described in the protocol:

A clinical events committee (CEC) was comprised of at least 2 non-Investigator neuroradiologists and 1 neurosurgeon who reviewed all adverse events occurring in the study according to the CEC Charter. Any event meeting the definition of serious adverse event (SAE) was reviewed by the CEC. The CEC was also provided with listings of all events and could choose to adjudicate events that were not serious in

nature. Adjudicated adverse events were used in analysis of the primary safety endpoint.

6.2.4 Additional Study Measures

The sponsor planned the following subgroup analyses of the primary endpoints.

- 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

6.3 Study Design

The overall study design was a prospective, single arm, open label and multi-center study of up to 100 subjects in up to 10 sites.

6.3.1 Statistical Methodology

The statistical analysis plan employed a Bayesian approach to interpretation of clinical trial success. The study was to be interpreted as a success if the following two conditions were met:

- Pr(pE > 0.50 | Trial Data) > 0.975 AND
- Pr(pS < 0.20 | Trial Data) > 0.975

That is, the posterior probability that the effectiveness rate (pE) exceeds 50% given trial data was to be at least 0.975 and the posterior probability that the safety rate (pS) was less than 20% was to be at least 0.975. The non-informative beta (1, 1) prior distribution was used for both calculations. Table 2 summarizes the definition and analysis of the primary effectiveness and safety endpoints.

In addition, a hierarchical approach to the statistical analysis of the secondary endpoints was specified, although no specific success criteria were defined. The order was as follows:

1. Complete occlusion of the target IA at 1, 3 and 5 years
2. Major ipsilateral stroke at 180 days
3. Change in modified Rankin Scale > 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

6.3.2 Sample size

Sample size for PUFS was based on assumptions regarding the probable safety and effectiveness of the device in the target population and the proposed thresholds for interpretation of study success. Data from a feasibility study (see PITA – Section 9.1) showed that effectiveness of PED was >90% in difficult-to-treat aneurysms and the

stroke/death rate was 6.5%. With a maximum sample size of 100, statistical power was high to meet both study co-primary endpoints (i.e., to confirm that the effectiveness rate exceeded the proposed 50% threshold and the safety rate was no higher than the proposed 20% threshold) provided that the underlying but unknown success rate was at least 70% and the stroke/neurologic death rate was <7%. The study also included an interim analysis plan that allowed early cessation of enrollment if the predicted probability of clinical trial success was very high. However, study enrollment met the maximum proposed sample size (100 subjects) before an interim analysis could be performed.

6.3.3 Schedule of assessments

Follow-up assessments were conducted at 30 days and 180 days after the index (or salvage) procedure, and also at 1, 3 and 5 years after the index (or salvage) procedure. At the 30-day, 180-day, and 1-, 3- and 5-year visits, the subject had a neurologic examination and assessment of the modified Rankin scale. The subject was to undergo angiography of the target IA at 180 days and at years 1, 3 and 5 after the index procedure. The final study visit will be at 5 years after the index (or salvage) procedure. Telephone assessments were to be conducted at 90 days, and at 2 and 4 years after the index (or salvage) procedure. The purpose of the telephone call is to encourage continued study participation and to assess for changes in clinical status. If the subject reports a change, an addition (i.e., unscheduled) visit may occur (if deemed necessary). Table 3 summarizes the schedule of assessments.

7. PUFS Subject accountability

The first subject was enrolled on November 3, 2008 and the last on July 17, 2009. The PUFS study enrolled 111 subjects, three of whom were excluded prior to any attempted treatment because of eligibility issues (1) or voluntary withdrawal (2). An attempt to treat with the PED was made in the remaining 108 subjects. FDA has used this population of 108 subjects with 110 qualifying aneurysms as the “all attempted” population. In one subject the guidewire could not be navigated distal to the target aneurysm and therefore per the protocol this subject was not included by the sponsor in the effectiveness analysis. The remaining 107 subjects who were treated with the PED comprise the safety population in sponsor and FDA analyses. In 3 of these 107 subjects the treated aneurysm was subsequently adjudicated by the Core Radiology Laboratory as not qualifying for the study based on aneurysm size or location. The remaining 104 subjects comprise the sponsor’s effectiveness population. Two of these 104 subjects were found to have a second qualifying aneurysm at the initial angiography. These two aneurysms were included in the sponsor’s effectiveness population for a total of 106 aneurysms.

Table 4 is a summary of subject accountability in the PUFS study. All 104 subjects (106 aneurysms) have had their 1-year follow-up. Although the pre-specified primary endpoint was at 180 days, clinical data is available on 97 of 104 subjects with 106 treated aneurysms assessed at one year. Angiography at one year is provided for 89 subjects with 91 treated aneurysms. Two-year follow-up began in November 2010; no subjects have reached the 3-year follow-up.

7.1 Demographics

7.1.1 Baseline characteristics – medical history

Baseline characteristics of the "all attempted" population are shown in Table 5. The mean age was 57.0 years with a preponderance of women (88.9%) as is common in studies of intracranial aneurysms. There were no differences in age, IA neck size and IA fundus size across study sites (ANOVA p-values 0.1373, 0.8480, 0.7641, respectively). Eight (8) subjects had undergone previous treatment for the target IA, 6 with coil embolization. Eight subjects (7.4%) had a previous subarachnoid hemorrhage, 7 (6.5%) had a previous stroke and 60 (55.6%) had concurrent hypertension. The population studied was predominantly white and female which is consistent with other reported populations with large/giant intracranial aneurysms. Demographic characteristics did not vary significantly by analysis population, gender, aneurysm size or location, smoking status or the presence of partial IA thrombosis at baseline. It was noted that all 6 subjects in the effectiveness population with a history of previous SAH had aneurysms less than 25 mm in size. However 5 of these 6 had a neck ≥ 6 mm. The baseline demographics and medical history of subjects from the United States did not differ significantly from those from outside the US (OUS).

7.1.2 Baseline characteristics – medications

Medications reported at baseline are summarized in FDA Table 6. In addition to anti-platelet aggregation agents, the most common medications at baseline were for hypertension and for depression.

7.1.3 Baseline characteristics - aneurysm characteristics

Table 7 shows characteristics of IAs treated for the all attempted population, thus including the one subject with a failed attempt to treat and the three that were subsequently deemed to not qualify by location or size. The location was cavernous in 41.7% and 32.4% were paraophthalmic. Eighty percent of the IAs were large and 19% were giant. Mean neck size was 8.8 mm and mean dome size was 14.6 mm. There was no variation in aneurysm size or neck length across sites (ANOVA p values of 0.7641 and 0.8480, respectively). Aneurysm characteristics of subjects from the US did not differ significantly from those from outside the US and supports pooling of US and OUS data.

7.1.4 Baseline physical examination

Results of the baseline physical examination are shown in Table 8. Cranial neuropathy at baseline possibly relevant to ICA aneurysms (i.e., CN II through VI) was fairly common, occurring in 45/108 (41.7%) subjects. Most subjects had a baseline NIHSS score of 0 or 1 and a baseline mRS of 0 or 1.

7.1.5 Baseline neurologic examination

Table 9 summarizes the cranial nerve deficits at baseline. Approximately 20% had involvement of the optic, oculomotor and abducens nerve at baseline.

7.2 Treatment data

7.2.1 Technical success

PED was placed successfully in 107 of 108 attempted (99.0%) subjects. In one subject, the parent artery distal to the IA could not be catheterized and the Pipeline procedure was abandoned; the subject was treated with additional coils and had safety follow-up but was not included in the safety analysis population. (In addition to the subject described in whom the procedure was not successful and the attempt abandoned, a second subject had an unsuccessful first procedure (guide wire inadvertently withdrawn and could not re-navigate parent artery) but was successful on a second attempt two weeks later). In total, 341 devices were implanted in the target IA in 107 subjects. PEDs of all currently manufactured lengths were used Table 11. On average, subjects in PUFS had 3.1 PEDs placed per target IA (median 3, range 1-13, Table 10). Given the need for telescoping multiple PEDs to treat many of the aneurysms, in PUFS, the sponsor has subsequently submitted a supplement requesting approval to manufacture lengths up to 35 mm which has been approved by FDA.

Table 12 summarizes the length of the procedure including fluoroscopy time. The duration of the procedure was on average approximately two hours with a mean fluoroscopy time of 48.4 minutes with a range up to 205 minutes. There was one adverse event of radiation-induced alopecia in PUFS.

The panel will be asked to discuss potential safety issues related to the total fluoroscopy time required for the use of the PED.

7.2.2 PEDs not placed

Of 364 PEDs used, 8 (2.2%) were inserted into the microcatheter but then removed for various reasons. None of these subjects had an adverse event directly related to removal of the PED from the microcatheter and all went on to successful PED placement. In 5 cases, the physician experienced excessive friction when trying to pass the delivery wire through the microcatheter (Renegade™ Hi-Flo, Boston Scientific). In 1 case, the physician passed a PED into the microcatheter but then decided not to deploy the device. In 1 case, user error was detected by the proctor and the delivery system was removed prophylactically. In 1 case, PED deployment position was too proximal, so the PED and catheter were simultaneously removed. In 1 case, the device was correctly placed but the physician mishandled the delivery wire after placement, resulting in inability to successfully complete the case. The case was completed via a subsequent procedure approximately 2 weeks later. In summary, physicians attempted to place 354 PEDs through the distal end of the microcatheter and 348 (98.3%) were successfully delivered in an appropriate location.

There were 6 subjects in whom delivery of one PED was unsuccessful. In 5 of the six subjects the PED was not delivered and in one it was delivered but placement was too proximal. In all subjects the procedure was completed successfully with other PEDs. Three of the 6 did have SAEs within days of the procedure. However on review of these events there is no apparent relationship to the unsuccessful placement.

7.2.3 Device Failures

Device failures occurred in 1 of 364 (0.3%) PEDs used. In a subject with very complex and tortuous IA in which 13 PEDs were used to bridge the IA's neck, a PED wire broke at the end of the case. After placement of the last PED, the capture coil of the PED delivery wire caught on one of the previously placed PEDs. The delivery wire was torqued according to the IFU to try to release the capture coil. However, the physician then pulled on the delivery wire (instead of advancing the wire), resulting in wire breakage and retention of a fragment in the ICA. The fragment was pulled down to the petrous segment of the ICA and fixed in place using one additional PED. Due to this event the sponsor proposed the following warning statement in the instructions for use: "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."

The panel will be asked to consider whether the label warning proposed above is adequate.

7.2.4 Antiplatelet Agent Use

Table 13 summarizes the pre- and post-procedure use of anti-platelet aggregation agents in the PUFS trial. PUFS protocol required use of aspirin and clopidogrel prior to the placement procedure, as is typical for intra-arterial implants. All subjects received both aspirin and clopidogrel and 103 followed the aspirin dosing regimen and 98 followed the clopidogrel dosing regimen according to the protocol.

7.2.5 Heparin Use

Heparin was administered in an IV bolus in all cases. The ratio of post-heparin ACT to pre-heparin ACT was >1 in all cases. After initial bolus, additional heparin was given in 54 cases.

7.2.6 Microcatheter Use

PED is designed to be placed through any 0.027" microcatheter, such as Renegade™ Hi-Flo (Boston Scientific) or Mass Transit (Cordis Neurovascular). All initial cases in PUFS were performed using Renegade™ Hi-Flo catheter. Following reports of friction, approximately 3 months after enrollment had begun, Chestnut Medical received approval to use the Marksman™ Catheter in the PUFS study. In total, Marksman™ was used in 56 of 108 subjects (52%).

7.2.7 Other Device Use

Twenty-seven angioplasty balloons were used during 23 cases. The use of other devices was not a protocol deviation. Angioplasty balloons were used in these 23 cases to fully appose the PED to the vessel wall. Balloons used were Hyperform (ev3, 13

cases), Hyperglide (ev3, 7 cases), Gateway or Gateway 2 (Boston Scientific, 5 cases), and Sprinter (Medtronic, 2 cases). It should be noted that while PED is designed to conform to very tortuous vessels, some cases required use of an angioplasty balloon to fully open PED. In one subject overinflation of an angioplasty balloon just proximal to PED resulted in a small carotid tear causing a carotid cavernous fistula.

The proposed label does not include any warnings or precautions regarding the use of the PED with other devices such as an angioplasty balloon. The panel will be asked to discuss the need for label language regarding the use of ancillary devices with the PED

7.2.8 Operator experience

Table 14 shows the relationship between operator experience and effectiveness success and safety failure. No significant trends were observed.

7.3 Deviations

Table 15 summarizes all protocol deviations in PUFS.

7.3.1 Study Eligibility Criteria Deviations

Table 16 includes the 8 deviations that 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 deviations from planned assessments. Of the eight protocol deviations considered major, 3 involved exclusion criteria primarily intended to avoid a potential subject safety issue:

- Subject [redacted] had a contralateral carotid artery occlusion and it was felt that this may increase the risk of an ischemic event during treatment with PED. No adverse event occurred and there was no effect on interpretation of effectiveness
- Subject [redacted] had a genetic hypercoagulable state and an increased risk of a thrombotic event since anti-thrombotic therapy would have to be temporarily withdrawn. A serious adverse event did occur but interpretation of effectiveness was not affected and this subject was considered an effectiveness success.
- Subject [redacted] was found to have had a subarachnoid hemorrhage within 60 days of treatment. This poses a theoretical safety risk. No adverse event occurred. Interpretation of effectiveness was not compromised.

Of the remaining 5 major deviations all involved inclusion of subjects whose aneurysm did not meet all entry criteria:

Two involve treatment and inclusion of a second qualifying aneurysm discovered at the time of enrollment and treatment – subjects [redacted] and [redacted]. Each had a contralateral aneurysm that would have qualified for the study. The aneurysm for

subject [redacted] was treated at the same time as the target aneurysm and was included in the sponsor's effectiveness cohort but the contralateral aneurysm in subject [redacted] was not included since it had been initially treated with the Silk flow diverting device. Subject [redacted] should also be included as a third deviation of this type. This subject also had a second qualifying aneurysm that was treated at the time of the 180 day assessment for the initial target and was included in the sponsor's effectiveness cohort. The sponsor has provided an analysis of the primary endpoint with the two "second qualifying" aneurysms eliminated. See Section 8.2.1. The remaining five deviations in this category are as follows:

- Subject [redacted] had a second non-qualifying IA treated at the time of treatment of the qualifying IA. No adverse events were reported. This subject's qualifying aneurysm was included in the effectiveness cohort for the target qualifying aneurysm only. This would have no effect in the primary effectiveness analysis.
- Subject [redacted] is described in this section as a deviation because a previously placed Neuroform® stent partially covered the target area. The IA was also considered by the core radiology laboratory to not be in a qualifying location. This subject was not included in the sponsor's primary effectiveness cohort but was included in the FDA "all attempted" population.
- Subject [redacted] had an IA treated that was not in a location included by the protocol. This subject was not included in the sponsor's effectiveness cohort for this reason but was included in the FDA "all attempted" population.

Subject [redacted] is described n PMA section 12.5.4.11. This subject should be considered a deviation since two IAs needed treatment. The subject had an non-qualifying IA that was located about 5 mm proximal to the qualifying target IA; PED was used to cover both the target IA and the more proximal IA. This subject was included for the target IA only and therefore interpretation of the effectiveness result was not affected.

Given the somewhat inconsistent inclusion or exclusion of subjects from the effectiveness analysis, FDA has also analyzed results based on inclusion of all of the above subjects as an "all attempted" population of 108 subjects with 110 aneurysms. All but one of the "all attempted" subjects [redacted]) was treated with PED and an attempt was made to follow them per protocol. The safety population of 107 subjects (excluding only subject [redacted] treated with the device were included in the sponsor's safety population which FDA considers acceptable.

7.3.2 Medication not taken according to protocol

Seventy-seven subjects took medications in a manner not consistent with the protocol as follows:

- ***All subjects received preoperative aspirin and clopidogrel.*** The protocol-recommended dosing was aspirin 325 mg daily for 2 days and clopidogrel 75

mg daily for 7 days or a 600 mg bolus the day prior to the procedure. In 5 cases, preoperative aspirin was administered in the wrong dose or via the wrong route. In one case, the subject had a history of aspirin allergy. In one case, aspirin and clopidogrel were given immediately preoperatively because the subject had undiagnosed anemia and was being worked up for possible GI bleeding. In none of these cases did the subject suffer a stroke. In 10 cases, preoperative clopidogrel was given for the wrong number of days; in several cases, this deviation was justified as "standard institutional procedure." In one case, both preoperative medications were administered in a manner different from the protocol recommendations. A review of all SAEs and AEs reveals no clear relationship to variations in pre-procedural dosing of these agents.

- ***Heparin was* administered *in all subjects undergoing PED placement.*** The protocol recommended dosing of 50-100 U/kg. In 35 cases, the bolus dose of heparin given by the investigator was not in the targeted dosing range. Of the 16 instances at site 04, there was one SAE of ischemic stroke at approximately 8 hours after the procedure. This was due to acute internal carotid artery occlusion. Of the remaining subjects, one had a retroperitoneal hematoma immediately after the procedure, one a spontaneous intracerebral hemorrhage on POD 1. Additional information was requested from the sponsor regarding the actual heparin dosing in these subjects along with their ACT results in comparison to subjects who received the recommended heparin dosing. Adverse events occurring at three broad levels of heparin bolus dosing are shown in Table 17.

- ***All subjects received* aspirin *and clopidogrel postoperatively.*** The protocol required aspirin 325 mg daily for at least 6 months and clopidogrel 75 mg daily for at least 3 months, after which the medications could be continued at the investigator's discretion. In 19 cases, postoperative aspirin was stopped or lowered during the first 6 months of follow-up, often in response to signs of excessive platelet inhibition (bleeding or bruising). In one case, the subject did not receive PED and therefore aspirin was not indicated. In 5 cases, postoperative clopidogrel was stopped or the dose was lowered during the first 3 months, typically due to signs of excessive platelet inhibition (skin bruising). In 2 cases, ticlopidine was substituted for clopidogrel in subjects who had a reported allergy to clopidogrel. Feedback to sites regarding lowering the doses of protocol-required antiplatelet agents was not given because the reasons for dose modification were in all cases clinically acceptable.

8. Clinical Study Results and Analyses

8.1 Safety results and analyses

The primary safety endpoint was the proportion of subjects who experienced either death due to neurologic reasons or major ipsilateral strike by 180 days after the last IA treatment procedure. Major stroke was defined as a stroke present after 7 days that increased the NIH Stroke Scale score by at least 4 points. The success criterion was that the upper limit of the credible interval for the proportion of subjects meeting the endpoint at 180 days must be < 20%, i.e. Pr ($p<0.20$ | Trial Data)>0.975

8.1.1 Primary Safety endpoint

One hundred eight (10) subjects were enrolled and treated in PUFS. One subject (P15-004) was excluded from the safety analysis because the physician could not pass the micro-guidewire could beyond the target aneurysm. No attempt at treatment with Pipeline™ was made. The case was abandoned and the subject was re-treated with coils. Therefore the safety cohort consists of 107 subjects.

Ipsilateral major stroke or neurologic death as adjudicated by the core laboratory 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, i.e. the sponsor met the prespecified primary safety endpoint.

Based on our review, FDA believes that there are two additional subjects [redacted] and [redacted]) with events that could be interpreted as major strokes based on the level of intervention required. Our calculation with these two subjects included yields a proportion of 8/107 = 7.5% with an exact confidence interval of 3.3%-14.2%, and thus would still meet the primary safety endpoint.

Table 18 lists the 6 subjects who met the definition of a safety "failure" for the primary safety endpoint, 3 due to neurologic death and 5 due to major stroke by 180 days (two subjects in both categories).

Primary safety endpoint was also analyzed by subgroups. This is displayed in Table 19.

There were no statistically significant differences in the primary safety outcome in these exploratory subgroup analyses. However, the study does not have sufficient power to detect significant differences in the subgroups analyzed. The following are observations of note. The numbers of males is too small to be informative regarding gender differences. More subjects with hypertension met the primary safety endpoint compared to those without a history of hypertension (unadjusted p-value = .087). All 6 primary safety failures were in the hypertension "yes" group. Of subjects treated by operators who performed more than 5 cases, 6/84 (7%) met the primary safety endpoint compared to 0/23 for those who performed 5 or fewer cases. Thus, there was

no apparent indication of a high complication rate for those operators who performed relatively few cases. However it should be noted that all investigators were experienced in the embolization of IAs prior to undergoing training in the use of the PED. There was no indication that the number or length of devices used had an effect on the number meeting the primary safety endpoint.

8.1.2 Serious adverse events

A summary of all 44 serious adverse events occurring in PUFS up to the 90 day update is shown in Table 20. There were 37 SAEs to 180 day follow-up. Of the 7 SAEs occurring between Day 180 and 1 year, two were neurologic (amaurosis fugax), one was asymptomatic occlusion of the treated carotid artery, and the remaining events were non-neurologic.

The most relevant SAEs are described in detail below:

Deaths. There were 3 deaths in the study. One was due to a spontaneous intracerebral frontal lobar hemorrhage ipsilateral to the treated IA on POD 14. Autopsy showed no indication of aneurysm rupture. One subject had a post-procedural ischemic stroke due to acute parent artery occlusion. A slowly evolving ipsilateral intracerebral hemorrhage following a fall during recovery at a skilled nursing facility led to death. One subject died abruptly on POD 3, most likely due to ventricular fibrillation although the event was adjudicated as a neurologic death of unknown cause by the CEC. No neurologic studies were done and no autopsy was conducted. The overall death rate (3/107 = 2.8%) is within an acceptable range.

Cerebral hemorrhagic events. There were 5 SAEs of intracerebral hemorrhage. Three occurred in the immediate peri-procedural period (immediate post-procedure or post-procedure prior to discharge). The overall incidence of intracerebral hemorrhagic events was 5/107 = 4.7%. One was probably primarily ischemic, one traumatic and one in part related to the use of warfarin for an underlying genetic coagulopathy. In addition there were 5 SAEs of non-neurologic hemorrhage, three in the periprocedural period.

In addition to the above SAEs of hemorrhage, there were 22 non-serious AEs of non-neurologic hemorrhage (FDA Table 21 extracted from sponsor Table 3 of amendment 3). There were 7 AEs of puncture site hemorrhage. One vitreous hemorrhage, one urogenital hemorrhage and one subcutaneous hematoma also occurred in the peri-procedural period. The remaining hemorrhagic events occurred outside the peri-procedural period. This included 3 AEs of epistaxis, two AEs of menstrual bleeding and 3 further skin ecchymoses. These additional adverse events are not unexpected but underscore the morbidity of anti-platelet therapy.

Ischemic stroke. There were 4 SAEs of ischemic stroke. Only one occurred in the peri-procedural period and was related to parent artery occlusion. The other 3 were delayed. The event at POD 62 in subject one subject was related to in-stent stenosis and was treated with angioplasty. This subject had been treated with stent-assisted

coiling for a contralateral IA with stenosis of that parent artery noted on the angiogram performed for this ischemic event. The ischemic stroke in one subject was presumed to have occurred between 3 and 12 months post-procedure because of limited compliance with antiplatelet therapy and follow-up. This subject had a history of an ischemic stroke prior to entry into the trial. The subject did have a computed tomography angiogram (CTA) at 10 months post-PED treatment which showed new infarction and parent artery occlusion. The event that occurred in one subject appears to have been associated with a minor deficit. There were pre-existing scattered small artery occlusions on MRI and ipsilateral carotid stenosis in this subject. However the angiogram at one year did show total occlusion of the parent artery. In addition to these 4 ischemic strokes, an additional subject had a post-procedure ischemic event after placement of 15 PEDs. The event was recorded as an intracerebral hemorrhage but this event occurred after treatment of the ischemic event with tirofiban. There were therefore 2 peri-procedural and 3 delayed ischemic strokes (5/107 = 4.7%).

Amaurosis fugax was somewhat more frequent than expected, most likely in part related to the location of the aneurysms being treated. None occurred in direct relationship to the procedure itself and 4 of 5 occurred after day 90. Five events occurred in 4 subjects. In addition to these 5 retinal vascular events, there was one additional event of an ipsilateral cilioretinal artery occlusion in subject P08-004 on the day of the procedure. There were no non-serious events suggestive of retinal vascular events.

Cardiac arrhythmias. The three SAEs of cardiac arrhythmia were atrial fibrillation, transient bradycardia in the immediate post-procedure period and an episode of hypotension and bradycardia on post-operative day (POD) 1.

8.1.3 Device related adverse events

There were 15 SAEs and 6 non-serious AEs considered probably or definitely related to the PED device. This does not include the carotid-cavernous fistula occurring in one subject during a salvage procedure 2 weeks after a failed initial procedure. This was related to balloon angioplasty required to fully expand a PED. Thus the overall incidence of device related SAEs is 16/107 = 15%.

Of the device-related cerebrovascular events, 4 ischemic strokes were related to the device. One was due to acute parent artery occlusion and one was related to delayed in-stent stenosis. One occurred in a subject with known small artery occlusive disease by MRI and with no indication of parent artery stenosis or occlusion at the time of the event. However this subject did have parent artery occlusion subsequently at one year follow-up. The 4th such event was poorly documented due to limited subject compliance with follow-up assessments. None of the 5 intracranial hemorrhages were adjudicated by the CEC as definitely or probably related to the PED or the placement procedure. The incidence of device-related stroke is 5/107 (the 4 ischemic events plus one ischemic event coded as a hemorrhagic event or 4.7%. The 5 events of amaurosis fugax (in 4 subjects) were also vascular events considered probably or definitely

related to the device. There were also 4 instances of parent artery occlusion only one of which was symptomatic and two instances of parent artery stenosis one of which was symptomatic.

8.1.4 Non-serious adverse events

Table 23 lists the non-serious adverse events in PUFS. Headache was the most common adverse event. Fifteen of 34 such events were peri-procedural. Nausea/vomiting were also relatively common. There were 15 events of diplopia or ptosis that are not unexpected given the location of the aneurysms being treated. There was one event of "application site alopecia". The sponsor has confirmed that this event was considered by the investigator to be due prolonged radiation exposure during the procedure.

8.1.5 Adverse events vs Operator experience

The sponsor has provided an analysis of adverse events (AEs) by site. Table 24 shows the number of subjects with serious adverse events (SAEs) by site and Table 25 shows the number of subjects with AEs by site. There was no difference in the proportion of subjects with SAEs across sites (chi-squared exact p-value 0.1049). However, the proportion of subjects with AEs across sites shows statistically significant variation (p-value 0.0165). The low p-value appears to be driven by events at the site in Turkey; an analysis excluding the Turkey site showed a p-value of 0.3087. According the sponsor, the lower proportion of events at the sites in Budapest and Turkey could be due to:

a. Chance: FDA requested numerous post-hoc analyses, and this analysis could be "positive" due to chance alone.

b. Experience: The center in Budapest had experience with PED in >20 cases prior to starting PUFS. The center in Turkey is the busiest in the world, treating >450 aneurysm cases per year. Such extensive experience with PED or with aneurysm treatment in general may be associated with a lower likelihood of adverse events.

c. Cultural differences: Subjects in Budapest or Turkey may have a lower likelihood of reporting adverse events to their physicians.

8.2 Effectiveness results and analyses

8.2.1 Primary effectiveness endpoint

The primary effectiveness endpoint was the proportion of subjects with complete occlusion of the target IA and ≤50% stenosis of the parent artery at the target IA location as judged by the core lab on 180-day angiography in which an alternative treatment on the target IA had not been performed. The success criterion was that the lower limit of the credible interval proportion of subjects should be greater than 50%, i.e. >50% of subjects, i.e., $Pr(p>0.50 \mid \text{Trial Data})>0.975$.

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%). All 106 target IAs in the effectiveness cohort were adjudicated by all members of the core radiology laboratory. Seventy-eight IAs (73.6%, 95% posterior credible interval 64.4- 81.0%) met the study effectiveness success criteria (complete IA occlusion in the absence of stenosis >50%). 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, i.e. the statistical objective for the primary effectiveness endpoint was met. Ninety-seven subjects with 99 target IAs underwent catheter angiogram at 180 days. Amongst these 99 IAs, 78.8% met the study's effectiveness endpoint. There was no significant site × treatment effect for the primary effectiveness endpoint across site (exact chi-squared p-value 0.8287).

The analysis of the primary endpoint above is based on the initial 106 aneurysms for which treatment was attempted including the two additional qualifying aneurysms found in 2 study subjects. The "all attempted" population would include one subject with a failed attempt and the three subjects excluded for aneurysm size or location by the core radiology review. The latter three were treated with the device and there is angiographic follow-up data for these subjects at 180 days and one year. Two of the three subjects were efficacy successes but one was not. FDA has calculated the primary effectiveness endpoint for the "all attempted" population of 108 subjects/110 aneurysms. This population had a success rate of 80/110 or 72.7% with confidence interval of 63.4%-80.8% which still meets the agreed upon lower limit rate of 50%. Similarly the sponsor has provided an additional "per protocol" analysis of the primary effectiveness endpoint based on 104 subjects (considering only the first aneurysm in the two subjects with a second qualifying aneurysm). In that analysis the success rate was 76/104 or 73.1% with a confidence interval of 63.8-80.7% and a posterior probability of 0.99999907 that the lower limit is over 50%.

Table 26 lists the specific reasons that 28 subjects did not meet the primary effectiveness endpoint. Fourteen of the 28 were due to persistence of the aneurysm. Five were due to stenosis or occlusion of the parent artery. Four were due to refusal to undergo the 180 day angiogram or being lost to follow-up/withdrawal – in these subjects the absence of a result is imputed as a failure in the FDA analysis. Three are due to death of the subject. A procedural complication of carotid-cavernous fistula and a subject in whom coils were used were the remaining two failures.

8.2.1.1 Effectiveness endpoint at one year

At FDA request the sponsor has assessed the primary effectiveness endpoint at one year. This is displayed in Table 27 using the "all angiogram" population at 180 days and at one year.

As seen in Table 27, at one year 75 subjects (of the 91 who had an angiogram at one year) had complete aneurysm occlusion without significant parent artery stenosis. However Table 27 is based on those who had an angiogram which does not include the outcome of a relevant group of subjects. Based on the effectiveness cohort of 106 aneurysms, this would represent a success rate of 70.8% with an exact 95% confidence interval of (61.1%, 79.2%) with a two-sided p-value of approximately p = 0.00003. In the "all attempted" population of 110 aneurysms, the percent effectiveness success would be 77/110 = 70%, 95% CI: (58.6%, 76.7%) p = 0.00017 since it is known that of the added cases two met efficacy success criteria and two did not (the one failed attempt included).

8.2.2 Secondary Treatments

Retreatment or secondary treatment was an indication of failure of the primary treatment. In this study one subject underwent secondary treatment. Subject P 12-014 showed continued IA filling at 180 days. This subject underwent placement of 2 additional PEDs in April 2010. Follow-up angiography is pending. No other subject has undergone additional treatments for the target IA.

8.2.3 Subgroup analyses of primary effectiveness endpoint

The protocol specified subgroup analysis for the primary effectiveness endpoints are included in Table 28. In addition to the subgroups pre-specified by the protocol, at FDA request the sponsor has added additional exploratory subgroup analyses. Sponsor interpretation is that no subgroup analysis showed significant differences in the proportion of subjects meeting the primary effectiveness or safety endpoint. There do not appear to be any differences in effectiveness when the result is subgrouped by gender, history of hypertension, US vs OUS site, individual sites or individual operators. The success rate in females aged 55-65 was lower than the groups above and below that age range with an unadjusted p-value of 0.0131. This is of uncertain significance and most likely a chance finding given the number of analyses done. The number of males was too small to be informative.

8.2.4 Stenosis of the parent artery

Stenosis of the parent artery is reported in this section because it is a component of the primary effectiveness endpoint. That is, to be an effectiveness success, the 180-day angiogram had to demonstrate both complete IA occlusion and stenosis of ≤50% as adjudicated by the core radiology laboratory. Stenosis was judged according to the method of Samuels[24], which was used in the Warfarin and Aspirin for Symptomatic

Intracranial Arterial Stenosis (WASID) study[25]. Two subjects had stenosis by these criteria (2/107, 1.9%). One subject was symptomatic (stroke on postoperative day 62).

In addition to the two subjects with parent artery stenosis there are 3 cases of parent artery occlusion which appear to have been asymptomatic (see stenosis data in Table 29). Therefore the stenosis/occlusion rate at 180 days is 5/99 angiograms of parent arteries completed (on 97 subjects) = 5.0%. There was no angiographic data on 7 of the 106 subject parent arteries in this analysis population at this time point. One could be presumed to be totally occluded (known post-operative thrombosis of parent artery) and one could be presumed to not be stenotic (no stenosis at 1 year) and the 5 others are unknown. In a worst case scenario if the unknowns are considered occluded then the stenosis rate would be 11/106 parent arteries = 10.4%. For the same worst case scenario analysis for the "all attempted" population the stenosis/occlusion rate would be 11/110 = 10% since it is known that three of the 4 added subjects in this analysis did not have significant stenosis at 180 days.

The stenosis rate at one year appears to be 4 cases of occlusion (one known to be occluded at 180 days, one new after 180 days – plus 2 who had carotid occlusion at 180 days and did not have a 1 year angiogram)– plus two cases of 50% or more stenosis. The rate of stenosis/occlusion at one year would then be 6/91 angiograms of parent arteries (89 subjects) = 6.6%. The same assumptions were made regarding those who did not have an angiogram at one year as were made for those at 180 days. If the one subject who withdrew between 180 days and 1 year is assumed to have parent artery occlusion at one year, then the stenosis/occlusion rate at one year in this population was 12/106 = 11.3%. For the "all attempted" population the rate was 12/110 = 10.9% since it is known that three of the added subject did not have significant stenosis at one year.

8.2.5 Secondary endpoints

8.2.5.1 Complete IA occlusion

Table 29 displays the aneurysm occlusion status for 99 IAs at 180 days and for 91 IAs at one year. The rate of complete IA occlusion at 180 days in the full primary efficacy population is 81/106 IAs = 76.4% and for the "all attempted" group it is 83/110 = 75.5% since two of the 4 additional subjects in this group are known to have complete IA occlusion at 180 days. At one year the complete IA occlusion rate in the full primary effectiveness group is 78/106 = 72.7% at 180 days and 80/110 at one year (2 of the 4 added subjects for this population did have a follow-up angiogram at one year and are known to have complete IA occlusion).

8.2.5.2 Incidence of ipsilateral major stroke by 180 days

Six of 107 subjects (5.6%, 95% CI 2.6 – 11.7%) had a major ipsilateral stroke, as adjudicated by the CEC. Further clinical data on these 6 major strokes is provided in Table 30. Given the requirement for intervention with intraarterial

platelets and a period of barbiturate-induced coma, the stroke in one additional subject should be considered major. In another subject the need for an external ventricular drain for ICH is indicative of a major event. Although the recorded NIHSS scores of less than 4 support the sponsor's reported incidence of major stroke, the addition of these two cases would result in a major stroke rate of 8/107 = 7.5% (3.3%, 14.2%). Of note is the fact that imaging studies were not collected systematically in PUFS or any of the supporting studies of PED and therefore the sponsor cannot provide data regarding the incidence of asymptomatic hemorrhages or areas of infarction.

8.2.5.3 Change in modified Rankin scale score at 180 days

Table 31 displays the shift in mRS from baseline to 180 days. Shaded cells show those who worsened. Eleven of 107 in the safety population had a worse mRS score at 180 days. Three had died and 3 subjects declined to a mRS of 2 – thus 5 of 107 (4.7%) had declined by 2 points or more, a secondary endpoint in the study. Five had declined from a baseline mRS of 0 to a mRS of 1 at 180 days.

8.2.5.4 Device-Related AEs

See section 8.1.3

9. Additional clinical data submitted

In addition to PUFS, the sponsor provides data from four other studies/data sources:

- Pipeline™ Embolization Device for Intracranial Treatment of Aneurysms or "PITA", a controlled study conducted entirely outside the United States
- Complete Occlusion of Coilable Aneurysms - "COCOA", an ongoing study in the US under IDE [redacted]
- Uncontrolled clinical data from compassionate/emergency use experience in the US under IDE [redacted]
- Uncontrolled clinical data from the use of PED at centers in Canada
- ENERI Vascular Reconstruction Trial (EVRT), Dr. Pedro Lylyk's trial conducted at a single center in Buenos Aires, Argentina

FDA Table 32 provides a brief description of these additional studies along with the PUFS trial.

The differences between the PUFS study and the other studies or case series are listed below:

- With the exception of COCOA the target aneurysms are not limited to the cavernous and paraophthalmic carotid artery.
- Target aneurysms may not have both a large neck and size >10mm.
- Treatment is not limited to PED alone.
- Outcome was not determined by an independent review committee.

Hence, the data from these studies are provided only to further support the safety profile of the PED.

9.1 PITA (Pipeline™ for Intracranial Treatment of Aneurysms) Clinical Study

9.1.1 PITA eligibility criteria

Of note, PITA differed from PUFS in that subjects did not necessarily have giant and wide-necked aneurysms and carotid location was not required. The study was primarily a safety and feasibility study with inclusion and exclusion criteria that are similar but not identical to those of the pivotal PUFS study. The adjunctive use of coils was allowed, unlike in PUFS. Since there are a significant number of smaller aneurysms and since not all are in the cavernous or paraclinoid carotid region as in the pivotal PUFS trial, no conclusions can be made regarding effectiveness for the population studied in PUFS.

9.1.1.1 PITA Key Inclusion criteria

a. In the opinion of the physician, placement of the Pipeline™ Embolization Device is technically feasible and clinically indicated in at least one IA
b. Angiographic inclusion criteria (candidate must meet at least ONE of the following):
    - Subject has a wide necked intracranial aneurysm defined as a neck length of 4 mm or greater, or a dome to neck ratio of less than two
    - Subject has an aneurysm that has failed previous attempts at treatment as evidenced by aneurysm regrowth, coil compaction, or incomplete coiling

9.1.1.2 PITA Key Exclusion criteria

a. Subarachnoid Hemorrhage (SAH) within the last 60 days
b. Extracranial stenosis greater than 50% in the carotid artery for anterior circulation aneurysms or vertebral artery for posterior circulation aneurysms
c. Intracranial stenosis greater than 50% in the treated vessel

9.1.2 PITA Study objectives and outcome measures

The objective of the trial was to assess the safety and performance of the Pipeline™ Embolization Device in the minimally invasive endovascular treatment of intracranial aneurysms.

Primary Endpoints: Device placement success. Death and ipsilateral stroke at 30-days post-procedure.

Secondary Endpoints: Device deployment success. Clinical procedure success.

9.1.3 PITA Study design

PITA was a single-arm, non-randomized clinical trial conducted in 4 centers in Europe (Germany, 2; Austria 1; Hungary, 1) and 1 center in South America (Argentina). Adjunctive coil placement was allowed (unlike in the PUFS trial). At 180 days, all subjects underwent repeat angiography.

9.1.4 PITA subject accountability

Thirty-one subjects were recruited and treated between January and November 2007. Twenty-five (81%) were female, and mean age was 54.6 years. Four of 31 (13%) had a history of stroke. Nearly half (15/31) of IAs treated were in the paraophthalmic segment of the ICA. Other treated segments included cavernous (5), superior hypophyseal (4), posterior communicating (4), MCA proximal segment (1), vertebral artery (1) and vertebrobasilar junction (1). Twelve of 31 (39%) had undergone previous treatment of the target IA. Aneurysm characteristics are shown in Table 33. Seventy-one percent of IAs had wide necks and slightly more than 1/3 were considered large (>10 mm maximum dimension). In total, 47 PEDs were placed in 31 subjects; 18 subjects had 1 PED placed, 11 had 2 PEDs placed, and 1 each had 3 and 4 PEDs placed. Embolic coils were used in 15/31 (48%) of cases. In one case, a Neuroform® stent was also placed.

9.1.5 PITA Results and analyses

9.1.5.1 Primary Endpoints

Device placement success.

Investigators judged that in all cases but 1 (46/47 implants, 97.9%), PED placement was successful (i.e., was delivered to the target area and functioned properly). In one case, the device was delivered successfully to the target location but device placement was considered unsuccessful and the subject experienced a stroke after device removal (see below).

Death and ipsilateral stroke.

No subject died after PED placement or during follow-up. Two subjects (6.5%) experienced ipsilateral stroke soon after the placement procedure. One subject ([redacted]) had right-sided hemiparesis with motor aphasia immediately upon awakening. Imaging showed a left basal ganglion infarct 2 days after the procedure. Speech improved during the subsequent hospital stay and improved further after hospital discharge. One subject [redacted]) 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 subject underwent carotid artery ligation with removal of PED and coils. CT scan performed 3 days later showed a left hemispheric stroke. The event was deemed probably related to the placement procedure but only remotely related to PED itself.

9.1.5.2 Secondary Endpoints

Device deployment success.

Device deployment success, defined as the ability of the investigator to pass a PED through the guide catheter and release it into the target site, occurred in 47 of 54 PED deployments (87%). In 6 cases (5 subjects), a delivery wire with PED was passed into the microcatheter but the physician could not pass the delivery wire all the way through the microcatheter. In one additional case, delivery wire position was unfavorable and the device was removed. No subject harm occurred because of inability to pass the delivery wire. In all subjects, subsequent successful device deployments were possible.

Clinical procedure success.

Clinical procedure success, defined as device placement success without in-hospital neurologic death or ipsilateral stroke, occurred in 29/31 (93.5%) subjects. The two failures were attributed to stroke (see above).

9.1.5.3 Additional Endpoints

IA Occlusion at 180 days.

All subjects underwent a day-180 angiogram. The ability of PED to occlude the target IA could not be evaluated in one subject who underwent parent artery ligation. Among the other 30 subjects, complete IA occlusion was seen in 28 (93.3%). Residual filling of the IA was seen in 2 (6.7%) cases.

The sponsor reports a complete occlusion rate of 100% (15/15) when PED was used with coils and a rate of 86.7% (13/15) when PED was used alone.

New neurologic deficits.

Two subjects (described above) had stroke during or after the PED placement procedure. No other subjects developed new neurologic deficits during follow-up.

Neurological outcomes.

At 30 days, 3 subjects reported improvement in IA-related symptoms and at 180 days, 2 additional subjects reported improved IA-related symptoms. The mean Barthel score showed very little change (99.8 at baseline to 97.9 at 180-day follow-up).

9.2 Complete Occlusion of Coilable Aneurysms (COCOA) Clinical Study (IDE G080072)

9.2.1 COCOA eligibility criteria

The COCOA study was conducted under IDE [redacted]. Of note, the study included a population whose major difference from that in PUFS is that the aneurysms must be determined to be treatable with coils on review by an independent committee. They may not have both a neck > 4mm and a size > 10 mm. Most importantly the aneurysms must be such that the likelihood of coil placement and retention are deemed to be very high. Since that is often not the case with wide-necked aneurysms there have been relatively few subjects enrolled in this study. Subjects are randomized to treatment with either PED or FDA-approved coils.

9.2.1.1 Key Inclusion criteria

a. Subject has a single target IA that

1) is located in the following regions of the internal carotid artery
   i. Paraophthalmic (including paraclinoid ophthalmic and hypophyseal segments)
   ii Cavernous
   iii Petrous
2) is saccular
3) has a parent vessel with diameter 2 5 - 5 0 mm

b. If target IA has a neck >4 mm and at least 2 of 3 members of an independent expert committee (lEC) have confirmed that coil embolization with optional adjunctive techniques has a very high likelihood of procedural success (i.e. coil placement and retention)

9.2.1.2 Key Exclusion criteria

a. Target IA has BOTH neck >4 mm AND size (maximum fundus diameter) >10 mm
b. More than one IA requires treatment in the next 6 months
c. Subarachnoid hemorrhage in the past 60 days
d. Any intracranial hemorrhage in the last 42 days
e. Coils in place in the target IA
f. Prior stent placement at target site
g. Extracranial stenosis greater than 50% in the carotid artery
h. Intracranial stenosis greater than 50% in the treated vessel

9.2.2 COCOA study objectives and outcome measures

To compare the safety and effectiveness of Pipeline™ Embolization Device to coil embolization in the minimally invasive endovascular treatment of coilable intracranial aneurysms.

The primary effectiveness endpoint was defined as complete occlusion of target IA at 180-day angiography in the absence of additional treatments and ≤50% stenosis of the parent artery, the same as in PUFS.

The primary safety endpoint was the occurrence of major ipsilateral stroke or neurologic death by 180 days, also the same as in PUFS.

9.2.3 Study design

The COCOA study is a prospective, randomized controlled multi-center open label two arm parallel group study comparing the safety and effectiveness of the PED to FDA-approved coils in the treatment of wide-necked intracranial aneurysms in the paraclinoid, cavernous and petrous regions of the internal carotid artery. Subjects are randomized to either PED or coils in a 2:1 ratio. Assessments are prior to hospital discharge, and study visits at 30 days, 180 days and 1, 3 and 5 years after the procedure. Telephone contact is at 90 days, 2 and 4 years after the procedure.

9.2.4 Subject accountability (from the 2010 annual report)

Enrollment in COCOA began in October, 2008. As of the most recent annual report (data extracted May 12, 2010) 16 subjects have been enrolled (13 since the preceding annual report in June, 2009). Three withdrew prior to randomization, 2 voluntary withdrawals and one due to discovery of illicit drug use.

9.2.5 COCOA Results and analyses

Eight enrolled subjects were assigned to PED. One died and 7 have had 180-day follow-up visits. Five subjects were assigned to coils. One subject crossed over to PED, one subject withdrew due to hip fracture and one subject refused the 180-day angiogram.

Primary Safety Endpoint

One PED subject had a fatal stroke 3 days after discharge. This event was judged by the clinical events committee to have met the primary safety endpoint (major ipsilateral stroke or neurologic death). Although there was no product complaint, a device investigation was performed.

Serious Adverse Events (COCOA 2010 annual report section 6.6.2)

Eight serious adverse events have been reported to date (Table 37). All events but 1 were evaluated by the clinical events committee (CEC). There were no unanticipated adverse device events. The rate of serious adverse events was not unexpected.

Other Adverse Events

Other, non-serious adverse events were primarily related to the angiographic procedure and not PED itself. Table 38 lists non-serious adverse events reported up to the time of the annual report. Note that data collection is ongoing so the list is not necessarily complete.

9.3 Compassionate use

Compassionate use cases treated in the US met the criteria for treatment with an unapproved device and did not qualify for inclusion in open studies. These subjects were seriously ill and did not have other reasonable alternative treatments.

US Compassionate Use Cases

A total of 23 subjects with IAs of the ICA and 14 subjects with IAs of the posterior circulation have undergone PED placement (or attempted placement) as compassionate use cases.

Anterior Circulation Cases

Compassionate use cases in the anterior circulation were primarily with large/giant IAs of the ICA who were not candidates for PUFS because of age, aneurysm location (e.g., IA extended beyond region included in PUFS), or other reasons.

Twenty-three subjects with anterior circulation lesions were treated. Twenty-one of the ICA cases were large/giant and wide-necked. Of these 21, 7 adverse events occurred in 6 subjects (Table 39). Follow-up has ranged from <3 months (for more recently treated cases) to >3 years. There was 1 minor stroke and no deaths. Two additional cases of pseudoaneurysm due to intrasurgical vascular injury were successfully treated without adverse events.

Posterior Circulation Cases

14 subjects with posterior circulation lesions have undergone PED placement or attempted placement. In these 14 subjects there were 13 adverse events (Table 40). Compassionate use cases in the posterior circulation were subjects with complex vascular disease referred from other medical centers by neurosurgeons and neuroradiologists in whom no other feasible treatment was available.

9.4 Canadian Experience

Canada Special Access Cases

As of February 2010, 55 special access PED cases were performed in Canada from early 2008 until January 2009. All cases were performed under the Special Access provision of Canadian medical device law.

The 16 target IAs in the series from Dr. Alain Weill (Centre Hospitalier Université de Montréal, 7 cases) and Dr. Michael Kelly (University of Saskatoon, 9 cases), were in the carotid and

vertebral-basilar circulation and varied in neck size from 2.2 to 23 mm with a dome size of 5-30 mm. From 1 to 7 PEDs were placed. No adverse events were reported in this series.

PED has been used in 39 special access cases by Dr. Tom Marotta (St. Michael's Hospital) and Dr. Robert Willinsky (Toronto Western Hospital). Thirty-three of 39 subjects were women and the mean age was 58 years. Twenty-eight of 40 aneurysms were in the anterior circulation and 12 were in the posterior circulation. Mean aneurysm diameter was 20 mm. PED was used alone in most cases; in 3 cases (1 case with SAH) additional coils were used. Subject follow-up ranged from 1-361 days (mean 90 days).

Effectiveness was judged by the physician-operators angiographically and using CT angiogram, and MRI. By 180 days, 60% aneurysms with 180-day follow-up were completely occluded angiographically. 70% asymptomatic stenosis inside PED occurred in one subject and spontaneous occlusion of the carotid artery occurred in one case (no symptoms, but radiographic evidence of a new infarction).

Three deaths occurred. One subject developed an infection of a femoral pseudoaneurysm, which resulted in death from progressive sepsis despite aggressive treatment. One subject with a giant, partially thrombosed basilar aneurysm had ultimately fatal symptomatic brainstem compression postoperatively. One subject had intracranial hemorrhage postoperatively while taking increasing doses of aspirin during a desensitization protocol.

Morbidity was seen in 5 additional cases:

- One subject (vertebrobasilar junction aneurysm) had hemiparesis after a brainstem perforator stroke.
- One subject with a giant cavernous aneurysm had multiple emboli (presumed to have occurred during access across the aneurysm) and new cranial neuropathy.
- One subject had hydrocephalus after treatment of a vertebrobasilar aneurysm
- 3 subjects (including the subject above) with giant cavernous aneurysm had new cranial neuropathy (1 permanent, 1 resolved, 1 resolving).

9.5 Argentina experience

PED was used in a single-center series of cases in Buenos Aires, Argentina by Dr. Pedro Lylyk. At last report PED has been used in 180 cases.

Dr. Lylyk reports on the treatment of 217 IAs in 180 subjects with 301 PEDs[26]. One hundred seventy four of the IAs were in the territory for which the sponsor seeks approval. Approximately 50% were large or giant and 65% had a neck > 4 mm. Ninety-eight% of 301 PEDs were successfully implanted. Seventy-eight% were treated with PED alone. The mean number of PEDs was 1.3 per aneurysm. The total occlusion rate was 57.8% (44/76)) at 3 months, 79% (51/64) at 6 months, 93% (43/46) at 12 months, 100% (14/14) at 24 months and 100% (4/4) at 36 months. Technical complications occurred in 26 (8.6%). There were 10 clinically significant adverse events. This includes 4 intracranial hemorrhages, three thromboembolic events, two symptomatic occlusion of perforators and one symptomatic in-stent stenosis in 180

subjects with an overall mortality of 4 /180 (2.2%). 7 instances of transient in-stent stenosis are mentioned, all of which are reported to have resolved.

"Indwelling endoluminal constructs (e.g., Neuroform® and Enterprise™) represent important potential impediments to the efficacy of the PED. These devices may impair the apposition of the PED construct to the wall of the parent artery, setting up the potential for "endoleaks" around the outside of the construct, which can maintain patency of the aneurysm sac and disrupt the overgrowth of a homogeneous, contiguous layer of neointima and neoendothelium over the surface of the construct. In addition, the presence of these devices can significantly complicate the navigation of the delivery catheter into position and the actual deployment of the PEDs, potentially increasing the technical difficulty and risks associated with the reconstruction"[26].

Additional concerns noted in this publication include the potential of PED to occlude perforators, lack of experience with the use of PED for ruptured aneurysms and the lack of experience with bifurcation aneurysms.

10. Post-approval studies

NOTE TO PANELISTS: FDA's inclusion of a section/discussion on a post-approval study (PAS) in this executive summary should not be interpreted to mean that FDA has made a decision on the approvability of this PMA. The presence of post-approval study plans or commitments does not in any way alter the requirements for premarket approval. A recommendation from the Panel on whether the data demonstrates reasonable assurance on device safety and effectiveness must be based solely on the premarket data. The issues noted below are FDA's comments regarding potential post-approval studies.

Overview of Proposed Post-Approval Studies

The proposed post-approval study is for continued follow-up of the existing PMA cohort (PUFS) as well as the Continued Access group (PUFS-CA) for a total of five years to primarily assess ipsilateral stroke and neurovascular death. Long-term follow-up of these cohorts will be called "PUFS-PAS" (for "post-approval study"). Due to the differing natural history of the disease based on anatomical location of the aneurysm, a powered subgroup analysis is also described. The primary outcome will be analyzed using survival analysis methods. The secondary outcomes will be analyzed using simple proportions. The hypothesis for this clinical study is that the cumulative incidence of ipsilateral stroke or neurovascular death at 5 years is less than 25%. Table 41 details the study components.

FDA Comments on the Post-Approval Study:

The proposed post-approval study protocols are the result of interactive review efforts involving FDA and Chestnut Medical. The applicant has proposed to continue to follow the PUFS cohort as well as the Continued Access arm of the study for a total of 5 years to observe safety primarily and sustained effectiveness secondarily. The proposed primary endpoint of ipsilateral stroke as defined and neurovascular death adequately captures the major safety concerns.

The FDA also recommended the study be powered to look at anatomical subgroups thought to have different outcomes. The applicant has satisfactorily described a powered subgroup analysis based on the anatomic location of the aneurysm for the primary outcome of interest.

Effectiveness questions will be addressed as the secondary outcome of the PUFS-PAS. The applicant will be performing angiograms at 3 and 5 years to record the occlusion of the aneurysm. Those angiograms will be evaluated by the core laboratory in a manner similar to the PUFS clinical trial. Those who undergo additional procedures to treat the target aneurysm will also be reported by the applicant. Additionally, device-related adverse events at 3 and 5 years will also be presented as secondary outcomes. The applicant has not described a method to determine device-relatedness in an unbiased manner.

The Panel will be asked to comment on the adequacy and appropriateness of the study design, endpoints, and length of follow-up of the study. In particular:

- **Please comment on the primary outcome proposed by the applicant (any ipsilateral stroke or neurovascular death) and whether it adequately captures the safety concerns associated with this type of device. If you think that this primary outcome is not sufficient, please suggest other items that should be considered.**
- **Please comment on whether the proposed safety threshold of less than 25% for the primary endpoint is reasonable for this device with its intended use population.**
- **Please comment on whether the two proposed anatomical subgroups are the only subgroups critical when calculating the necessary sample size for the study.**
- **Please comment on whether the proposed post-approval study addresses all the potential concerns with the use of the PED or whether additional post-approval studies are warranted.**

Tables

Table 1. Size range of PEDs

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

Source: PMA

Table 2. PUFS endpoints and success definitions

Endpoint type	Endpoint definition	Trial Success Criteria
Effectiveness	Proportion of subjects with complete occlusion of the target IA and ≤50% stenosis of the parent artery at the target IA location as judged by the core lab on 180-day angiography in which an alternative treatment on the target IA has not been performed	>50% of subjects, i.e., $Pr(p>0.50 \mid \text{Trial Data})>0.975$
Safety	Proportion of subjects who experience either death due to neurologic reasons or major ipsilateral strike by 180 days after the last IA treatment procedure. Major stroke is defined as a stroke present after 7 days that increases the NIH Stroke Scale score by at least 4 points	<20% of subjects, i.e., $Pr(p<0.20 \mid \text{Trial Data})>0.975$

Source: PMA Section 12.4.5 - Table 12-3

Table 3. Assessment schedule in PUFS

Assessment	Pre-procedure	Procedure. Second Procedure or salvage Procedure	Post-procedure/Prior to Discharge	30-Days Follow-up (+/- 7 days)	†90 days (+/- 14 days)	180-Day follow-up (day- +40/-20 days)	†2.4 years (+/- 42 days)	1,3,5* years (+/- 42 days)
Inclusion/exclusion criteria	X							
Demographics and medical history	X							
Intercurrent medical history and medication use				X	X	X	X	X
Neurologic exam	X		X	X		X		X
Fundus photograph	X							
Ophthalmologic examination	X					X		
Hematocrit/platelet count	X							
Pregnancy test	X							
Modified Rankin Scale	X		X	X		X		X
Angiogram		X				X		X
Adverse events review	X	X	X	X	X	X	X	X
Medications	X	X	X	X	X	X	X	X
Termination								X

*Termination at 5 years
†Telephone contact
Source: PUFS protocol section 3.19 - PMA Appendix 3

Table 4. Subject accountability - PUFS

Category	Exclusions	Number	FDA Comment	Total	
				IAs	Subjects
Enrolled					111
	Not treated	3			
Subjects with attempted intervention				**110**	**108**
	Excluded from efficacy only	1	unable to pass guidewire		
Safety population					**107**
	Excluded from efficacy analysis	3	Location (2), size (1)		
Efficacy subjects - intervention for qualifying lesion					**104**
	Subjects with second qualifying aneurysm	2	One treated at 180 day visit and one simultaneous with target IA		
Efficacy aneurysms - qualifying aneurysms with attempted intervention				**106**	**104**
	Deaths	3	At POD 6, 14 and 17		
	Withdrawal	1			
	Non-compliant	1			
Completed to 30 day visit				101	99
Completed to 90 day phone call				101	99
	Withdrew	1			
	Lost to follow-up	1			
Completed to 180-day visit				99	97
Completed 180 day angiogram				**99**	**97**
	Withdrew	1		98	96
	Subject added – no 180 day but did have 1 year angiogram	1		99	97
Completed 1 year visit				**99**	**97**
Completed 1 year angiogram				**91**	**89**

Source: FDA table

Table 5. Baseline characteristics - PUFS (n=108).

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

* Subject stopped in 1970. Current cocaine use was an exclusion criterion
Source: PMA Section 12.5.3.1 - Table 12-10

Table 6. Baseline medications in PUFS effectiveness cohort.

Drug	Total
Drugs for Acid related disorders	14
Clopidogrel	33
Acetylsalicylic acid	37
Diuretics	10
Beta blocking agents	16
Calcium channel blockers	12
Renin-angiotensin	28
Lipid modifying	15
Levothyroxine sodium	8
Antiepileptics	11
Antidepressants	26

Source: FDA table modified from Table 6, PMA Amendment 3

Table 7. Target IA characteristics in PUFS (n=108).

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

*: One subject qualified for revision B of PUFS, which allowed subjects with dome/neck ratio ≤ 1.5
Source: PMA Section 12.5.3.3 - Table 12-12

Table 8. Baseline characteristics of PUFS subjects (N=108)

Characteristic	Mean (SD, Range) or N (%)
Body mass index, mean (range), n=105	27.3 (5.2, 17.6-44.9)
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 (P13-001), stroke was due to emboli from the target IA.
Source: PMA Section 12.5.3.2 - Table 12-11

Table 9. Prevalence of baseline cranial neuropathy by IA size category.

Aneurysm size, mm	N	N (%) with neuropathy of …				
		CN 2	CN 3	CN 4	CN 5	CN 6
< 10*	1	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
10-15	41	3 (7.3%)	2 (4.9%)	1 (2.4%)	1 (2.4%)	1 (2.4%)
15-25	44	13 (29.5%)	11 (25%)	2 (4.5%)	4 (9.1%)	7 (15.9%)
>25	22	5 (22.7%)	7 (31.8%)	0 (0%)	2 (9.1%)	13 (59.1%)
All	108	21 (19.4%)	20 (18.5%)	3 (2.8%)	7 (6.5%)	21 (19.4%)

Source: PMA Section 12.5.3.3 Table 12-13.

Table 10. Number of PEDs placed per subject in PUFS (n = 107 subjects)

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

Source: PMA Section 12.5.4.1 – Table 12-17

Table 11. Characteristics of PED devices used in target aneurysm in PUFS

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

Source: PMA Section 12.5.4.1 – Table 12-16

Table 12. 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)

Source: PMA Section 12.5.4 Table 12-14

Table 13. Medications by study visit - PUFS

Medication	Dosing	Procedure N=108	Day 30 N=103	Day 90 N=103	Day 180 N=102
Aspirin	300 or 325 mg	102 (94.4%)	94 (91.3%)	91 (88.4%)	87 (85.3%)
	Other dose	6 (5.6%)	4 (4.9%)	8 (7.8%)	9 (8.8%)
	Not taking or dose unknown	0 (0%)	5 (4.9%)	4 (3.9%)	9 (8.8%)
Clopidogrel	75 mg	98 (90.7%)	97 (94.2%)	95 (92.2%)	65 (63.7%)
	Other dose	10 (9.3%)	2 (1.9%)	0	0
	Not taking or dose unknown	0	4 (3.9%)	8 (7.8%)	37 (36.3%)

Source: PMA Amendment 3 Table 8

Table 14. Relationship of operator experience to effectiveness and safety outcomes in PUFS

Experience	Effectiveness Success Succ/N (%) N=106	Safety Failure Fail/N (%) N=107
1st 10	43/60 (71.7%)	5/62 (8.1%)
2nd 10	15/20 (75.0%)	1/20 (5.0%)
3rd 10	17/21 (81.0%)	0/20 (0%)
4th 10	3/5 (60%)	0/5 (0%)
P-value*	0.8165	0.1836

*Cochran-Armitage trend test
Source: Table 3 - email response to query 11Oct2010

Table 15. Summary of protocol deviations in PUFS.

Deviation Class	Deviation	N
Major Deviations		
Not meet eligibility criteria (major deviations)	Increased risk of stroke	1
	Nontarget IA treated	3
	Not reversible coagulopathy	1
	SAH	1
	Stent in place	1
	Wrong location	1
Minor deviations		
Required tests 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

Deviation Class	Deviation	N
Test/visit outside of window		49
Test not done according 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

Source: PMA Amendment 1 Table 3-20.

Table 16. Deviations regarding eligibility criteria in PUFS

Subtype	Subject ID	Eligibility Criterion	Comments
Increased risk of stroke	[redacted]	Exclusion "p": other known conditions that carry a high risk of neurologic events	Subject had spontaneous contralateral carotid occlusion years prior to procedure due to atherosclerosis, which had been treated with a carotid stent.
Non-target IA treated	[redacted]	Exclusion "a": More than one IA requires treatment in the next 6 months	Subject had a 17.1 mm right-sided paraophthalmic aneurysm (target IA) as well as a contralateral 10.2 mm paraophthalmic aneurysm. Physician decided that it would not be in subject's best interest to leave the contralateral aneurysm untreated. The contralateral aneurysm was treated with PED and showed complete occlusion at 180 days

Subtype	Subject ID	Eligibility Criterion	Comments
Nontarget IA treated	[redacted]	Exclusion "a": More than one IA requires treatment in the next 6 months	Subject had large (24.7 mm) complex fusiform contralateral ICA aneurysm that recurred despite treatment with Silk (manufactured by Balt, France). Investigator felt uncomfortable leaving other aneurysm untreated. PED was successfully placed in contralateral aneurysm inside previously placed Silk
Nontarget IA treated	[redacted]	Exclusion "a": More than one IA requires treatment in the next 6 months	Subject had a 24.3 mm right-sided paraophthalmic IA (target IA). In addition, subject had an ipsilateral distal middle cerebral artery aneurysm. Investigator felt uncomfortable leaving the other aneurysm untreated. The other aneurysm was treated first with coil embolization, then PED was placed.
SAH	[redacted]	Exclusion "b": subarachnoid hemorrhage in the past 60 days	Subject had SAH 2 months prior to procedure. However, SAH originated from a different source, not the target aneurysm.
Stent in place	[redacted]	Exclusion "i": stent in place at the target IA	The subject was referred to the study center by an outside physician. On the day of the procedure, the subject was noted to have a Neuroform stent in the parent vessel that had been placed to treat another aneurysm but which extended into the planned treatment zone of the target aneurysm. Available preoperative information from the referring physician did not describe preexisting stent. Pipeline was placed because the treating physician thought it was the best treatment for the target aneurysm.
Wrong location	[redacted]	Inclusion "b1": aneurysm location	Investigator believed aneurysm location was intracranial. Subsequent review of angiograms by core laboratory radiologists showed that aneurysm was in cervical region of ICA, not intracranial. Subject was excluded from effectiveness analysis but included in safety analysis.
Irreversible coagulopathy	[redacted]	Exclusion "f": History of Irreversible bleeding disorder	Subject had Factor V Leiden, a genetic mutation causing a hypercoagulable state and requiring chronic anti-coagulation with Coumadin. Use of PED would require the subject to take aspirin and clopidogrel (as per the PUFS protocol) plus Coumadin for treatment of hypercoagulable state. A

Subtype	Subject ID	Eligibility Criterion	Comments
			consulting hematologist suggested that the risk of bleeding on these 3 agents was low, and the investigator believed that the benefits of PED treatment for the subject's IA outweighed the risks. Coumadin was held preoperatively and the subject was managed on heparin, which was continued for >24 hours after the procedure. The subject had an intracerebral hemorrhage on postoperative day 3 (POD #3). At the time of her hemorrhage, the prothrombin time was elevated (19.6 seconds)

Source: PMA Section 12.5.12 - Table 12-42

Table 17. Heparin bolus dose and adverse events occurring within first 14 days after PED treatment in PUFS

Heparin dose	Adverse Event	N (%)
<50 U/kg (n=26)	Anemia	1 (6.3%)
	Arrhythmia: atrial fibrillation	1 (6.3%)
	Back pain	1 (6.3%)
	Carotid cavernous fistula	1 (6.3%)
	Corneal abrasion	1 (6.3%)
	Fever	1 (6.3%)
	Headache	4 (25%)
	Hypotension	1 (6.3%)
	Intracranial hemorrhage	1 (6.3%)
	Ischemic stroke	1 (6.3%)
	Nausea	2 (12.5%)
	Possible intracranial hemorrhage	1 (6.3%)
	Ptosis	2 (12.5%)
	Sore throat	1 (6.3%)
50-100 U/kg (n=65)	Achiness	1 (1.5%)
	Arrhythmia: bradycardia	1 (1.5%)
	Arterial line site swelling	1 (1.5%)
	Blurry vision	1 (1.5%)
	Cilioretinal artery embolism	1 (1.5%)
	Deep/superficial venous thrombosis	1 (1.5%)
	Diplopia	4 (6.2%)
	Diplopia (CN6), ptosis (CN3)	1 (1.5%)
	Dizziness	1 (1.5%)
	Eye floater	1 (1.5%)
	Facial pain	1 (1.5%)

Heparin dose	Adverse Event	N (%)
	Femoral puncture site infection	1 (1.5%)
	Floaters in vision	1 (1.5%)
	Headache	17 (26.2%)
	Intracranial hemorrhage	3 (4.6%)
	Nausea	8 (12.3%)
	Nausea / vomiting	1 (1.5%)
	Non-neuro bleeding: Groin bleeding	1 (1.5%)
	Non-neuro bleeding: Groin hematoma	2 (3.1%)
	Non-neuro bleeding: Hematuria	1 (1.5%)
	Non-neuro bleeding: Scalp hematoma	1 (1.5%)
	Non-neuro bleeding: Vitreal hemorrhage	1 (1.5%)
	Non-neuro bleeding: compartment syndrome	1 (1.5%)
	Non-neuro bleeding: groin bleeding	1 (1.5%)
	Non-neuro bleeding: groin hematoma	1 (1.5%)
	Non-neuro bleeding: ruptured splenic artery aneurysm	1 (1.5%)
	Numbness in fingertips	1 (1.5%)
	Pulmonary embolism	1 (1.5%)
	UE vein thrombosis	1 (1.5%)
	Urinary tract infection / pneumonia	1 (1.5%)
	Vomiting	1 (1.5%)
>100 U/kg (n=13)	Anemia	1 (7.7%)
	Diplopia	2 (15.4%)
	Headache	2 (15.4%)
	Intracranial hemorrhage	1 (7.7%)
	Non-neuro bleeding: Groin hematoma	1 (7.7%)
	Non-neuro bleeding: retroperitoneal hematoma	1 (7.7%)

Source: Table 27 email communication 02Jan2011

Table 18. Primary Safety Failures in PUFS

Cause of failure	Subject ID
Major stroke	[redacted]
Neurologic death	
Total	6

Source: FDA table

Table 19. Subgroup analysis of primary <u>safety</u> endpoint in PUFS
showing proportion of subjects in a subgroup who met the primary safety endpoint definition (major stroke or neurologic death as judged by the study's CED). Shaded boxes represent previously reported, pre-specified subgroup analyses. (Safety population)

	Overall		Women		Men	
Subgroup	Results	P-value	Results	P-value	Results	P-value
Gender						
Male	2/12 (17%)	0.1344	NA		NA	
Female	4/95 (4%)					
Aneurysm location						
Cavernous	1/49 (2%)	0.3375	1/44 (2%)	0.3369	0/5 (0%)	1.000
Ophthalmic	3/36 (8%)		1/31 (81%)		2/5 (40%)	
Supraclinoid	2/22 (9%)		2/20 (75%)		0/2 (0%)	
Aneurysm size						
≥25 mm	0/22 (0%)	0.3419	0/21 (0%)	0.5724	0/1 (0%)	1.0
< 25 mm	6/85 (7%)		4/74 (5%)		2/11 (18%)	
Neck size						
< 6 mm	1/22 (5%)	0.2363	1/20 (5%)	1.0	0/2 (0%)	1.0
≥ 6 mm	5/85 (6%)		3/75 (4%)		2/10 (20%)	
Current/former smoker						
No	4/45 (72%)	0.2363	3/38 (71%)	0.2983	1/7 (14%)	1.0
Yes	2/62 (75%)		1/57 (78%)		1/5 (20%)	
IA partially thrombosed						
No	6/90 (7%)	0.5866	4/80 (5%)	1.0	2/10 (20%)	1.0
Yes	0/17 (69%)		0/15 (0%)		0/2 (0%)	
Age range						
< 55 yo	1/40 (3)	0.4430	1/34 (3%)	1.0	0/6 (0%)	0.0152

	Overall		Women		Men	
55-65 yo	2/39 (5%)		2/35 (6%)		0/4 (0%)	
> 65 yo	3/28 (11%)		1/26 (4%)		2/2 (100%)	
History of hypertension						
No	0/47 (0%)		0/41 (0%)		0/6 (40%)	
Yes	6/59 (10%)	0.0869	4/54 (7%)	0.1311	2/5 (0%)	0.3182
Unknown	0/1 (0%)		0/0 (0%)		0/1 (0%)	
Site geography						
US	4/75 (5%)	1.0	2/68 (3%)	0.3191	2/7 (29%)	0.4697
OUS	2/32 (6%)		2/27 (7%)		0/5 (0%)	
Clinical study site						
Site 01	0/3 (0%)		0/3 (0%)		0/0	
Site 02	0/5 (0%)		0/5 (0%)		0/0	
Site 04	2/29 (7%)		1/27 (4%)		1/2 (50%)	
Site 05	2/20 (10%)		1/17 (6%)		1/3 (33%)	
Site 08	0/7 (0%)	0.8871	0/7 (0%)	0.6368	0/0	0.4697
Site 09	0/4 (0%)		0/3 (0%)		0/1 (0%)	
Site 10	0/14 (0%)		0/14 (0%)		0/0	
Site 12	2/18 (11%)		2/13 (15%)		0/5 (0%)	
Site 13	0/1 (0%)		0/0		0/1 (0%)	
Site 15	0/6 (0%)		0/6 (0%)		0/0	
Primary operator						
Investigator A	2/29 (7%)		1/27 (4%)		1/2 (50%)	
Investigator B	2/8 (25%)		2/7 (29%)		0/1 (0%)	
Investigator C	2/21 (80%)		1/18 (6%)		1/3 (33%)	
Investigator D	0/1 (0%)		0/1 (0%)		0	
Investigator E	0/1 (0%)		0/1 (0%)		0	
Investigator F	0/6 (0%)		0/6 (0%)		0	
Investigator G	0/5 (0%)	0.6481	0/5 (0%)	0.4451	0	0.6970
Investigator H	0/2 (0%)		0/2 (0%)		0	
Investigator I	0/4 (0%)		0/3 (0%)		0/1 (0%)	
Investigator J	0/6 (0%)		0/2 (0%)		0/4 (0%)	
Investigator K	0/2 (0%)		0/2 (0%)		0	
Investigator L	0/14 (0%)		0/14 (0%)		0	
Investigator M	0/4 (0%)		0/4 (0%)		0	
Investigator N	0/3 (0%)		0/3 (0%)		0	
Number of PEDs used						
1 or 2	2/36		1/34		1/2	
3 or 4	3/62	1.0	2/55	0.4581	1/7	0.3636
5 or more	1/9		1/6		0/3	
Mean length of PEDs used						
10-15	1/38	0.4191	1/36	1.0	0/2 (0%)	1.0

	Overall		Women		Men	
16-20	5/69		3/59		2/10 (20%)	
Mean diameter of PEDs used						
<4.0	2/53 (4%)	0.7057	2/52 (4%)	1.0	0/1 (0%)	1.0
4.0-<4.5	3/44 (7%)		2/37 (5%)		1/7 (14%)	
4.5-5.0	1/10 (10%)		0/6 (0%)		1/4 (25%)	
Procedure duration						
< 2 hours	3/55 (6%)	0.4141	2/48 (4%)	0.1991	1/7 (14%)	1.0
2-4 hours	2/47 (4%)		1/43 (2%)		1/4 (25%)	
> 4 hours	1/5 (20%)		1/4 (25%)		0/1 (0%)	

Source: Amendment 3 Table 18

Table 20. Serious adverse events in PUFD by MedDRA body system and term (N=107 subjects)

Each entry indicates that event occurred at or before the assessment period.

MedDRA category	MedDRA term	Index proc	Immed post-proc	Prior to discharge	Day 30	Day 90	Day 180	1 year	Cum to 180 days
Arteriosclerosis, stenosis, vascular insufficiency and necrosis	Carotid artery occlusion	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)
	Compartment syndrome	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Cardiac arrhythmias	Atrial fibrillation	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Sinus bradycardia	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Sudden cardiac death	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Central nervous system vascular disorders	Cerebral haematoma	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Haemorrhage intracranial	0 (0%)	1 (0.9%)	2 (1.9%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	4 (3.7%)
	Ischemic stroke	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	2 (1.9%)	0 (0%)	3 (2.8%)
	Thrombotic stroke	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Decreased and nonspecific blood pressure disorders and shock	Procedural hypotension	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Ear and labyrinth disorders	Tinnitus	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	1 (0.9%)
Embolism and thrombosis	Deep vein thrombosis postoperative	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Retinal artery thrombosis	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Gastrointestinal hemorrhages	Colitis (excl infective)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Rectal haemorrhage	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	1 (0.9%)
Infections - pathogen unspecified	Urinary tract infection	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Neoplasms benign, malignant and unspecified	Breast cancer recurrent	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)
Nervous system disorders	Amaurosis fugax	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	2 (1.9%)	2 (1.9%)	3 (2.8%)
	Headache	0 (0%)	0 (0%)	0 (0%)	2 (1.9%)	2 (1.9%)	1 (0.9%)	0 (0%)	5 (4.7%)
Neurological disorders NEC	Dizziness	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.9%)	0 (0%)
Pulmonary vascular disorders	Post procedural pulmonary embolism	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Reproductive system and breast disorders	Female genital tract fistula	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)
Respiratory tract neoplasms	Lung squamous cell carcinoma stage I	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)
Vascular disorders	Aneurysms and dissections site specific NEC	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Vascular disorders NEC	Arteriovenous fistula	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	2 (1.9%)
Vascular hemorrhagic disorders	Epistaxis	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Retroperitoneal haemorrhage	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Vision disorders	Diplopia	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Visual field disorders	Visual field defect	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)
Total		1 (0.9%)	4 (3.7%)	11 (10.3%)	8 (7.5%)	5 (4.7%)	8 (7.5%)	7 (6.5%)	37 (34.6%)

Source: Amendment 3 Table 2

Table 21. Non-serious hemorrhagic events in PUFS

MedDRA Category	MedDRA Term	Immed Post-Proc	Prior to Disch	Day 30	Day 90	Day 180	1 Year	Cum to 180 Days
Gastrointestinal hemorrhages	Lower gastrointestinal haemorrhage	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)
Reproductive system and breast disorders	Menometrorrhagia	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	1 (0.9%)
	Menorrhagia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)
Vascular disorders	Ecchymosis	0 (0%)	0 (0%)	0 (0%)	4 (3.7%)	0 (0%)	0 (0%)	4 (3.7%)
Vascular hemorrhagic disorders	Conjunctival haemorrhage	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Epistaxis	0 (0%)	0 (0%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0%)	3 (2.8%)
	Subcutaneous haematoma	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Urogenital haemorrhage	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	2 (1.9%)
	Vessel puncture site hemorrhage	4 (3.7%)	3 (2.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (6.5%)
	Vitreous haemorrhage	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Total		**6**	**4**	**2**	**6**	**4**	**0**	**22**

Source: FDA table

Table 22. Definitely or probably device related serious and non-serious adverse events in PUFS

SAE	PED-related		Procedure-related	
Definitely related				
	SAE	Non-SAE	SAE	Non-SAE
Thrombotic stroke	1		1	
Ischemic stroke	2			
Retinal artery thrombosis			1	
Intracerebral hemorrhage			1	
Arteriovenous fistula			1	
Headache	2			
Diplopia	1			1
Compartment syndrome			1	
Retroperitoneal hemorrhage			1	
VI nerve disorder			1	
III nerve disorder				1
Alopecia				1
Probably related				
Ischemic stroke	1			
Carotid artery occlusion	1			
Intracerebral hemorrhage			1	
Arteriovenous fistula	1			
Headache	1	4	1	
Amaurosis fugax	5			
Nausea		1		
Diplopia		1		
Pharyngitis				1
Nausea				1
Ptosis				1
Urinary tract infection				1
Puncture site hemorrhage				3
Hypoesthesia				1
Total	15	6	9	11
All AEs	21		20	

Source: FDA table

Table 23. Non-serious adverse events in PUFS by MedDRA body system and term (N=107 subjects). Each entry indicates that event occurred at or before the assessment period.

MedDRA Category	MedDRA Term	Immed Post-Proc	Prior to Disch	Day 30	Day 90	Day 180	1 Year	Cum to 180 Days
Allergic conditions	Drug eruption	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Anxiety disorders and symptoms	Panic attack	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)
Blood and lymphatic system disorders	Anemia	1 (0.9%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.9%)
Body temperature conditions	Postoperative fever	0 (0%)	2 (1.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.9%)
Ear and labyrinth disorders	Tinnitus	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)
Embolism and thrombosis	Deep vein thrombosis postoperative	0 (0%)	2 (1.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.9%)
Epidermal and dermal conditions	Pruritis	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Eye disorders NEC	Eye pain	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Gastrointestinal disorders	Constipation	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	1 (0.9%)
Gastrointestinal hemorrhages	Lower gastrointestinal haemorrhage	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)
Gastrointestinal signs and symptoms	Nausea	0 (0%)	0 (0%)	5 (4.7%)	0 (0%)	0 (0%)	0 (0%)	5 (4.7%)
	Procedural nausea	0 (0%)	7 (6.5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (6.5%)
	Procedural vomiting	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
General system disorders	Discomfort	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Facial pain	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Peripheral edema	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)
Infections - pathogen unspecified	Acute sinusitis	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	1 (0.9%)
	Bronchitis	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)
	Pharyngitis	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	2 (1.9%)
	Puncture site infection	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Urinary tract infection	0 (0%)	0 (0%)	2 (1.9%)	0 (0%)	0 (0%)	0 (0%)	2 (1.9%)
Injuries NEC	Corneal abrasion	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Musculoskeletal and connective tissue disorders NEC	Back pain	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Pain in extremity	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)
Nervous system	Headache	0 (0%)	1 (0.9%)	11 (10.3%)	4 (3.7%)	2 (1.9%)	0 (0%)	18 (16.8%)

MedDRA Category	MedDRA Term	Immed Post-Proc	Prior to Disch	Day 30	Day 90	Day 180	1 Year	Cum to 180 Days
disorders	Post-traumatic headache	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)
Neurological disorders NEC	Dizziness	0 (0%)	1 (0.9%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	2 (1.9%)
	Hyperesthesia	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Hypoesthesia	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Hypoesthesia facial	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Ocular neuromuscular disorders	Eyelid ptosis	1 (0.9%)	1 (0.9%)	2 (1.9%)	0 (0%)	0 (0%)	0 (0%)	4 (3.7%)
	IIIrd nerve disorder	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	IVth nerve disorder	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	VIth nerve disorder	0 (0%)	0 (0%)	2 (1.9%)	0 (0%)	1 (0.9%)	1 (0.9%)	3 (2.8%)
Procedural and device related injuries and complications NEC	Procedural headache	1 (0.9%)	15 (14%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	16 (15%)
Reproductive system and breast disorders	Menometrorrhagia	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	1 (0.9%)
	Menorrhagia	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)
Skin and subcutaneous tissue disorders	Skin bacterial infection	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Skin appendage conditions	Application site alopecia	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	1 (0.9%)
Vascular disorders	Ecchymosis	0 (0%)	0 (0%)	0 (0%)	4 (3.7%)	0 (0%)	0 (0%)	4 (3.7%)
Vascular hemorrhagic disorders	Conjunctival haemorrhage	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Epistaxis	0 (0%)	0 (0%)	1 (0.9%)	1 (0.9%)	1 (0.9%)	0 (0%)	3 (2.8%)
	Subcutaneous haematoma	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
	Urogenital haemorrhage	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	2 (1.9%)
	Vessel puncture site hemorrhage	4 (3.7%)	3 (2.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	7 (6.5%)
	Vitreous haemorrhage	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Vision disorders	Diplopia	0 (0%)	1 (0.9%)	5 (4.7%)	0 (0%)	0 (0%)	0 (0%)	6 (5.6%)
	Photopsia	1 (0.9%)	1 (0.9%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)	3 (2.8%)
	Vision blurred	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Visual field disorders	Visual field defect	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	2 (1.9%)	0 (0%)	3 (2.8%)
Total		**12 (11.2%)**	**40 (37.4%)**	**42 (39.3%)**	**14 (13.1%)**	**14 (13.1%)**	**4 (3.7%)**	**122 (114%)**

Source: PMA Amendment 3 Table 3

Table 24. Subjects with SAEs by PUFS site.

Site ID	Num with SAE / Num at Site
1	0/3
2	2/5
4	8/29
5	6/20
8	5/7
9	0/4
10	2/14
12	4/18
13	0/1
15	0/6
Total	**27/107**

Source: email response 11Oct2010 Table 4

Table 25. Subjects with AEs by PUFS site.

Site ID	Num with AE/ Num at Site
1	2/3
2	5/5
4	22/29
5	15/20
8	7/7
9	3/4
10	7/14
12	6/18
13	1/1
15	5/6
Total	**73/107**

Source: email response 11Oct2010 Table 5

Table 26. Reasons for primary effectiveness endpoint non-success in PUFS.

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

Source: PMA Table 12-20

Table 27. Effectiveness for subjects who had angiogram at either time point

	180 days (N = 99 (IAs))	1 year (n = 91 (IAs))
Effectiveness rate	78/99 (78.8%)	75/91 (82.45%)

Source: email response 02Dec2010 Table H.

Table 28. Subgroup analysis of the primary effectiveness endpoint
Showing proportion of subjects in a subgroup who met the primary effectiveness endpoint success definition (complete aneurysm occlusion with PED alone in the absence of stenosis > 50% of the parent artery). Shaded boxes represent previously reported, pre-specified subgroup analyses. P-values are Fisher's exact or Pearson chi-squared exact values

	Overall		**Women**		Men	
Subgroup	Results	P-value	Results	P-value	Results	P-value
Gender						
Male	6/10 (60%)	.4501	NA		NA	
Female	72/96 (75%)					
Aneurysm location						
Cavernous	33/47 (70%)	0.7137	31/44 (70%)	0.5903	2/3 (67%	1.000
Ophthalmic	29/37 (78%)		26/32 (81%)		3/5 (60%)	
Supraclinoid	16/22 (73%)		14/20 (75%)		1/2 (50%)	
Aneurysm size						
≥25 mm	15/22 (68%)	0.5891	15/21 (71%)	0.7764	0/1 (0%)	0.400
< 25 mm	63/84 (75%)		57/75 (76%)		6/9 (67%)	
Neck size						
< 6 mm	18/21 (86%)	0.2677	17/20 (85%)	0.3844	1/1 (100%)	1.0
≥ 6 mm	60/85 (71%)		55/76 (72%)		5/9 (56%)	
Current/former smoker*						
No	31/43 (72%)	0.8245	27/38 (71%)	0.4807	4/5 (80%)	0.5238
Yes	47/63 (75%)		45/58 (78%)		2/5 (40%)	
IA partially thrombosed						
No	67/90 (74%)	0.7588	63/82 (77%)	0.3291	4/8 (50%)	0.4667
Yes	11/16 (69%)		9/14 (64%)		2/2 (100%)	
Age range						
< 55 yo	36/41 (88)	0.0131	31/35 (89%)	0.0144	5/6 (83%)	0.3333
55-65 yo	21/36 (58%)		20/34 (59%)		1/2 (50%)	
> 65 yo	21/29 (72%)		21/27 (78%)		0/2 (0%)	
History of hypertension						
No	37/47 (79%)	0.3759	33/42 (79%)	0.6353	2/5 (40%)	0.5238
Yes	41/59 (70%)		39/45 (72%)		4/5 (80%)	
Site geography						
US	52/73 (71%)	0.4820	49/68 (72%)	0.4373	3/5 (60%)	1.0
OUS	26/33 (79%)		23/28 (82%)		3/6 (50%)	
Clinical study site						
Site 01	2/3 (67%)	0.8287	2/3 (67%)	0.6516	0/0	1.0
Site 02	4/5 (80%)		4/5 (80%)		0/0	
Site 04	19/29 (65%)		18/27 (67%)		1/2 (50%)	
Site 05	15/19 (79%)		14/17 (82%)		1/2 (50%)	
Site 08	6/7 (86%)		6/7 (86%)		0/0	
Site 09	2/4 (50%)		1/3 (33%)		1/1 (100%)	
Site 10	13/15 (87%)		13/15 (87%)		0/0	
Site 12	13/18 (72%)		10/13 (77%)		3/5 (60%)	
Site 15	4/6 (67%)		4/6 (67%)		0/0	
Primary operator						
Investigator A	19/29 (66%)	0.5833	18/27 (67%)	0.3879	1/2 (50%)	0.7968
Investigator B	6/8 (75%)		5/7 (71%)		1/1 (100%)	
Investigator C	16/20 (80%)		15/18 (83%)		1/2 (50%)	
Investigator D	0/1 (0%)		0/1 (0%)		0	

	Overall		Women		Men	
Investigator E	1/1 (100%)		1/1 (100%)		0	
Investigator F	4/6 (67%)		4/6 (67%)		0	
Investigator G	5/5 (100%)		5/5 (100%)		0	
Investigator H	1/2 (50%)		1/2 (50%)		0	
Investigator I	2/4 (50%)		1/3 (33%)		1/1 (100%)	
Investigator J	4/6 (67%)		2/2 (100%)		2/4 (50%)	
Investigator K	1/2 (50%)		1/2 (50%)		0	
Investigator L	13/15 (87%)		13/15 (87%)		0	
Investigator M	3/4 (75%)		3/4 (75%)		0	
Investigator N	3/3 (100%)		3/3 (100%)		0	

* The number of non-smokers changed from 45 in module 3 to 43 in this table – the difference is of no statistical significance.

Source: Source: Amendment 3 Table 17

Table 29. Angiogram data by follow-up visits for subjects who had an angiogram at the listed visit†

Angiographic reads		180 days (N=99 IAs)	1 year (N=91 IAs)
Occlusion ranking	Complete occlusion	81 (81.8%)	78 (85.7%)
	Residual neck	8 (8.1%)	5 (5.5%)
	Residual aneurysm	6 (6.1%)	5 (5.5%)
	Other	4* (4.0%)	3** 32.3%)
	Not yet read	0 (0%)	3 (3.4%)
Percent stenosis	0 - ≤25%	84 (84.8%)	80 (89.9%)
	25 - ≤ 50%	10 (10.1%)	1 (1.1%)
	50 - ≤ 75%	0 (0%)	1 (1.1%)
	75 – 100%	2 (2%)	1 (1.1%)
	Other	3# (3.0%)	2§ (2.2%) 1*** not read
Total		99 (100%)	4 (4.6%)

*: 1 case of carotid-cavernous fistula and 3 cases of carotid occlusion

**: 2 cases of carotid occlusion, 1 transvenous coil embolization

#: 3 cases of carotid occlusion

§: 2 cases of carotid occlusion, "stenosis not relevant"

***: 1 case of transvenous embolization in whom coils block visualization of the parent artery.

Source: email response 02Dec2010 Table 30

Table 30. Stroke location/severity in PUFS

Subject ID	Stroke location	Timing	Stroke severity	NIHSS Score after stroke
[redacted]	Left subdural hemorrhage and left posterior frontal lobe intraparenchymal hematoma	POD#14	Dead	ND*
[redacted]	Left anterior cerebral artery territory infarction	Immediately post-op	Major	11
[redacted]	Multifocal left lateral lenticulostriate region, basal ganglia, deep watershed infarction	POD#62	Major	10
[redacted]	Right posterior parietal lobe infarction	Between 3 and 12 months post-op	Major	7
[redacted]	Left frontal cortex hematoma	POD#1	Major	4
[redacted]	Left frontal cortex hematoma	POD#3	Minor	3
[redacted]	Right cephalad basal ganglia and corona radiata infarction	POD#138	Minor	ND, **, but symptoms resolved soon after stroke
[redacted]	Left caudate head and lateral ventricle hemorrhage	POD#6	Minor	0

* Not done, subject dead.
**Stroke evaluated at an outlying hospital. Subject did not tell investigator about stroke until 1-year visit. Subject visited neurologist 2 days after event. Medical records from this visit, which were reviewed by the Clinical Events Committee, showed that the subject's symptoms and signs had completely resolved, indicating a likely score of 0.
Source: Amendment 3 Table 1

Table 31. Change in modified Rankin scale at 180 days compared to baseline in PUFS. Shaded cells show subjects who worsened. Bolded values show subjects who were the same at baseline and follow-up. (Safety population)

Frequency		**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 but still in contact with study site.
Source: PMA Table 12-25 updated by Amendment 3 Table 35

Table 32. Summary of Clinical Studies

Controlled Clinical Trials				
Study	**Design**	**Subjects**	**N**	
PUFS	Multicenter, prospective single arm open label study of PED without use of coils	Cavernous, paraophthalmic carotid, diameter ≥ 10 mm, neck ≥ 4 mm	110	US, Hungary, Turkey
PITA	Multicenter, prospective single arm open label study of PED with or without coils	All aneurysm locations. Large and wide neck aneurysms or those which failed previous treatment attempt	31	Hungary, Turkey, Argentina
COCOA	Multicenter prospective randomized controlled open label study of PED vs coils	Petrous, cavernous and paraophthalmic carotid that are "coilable" and do not have both a neck > 4 mm and a size > 10 mm	13	US
Uncontrolled clinical data provided				
Emergency and compassionate use	Single subjects not qualified for PUFS	All aneurysm locations	37	US only
Canadian	Case series from several centers in Canada	All aneurysm locations	55	Canada only
EVRT	Single center open label	All aneurysm sizes and locations	180	Argentina only

Source: FDA table

Table 33. Aneurysm description - PITA

Dimension	Description
Aneurysm neck	21% < 4 mm 71% > 4 mm
Aneurysm maximum dimension	Mean 11.5 mm Range 2.5-26.6 mm 65% < 10 mm 29% 10-25 mm 6% > 25 mm

Source: PMA Appendix 1 Table 1

Table 34. Characteristics of study procedure - PITA

Category	n = 31
Affected side	
Left	13 (41.9%)
Right	10 (32.3%)
Not stated	8 (25.8%)
Location of Target IA	
Cavernous segment – Internal Carotid Artery	5 (16.1%)
Paraophthalmic segment – Internal Carotid Artery	15 (48.4%)
Superior hypophyseal segment – Internal Carotid Artery	4 (12.9%)
Posterior communicating segment – Internal Carotid Artery	4 (12.9%)
Proximal segment - Middle Cerebral Artery	1 (3.2%)
Vertebral artery	1 (3.2%)
Vertebrobasilar junction – Vertebral Artery / PICA	1 (3.2%)
Aneurysm Neck	
Less than 4 mm	9 (29.0%)
Equal to or greater than 4 mm	22 (71.0%)
Maximum Aneurysm Dimension (greater of width or height)	
Average	11.51 mm
Standard Deviation	7.52 mm
Range	2.5 mm – 26.6 mm
Maximum Aneurysm Dimension	
<10 mm	20 (64.5%)
10 – 25 mm	9 (29.0%)
>25 mm	2 (6.5%)

Source: PMA Appendix 1 Table 6

Table 35. Baseline characteristics of treated patients - COCOA.

	PED (n=8)*	Coils (n=5)
Age, mean (SD, range)	58 (13.8, 31.8-75.8)	46 (12.3, 34.3-69.0)
Female, n (%)	7 (87.5%)	5 (100%)
Aneurysm		
Maximum fundus diameter, mean (SD, range)	7.2 (3.9, 2.2-13.0)	6.6 (2.7, 4.5-10.6)
Neck, mean (SD, range)	3.5 (1.4, 1.8-6.0)	3.7 (1.0, 2.8-5.2)

*: The number of PED subjects is larger than coil subjects because randomization favors PED by a 2:1 ratio

Source: COCOA 2010 Annual report Table 3.

Table 36. Procedure characteristics - COCOA.

Characteristic	PED (n=8)*	Coils (n=5)
Procedure time, mean (SD, min max)	93.1 (36.3, 48 157)	126.8 (13.6, 111-140)
Fluoroscopy time, mean (SD, min-max)	36.0 (15.1, 16-55)	65.3 (20.0, 45-85)
PED diameter, mm		
3.5	2	*N/A*
3.75	7	
4.0	4	
4.25	1	
4.5	1	
5.0	1	
PED length, mm		
10	5	*N/A*
12	3	
14	2	
16	1	
18	3	
20	2	
Number of PEDs used		
1	3	*N/A*
2	2	
3	3	

Source: COCOA 2010 annual report Table 4

Table 37. Serious adverse events - COCOA

Treatment	*Description*
PED	Hospitalization for toe cellulitis vs. gout on postoperative day 212. Subject treated with medications and discharged to home 2 days later.
PED	Retroperitoneal hematoma developed immediately after PED placement. No specific therapy was provided but her hospitalization was prolonged.
PED	Same subject as above. One day after discharge, she presented to the local ER with increasing groin pain, increased hematoma and urinary urgency. A CTA of the abdomen showed a new pseudoaneurysm 2.4 x 2.1 cm in diameter. She was admitted to the hospital and underwent a local thrombin injection on July 19, 2009. Arterial duplex ultrasound 24 hours later showed no evidence of pseudoaneurysm.
PED	Experienced groin discomfort after PED procedure. CT of abdomen confirmed retroperitoneal hematoma. Subject required blood transfusion. Hospitalization was prolonged.
Coils	Experienced a GI bleed on POD 91, requiring brief hospitalization at an outside hospital and transfusion. Diagnosed with upper GI ulcer.
PED	Postoperative stroke, described above
Coils	Hip fracture with hip surgery x 2; subject eventually withdrew from study
Coils	The FemStop Femoral Compression Device was placed after PED procedure and was inadvertently left on all night. The subject had leg weakness in the morning but pulses were preserved. Doppler ultrasound showed preserved arterial and venous flow. Leg weakness resolved and the subject was discharged. The subject continues to have leg pain.

Source: COCOA annual report Table 7

Table 38. Non-serious adverse events in COCOA, including treatment assignment.

Description	**Treatment assignment***
Occasional blurry vision	P
Hypotension related to retroperitoneal hematoma	P
Nausea related to retroperitoneal hematoma	P
Intermittent fever related to retroperitoneal hematoma	P
Heavy menses	P
Headache	C
Headache	P
Headache	C
Nausea related to contrast sensitivity	C
Headache	P

*: P=PED; C=coil embolization

Source: COCOA annual report 2010 Table 4

Table 39. Summary of adverse events in 21 compassionate use cases of PED use in wide-necked large/giant IAs of the internal carotid artery

Event (MedDRA)	Frequency	Status
Headache	2	Resolved in 1, ongoing in other*
Gastrointestinal and hepatobiliary procedural complications	1	Resolved
Headache and optic neuropathy	1	Resolved
Epistaxis	1	Resolved
Ear pain (trigeminal neuropathy)	1	Ongoing
Minor stroke	1	Resolved

*: Cause of headache not known but thought by physician not to be due to aneurysm
Source: PMA Amendment 3 Table 24

Table 40. Summary of adverse events in 14 compassionate use cases of PED use in the posterior circulation

Event (MedDRA)	*Frequency*
Basilar artery thrombosis	2
Hydrocephalus	2
Basilar artery occlusion	1
Headache	1
Intracranial hemorrhage	1
Medial medullary infarct with pain syndrome*	1
Nausea/vomiting	1
Neurological complication from device (a non-Chestnut catheter)	1
Retroperitoneal hematoma	1
Sepsis	1
Subarachnoid hemorrhage	1

*: term not in MedDRA
Source: PMA Amendment 3 Table 25

Table 41. Overview of the "PUFS-PAS" Study

Study Component	Description	Additional Details
Study Objective	To document the long-term safety and effectiveness of PED for the treatment of large and giant wide-necked aneurysms of the internal carotid artery	
Study Design	Prospective Cohort Study	Continue follow up of the PUFS and PUFS-CA cohort for a total of 5 years
Hypothesis	H_o: Cumulative long-term rate of ipsilateral stroke or neurovascular death is ≥ 25%.	Will reject the null hypothesis if the upper confidence interval (97.5%) does not include 25%
Cohort Description	Wide-necked aneurysms in 94 subjects The same inclusion and exclusion criteria used in PUFS will be used for the post-approval study.	Inclusion Criteria a) Age 21 to 75 years, inclusive b) Patient has a single target IA that: 1) Is located in the following regions of the internal carotid artery: i. Petrous ii. Cavernous iii. Paraophthalmic (including paraclinoid, ophthalmic and hypophyseal segments) 2) Has a neck ≥4 mm or no discernible neck AND a size (maximum fundus diameter) ≥10 mm 3) Has a parent vessel with diameter 2.5 – 5.0 mm distal/proximal to the target IA PUFS-CA differs from PUFS only in the data that is collected, notably • Electronic case report forms used instead of paper forms • No neuro-ophthalmologist examinations
Subgroup Analysis	--Cavernous: At or below cavernous segment --Paraclinoid: Ophthalmic segment or above	Subgroups have 53 subjects each which provides 80% power to examine the aforementioned hypothesis.
Sample Size	94 subjects from PUFS and 11 subjects from PUFS-CA eligible for the five year study (total of 105). The applicant proposes to enroll another 1-2 subjects per month in the PUFS-CA study with no stated end to the enrollment period. Subjects were consented at baseline for 5 years of follow up. This sample size has over 90% power to examine the hypothesis.	Assumptions in the calculation: --survival methodology to be used --15% loss to follow up from 1.5 years to 3 years and 10% loss-to-follow-up from 3 years to 5 years --1% annual risk of stroke in the population yielding 25% threshold (20% from the PMA plus an additional accumulated 5%) --(NOTE: alpha not stated)

Endpoints *1. Primary* *2. Secondary*	1. Ipsilateral stroke or neurovascular death 2a. Complete occlusion of the IA diagnosed by angiogram and read by the core laboratory 2b. Device-related adverse events determined by a clinical events committee (CEC)	Ipsilateral stroke is defined as: • Focal neurologic deficit of presumed vascular origin persisting more than 24 hours AND a neuroimaging study or other quantitative study that does not indicate a different etiology • Includes patients presenting with clinical signs and symptoms suggestive of subarachnoid hemorrhage, intracerebral hemorrhage, or cerebral infarction. • Includes sudden loss or worsening of visual acuity due to retinal artery occlusion or retinal emboli. • The 24-hour criterion is excluded if the patient undergoes cerebrovascular surgery or dies during the first 24 hours • Excludes progressive cranial nerve palsies or progressive visual field deficits due to continued aneurysm growth • Excludes strokes from blood disorders (e.g., leukemia) or external events (e.g., trauma) There are no other definitions of the other outcomes.
Data Collection	Clinical visits and angiograms performed at 3 and 5 years Telephone contact with patients at 2 and 4 years.	The following will be collected at each clinic visit: • Medical history • Neurological examination • Modified Rankin Scale assessment • Concomitant medications • Cerebral angiogram
Analysis	Survival methods Secondary outcomes	Kaplan Meier estimate at 5-year upper confidence limit is <25% Proportion of subjects with the outcome divided by all subjects at risk for the outcome

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