

Appendix 2 – PMA Amendment 1: 90-Day Update

**Modular Premarket Approval Application
Pipeline Embolization Device
Module 3 / Amendment 1
90-Day Update**



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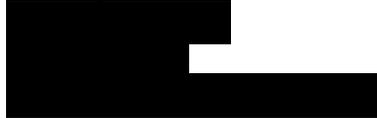


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1 Summary of Contents of PMA Amendment

This is a PMA Amendment submitted on the basis of a request by Dr. Joe Hutter for additional information as a 90-day update (email request June 14, 2010). This document focuses on information from the PUFs study, especially 1-year follow-up. Background information (see **Sections 1 and 9** of PMA Module 3) will not be repeated here.

2 Summary of Clinical Studies

Chestnut has submitted information describing 5 clinical experiences with PED (**Table 2-1**). This document focuses on updated information from the PUFs study. It should be noted that PED was recently approved for marketing in Canada.

Table 2-1. Summary of clinical studies supporting PED.

Study	Setting	Design	Patients	Results	Update
PITA	Europe and South America	Multicenter prospective single-arm study (n=31) run under compliance to ISO14155	Wide necked aneurysms unsuitable for treatment with coils	93% of patients had complete aneurysm occlusion at 6 months by angiogram judged by core lab, 6.5% had perioperative stroke	No further information
PUFS	US, Europe, Middle East	Multicenter prospective single-arm study (n=111) run under compliance to IDE	Wide necked large and giant aneurysms unsuitable for treatment with coils	74% of patients had complete aneurysm occlusion at 6 months by angiogram judged by core lab, 5.6% had stroke within first 180 days	This document
Comp Use	US	Compassionate use (n=28)	Individual patients with untreatable aneurysms not suitable for clinical trials	High rate of angiographic cure, low rate of stroke/death	No further information
Special Access	Canada	Special access (n>50)	Individual patients with untreatable aneurysms	High rate of angiographic cure, low rate of stroke/death	No further information
Clinical Use	Argentina	Clinical investigation (n=180)	Individual patients with untreatable aneurysms	High rate of angiographic cure, low rate of stroke/death	No further information

3 PUFs

3.1 Study Overview

PUFS (Pipeline for Uncoilable or Failed Aneurysms) is a multicenter, single-arm interventional clinical trial. PUFs was executed under investigational device exemption (IDE) approval (██████████) granted by US FDA. The PUFs protocol and a description of the protocol were provided in **Appendix 2** and **Sections 12.1-12.4**, respectively, of Module 3.

3.1.1 One-Year Angiograms

The primary effectiveness endpoint of PUFs was occlusion of the target intracranial aneurysm (IA) at 180 days after PED placement. Analysis of 180-day angiograms was thoroughly discussed in **Section 12.5.6** of Module 3 and showed that the primary safety and effectiveness goals of the study have been successfully met. Patients were asked to undergo additional scheduled angiograms at 1, 3 and 5 years after PED placement. It is expected that most angiographic analysis will occur in the post-market setting.

Information on >80 patients with 1-year angiograms is presented below. All analysis methods for 1-year angiograms were identical to those used for 180-day angiograms. See **Section 12.4.4.3** (p. 79) Module 3 for a description of radiographic analysis.

3.1.2 Serious Adverse Events

All adverse events meeting the definition for serious adverse event (SAE) were evaluated by a clinical events committee. See **Section 12.4.4.4** of Module 3 for a description of methods. Additional events and analysis are described below.

3.1.3 Secondary Endpoints

PUFS secondary endpoints are listed in **Table 3-1**. As discussed below, the two relevant secondary endpoints discussed in this document are endpoints #1 and 5.

Table 3-1. Secondary endpoints.

- | |
|---|
| <ol style="list-style-type: none"> 1. Complete occlusion of the target IA at 1, 3 and 5 years 2. Ipsilateral stroke at 180 days 3. Change in Modified Rankin Scale ≥ 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 |
|---|

3.1.4 Additional Endpoints

Additional study endpoints are listed in **Table 3-2**. Additional endpoints that were fully analyzed and discussed in Module 3 are shown in gray font; no further information became available since May, 2010 that would require additional analysis. Relevant additional endpoints discussed below are shown in normal font.

Table 3-2. Additional endpoints. Endpoints not relevant to follow-up after Day 180 are shown in gray font.

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

3.1.5 Protocol Deviations

Deviations from the protocol were captured continuously throughout the enrollment and follow-up periods. Deviations were characterized as major or minor (Table 3-3).

Table 3-3. Definition of protocol deviation types.

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

3.1.6 Data Set

The dataset for this study report was provided by the data entry firm on July 20, 2010.

3.2 **Results**

3.2.1 **Investigator List**

The investigator list has not changed. See **Table 12-7** of Module 3.

3.2.2 **Study Enrollment**

No information regarding PUFs enrollment has changed.

3.2.3 **Patient Characteristics**

No information regarding patient characteristics has changed. See **Section 12.5.3** of Module 3 for a description of patient characteristics in PUFs.

3.2.4 **Clinical Follow-Up**

Clinical follow-up in PUFs has been excellent (see **Figure 3-1**). The figure shows updated information in blue. One-year follow-up is just finishing at sites who enrolled patients in July 2009. One patient (██████████) withdrew from the study, and one patient (██████████), who previously refused 180-day angiogram, had a 1-year angiogram (which showed complete occlusion of the target IA).

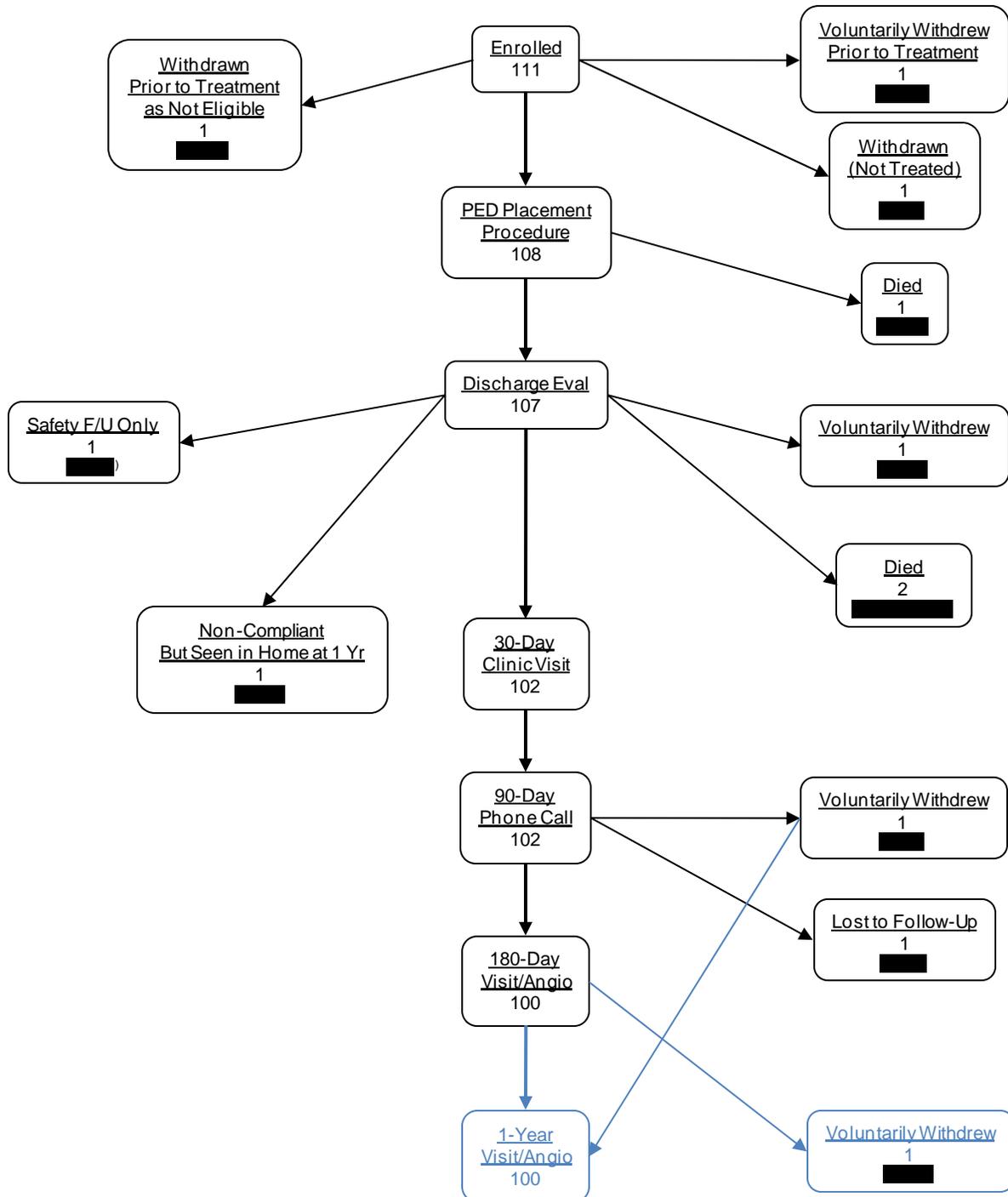


Figure 3-1. Patient flow in PUFs. Values in parentheses are patient name codes. Updated information is shown in blue arrow/font.

In summary, of the 107 subjects enrolled and treated with PED, nearly all patients are continuing in the study. Medical outcomes are unknown or unclear in only 3 cases and the last contact with these patients suggested that they had not experienced any adverse events.

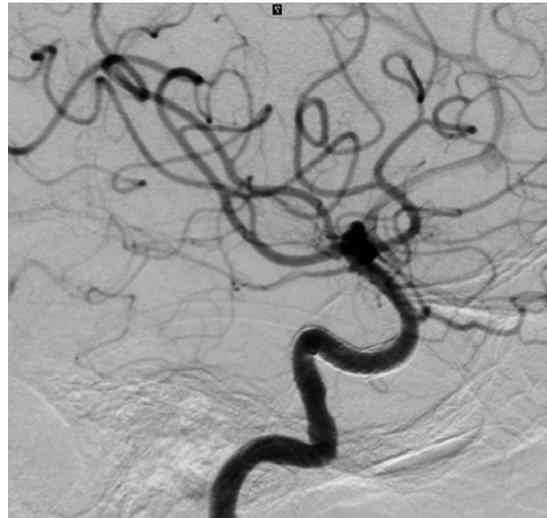
3.2.5 Primary Effectiveness Endpoint Analysis

The primary effectiveness endpoint analysis, which concerned angiographic occlusion at 180 days in 106 target IAs, has not changed and continues to meet the study's effectiveness goal. See **Section 12.5.6** of Module 3 for details.

At the time of PMA Module 3 submission, one patient (██████████) had refused 180-day follow-up angiography. She returned to the hospital at approximately 1 year after PED placement with headache. Angiogram at the time showed that the target IA had completely occluded without parent artery stenosis (**Figure 3-2**). Headache was likely due to other (contralateral) IAs that were observed on the 1-year angiogram.



Baseline 3D reconstruction



1-year angiogram

Figure 3-2. ██████████ **Baseline and 1-year angiogram.**

3.2.6 Primary Safety Endpoint Analysis

The primary safety endpoint of the study was the occurrence of major ipsilateral stroke or neurologic death by 180 days after PED placement. No aspect of the primary safety endpoint analysis has changed and the study continues to meet its predetermined safety goal. See **Section 12.5.7** of Module 3 for details.

3.2.7 Subgroup Analysis

Subgroup analysis has not changed. See **Section 12.5.8** of Module 3 for details.

3.2.8 Secondary Endpoints Analysis

The study's secondary endpoints are shown in **Table 3-4**. Secondary endpoints 2, 3 and 4 were fully described in **Section 12.5.9** of Module 3 and no new information has occurred to change those analyses. The remaining two secondary endpoints, complete IA occlusion at 1 year and device-related AEs at 1 year, are described below.

Table 3-4. PUFs Secondary Endpoints. Endpoints relevant to this report are shown in regular font.

Endpoint
1. Rate of complete IA occlusion at 1, 3 and 5 years of follow-up
2. Incidence of ipsilateral major stroke by 180 days
3. Change in modified Rankin scale (MRS) at 180 days.
4. Change from baseline in neurologic signs/symptoms related to target IA at 180 days
5. Incidence of device-related adverse events at 180 days, 1, 3 and 5 years

3.2.9 Complete IA Occlusion at 1 Year

PUFS' primary effectiveness endpoint was complete occlusion of the target IA at 180 days after PED placement. However, the study also asked patients to return to clinic for angiograms of the treated vessel at 1, 3 and 5 years. Study enrollment began in November 2008 and ended in July 2009. One-year angiograms were described briefly in the PUFs annual report, submitted to FDA on June 18, 2010 (**Section 6.9**), and are described further herein.

In PUFs, 108 patients were enrolled, of whom 107 received at least one PED (**Table 3-5**). As of July 28, 2010, 3 patients had withdrawn and 3 are dead. One patient (██████████) is considered non-participatory in the study in that she appears to be unwilling to have any study-related follow-up but has not yet been withdrawn from the study. Thus, 100 patients continue to participate in PUFs at 1 year. Of these 100, 1-year angiograms have been done in 82 cases. (It should be noted that 1-year angiograms are still being submitted by sites; the last angiogram due date is mid-July.) One-year angiogram was refused by 3 patients and was not possible due to insurance problems in 2. Two patients had conditions that made the 1-year angiogram irrelevant (carotid occlusion at 6 months or recent transvenous embolization^{*}).

^{*} Described in **Table 6** (p. 8) of the May 2010 PUFs Annual Report.

Table 3-5. Patient status at 1 year in PUFs

Received At Least 1 PED	Still Participating	Current Status	N	
Yes	Yes	1-year angiogram done	82	
		1-year angiogram refused or not done	3	
		1-year angiogram not done due to insurance reasons	2	
		1-year angiogram pending	11	
		Carotid occlusion at 6 months	1	
		Transvenous embolization at 6 months	1	
	No	No	Non-participatory	1
			Withdrew	3
			Dead	3
	No	Yes	Safety follow-up only	1
Total			108	

A comparison of 180-day and 1-year results amongst the 82 patients (83 target IAs*) who had 1-year angiograms is shown in **Table 3-6**. Of these, 52 showed complete occlusion, 3 showed residual neck, 3 showed residual aneurysm, 3 showed other findings and 22 have not yet been evaluated by the core radiographic laboratory. A comparison of 180-day and 1-year angiographic findings is as follows:

- Of 67 patients with complete IA occlusion at 6 months, 47 showed continued complete occlusion at 1 year, 19 were pending, and 1 (██████████) showed spontaneous carotid occlusion at 1 year. This last patient had several risk factors for stroke, as described in Module 3, **Appendix 18** (p. 1505).
- Of 5 patients with residual neck at 180 days, 1 progressed to complete occlusion (██████████ A), 3 had continued residual neck, and 1 has an angiographic read that is pending (██████████), but the residual neck is clearly visible on images). Residual necks at 1 year were the same size or smaller at 1 year compared to 180 days.
- Of 6 patients with residual aneurysm at 180 days, 3 had progressed to complete occlusion at 1 year (██████████ and ██████████) and 3 had continued residual neck. Patient ██████████ was remarkable in that her large aneurysm had failed both coils and Onyx treatment but was cured with PED.
- Of 4 patients with other findings at 180 days, angiographic reads are pending at 1 year in 2. In the other two:
 - 1 patient (██████████) had spontaneous carotid occlusion at 180 days, which was identical at 1 year. The target IA did not opacify

██████████ had a qualifying contralateral IA treated during the index procedure.

with contrast in either angiogram. (The patient essentially had a successful parent vessel occlusion with PED.)

- o 1 patient [REDACTED] had high-grade stenosis inside PED causing stroke at POD #62. At 1-year angiogram, stenosis was similar. Of note this patient also had stenosis when a contralateral IA was treated with stent-assisted coiling using Neuroform.

Table 3-6. Angiographic status at 1 year compared to at 180 days.

Angiographic Status at 180 days	Angiographic Status at 1 Year					
	Pending*	Complete Occlusion	Resid Neck	Resid Aneurysm	Other	Total
Not done	0	1	0	0	0	1
Complete occlusion	19	47	0	0	1	67
Resid neck	1	1	3	0	0	5
Resid aneurysm	0	3	0	3	0	6
Other	2	0	0	0	2	4
Total	22	52	3	3	3	83

*Angiogram completed but not yet read by all 3 core lab members.

Considering the 61 IAs with 1-year angiograms that have been read, complete occlusion was present in 52 (85.2%). Angiographic findings were stable or improved in all cases but 1 (98.4%). In the one case [REDACTED] that progressed from complete IA occlusion to spontaneous carotid occlusion, the target IA remained effectively treated, though now without flow in the carotid (i.e., she had a spontaneous parent vessel occlusion).

3.2.10 Device-Related AEs By 180 Days and By 1 Year

Device-related adverse events at 180 days. 21 events (15 SAEs and 6 non-SAEs) were judged to be probably or definitely related to PED (Table 3-7). No new device-related events have been reported since submission of Module 3 in May 2010. 18 events occurred prior to Day 180, 3 occurred between Day 180 and Day 365 and no events have occurred after day 365.

Table 3-7. Adverse events rated as probably or definitely related to PED.

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

3.2.11 Additional Endpoints

The PUFs protocol specified the additional endpoints shown in **Table 3-8**. All endpoints but two involved assessment only at the 180-day endpoint; these were fully reported in **Section 12.5.10** of Module 3.

Table 3-8. Additional endpoints in PUFs. Endpoints assessed at 180 days are shown in gray font.

- Technical success
- IA occlusion ranking
- Complete occlusion rate including salvage treatment
- Incidence of neurologic death by 180 days
- Change in visual field examination at 180 days
- Frequency of worsened eye alignment by clinical examination by the ophthalmologist
- Frequency of > 2 lines lost in visual acuity by Snellen chart
- Frequency of > 2 lines gained in visual acuity by Snellen chart
- Incidence of secondary treatments for the target IA
- Distal PED migration
- Stenosis in PED

3.2.11.1 IA Occlusion Ranking

As noted above, 1-year angiographic reads by all 3 core laboratory radiologists are available for 61 IAs. A complete analysis of IA ranking will be provided when all 1-year angiograms have been read.

3.2.11.2 Secondary Treatments

As reported previously (p. 93 of Module 3), one patient (██████████) showed continued IA filling at 180 days. This patient underwent placement of 2 additional PEDs in April 2010. Follow-up angiography is pending. No other patient has undergone additional treatments for the target IA.

3.2.11.3 Migration

Device migration refers to movement of a implant after deployment, and has been reported with Neuroform¹⁻³ and Enterprise⁴⁻⁶ intravascular stents. In PUFS, migration of PED was judged by the core radiology laboratory. To date, no PUFS patient has experienced distal or proximal migration of PED.

3.2.11.4 Stenosis

Stenosis inside a vascular implant is a well-known phenomenon. In Module 3, we reported 2 patients with stenosis:

- Patient [REDACTED] had intimal growth inside PED causing stroke at postoperative day 62 (described in **Section 12.5.10.10** [p. 115] of Module 3). Angiogram at 1-year showed unchanged stenosis.
- Patient [REDACTED] had asymptomatic stenosis at 180 days; stenosis appeared to be somewhat improved at 1 year (**Figure 3-3**).



Figure 3-3. Working views of [REDACTED] at baseline (left), 180 days (180 days (left)). Stenosis has improved somewhat at 1 year.

No other patient has developed stenosis >50% at the 1-year angiogram.

3.2.12 Adverse Events

Adverse events in PUFS were reported in Sections 12.5.11 of Module 3 (p. 115-119). Sites have continued to monitor patients for the occurrence of AEs.

3.2.12.1 Serious Adverse Events

Three additional serious adverse events have been reported to Chestnut since the May 2010 PMA submission and June 2010 Annual Report were submitted (**Table 3-9**). None of these events were related to PED or the placement procedure and none were neurologic in origin. These events have not yet been evaluated by the clinical events committee. A summary of all 44 serious adverse

events occurring to date in PUFs is shown in **Table 3-10**. One event (VF worsening) was inadvertently omitted from the previously submitted table. Timing of SAEs is shown in **Table 3-11**. 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 and unrelated to PED (**Table 3-12**). Relatedness is shown in **Table 3-13**.

Table 3-9. Additional SAEs since submission of Module 3 and Annual Report.

██████████. 48-year-old woman with 13.7 mm cavernous aneurysm. Patient has a history of Factor V Leiden and hyperhomocysteinemia treated with long-term Coumadin. Patient had hemorrhagic stroke after Coumadin was restarted (this event was described in detail on p. 1507, Module 3). While recovering from mild stroke, patient had urinary tract infection and pneumonia diagnosed on POD #8, both of which resolved after treatment with IV antibiotics. The event was unrelated to both PED and the PED placement procedure.

██████████ 57-year-old woman from rural northern Wisconsin with a right-sided 15.7 mm cavernous segment IA. She was referred by physicians at University of Wisconsin Madison to NYU. She had a history of frontal stroke from a previously treated aneurysm distal to the ICA terminus. The patient had an episode of bradycardia and hypotension the day after PED placement. She was treated with atropine and normal saline IV bolus and the event resolved.

██████████. The same patient experienced epistaxis requiring a visit to the emergency room on POD #66. Details of epistaxis are not known, but the event resolved. It is possible that the patient was taking clopidogrel intermittently (or perhaps stopped clopidogrel), which may have caused spontaneous carotid thrombosis a week later.

Table 3-10. Summary of SAEs to date. Underlined values represent new information.

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

Table 3-11. Timing of serious adverse events.

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

Table 3-12. Serious adverse events occurring between 180 days and 1 year.

Event Description	N
Amaurosis fugax	2
Breast cancer recurrence	1
Carotid occlusion	1
Dizziness and tinnitus*	1
Lightheadedness, palpitations, depression*	1
Lung cancer diagnosis	1
Total	7

*Both events occurred in same patient

Table 3-13. Relatedness of SAE to PED, PED placement procedure, use of antithrombotic medications and preexisting conditions as determined by CEC. 4 events have not yet been rated by the CEC.

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

3.2.12.2 Non-Serious Adverse Events

Twelve additional non-serious adverse events have been reported or detected during monitoring (Table 3-14). None of these were neurologic events attributable to PED.

Table 3-14. Additional adverse events reported since May 12, 2010.

Patient ID	Event	Time from Procedure to AE	Outcome
[REDACTED]	Blurry vision	0	Unknown*
	Bronchitis	Unk	Resolved
	Fever	366	Resolved
	Epistaxis	40	Resolved
	Epistaxis	171	Resolved
	Thigh pain, probably related to osteoarthritis	202	Ongoing but stable
[REDACTED]	Anxiety reaction	358	Resolved
	Diplopia	36	Resolved
	Fever	3	Resolved
	Back pain	1	Resolved
	Upper respiratory infection	172	Resolved
	Ptosis	29	Ongoing but stable**

*Patient saw primary care physician about 1 week later and blurry vision was not noted as a problem. Patient died of intracranial hemorrhage on POD#14. No further information regarding blurry vision is available.

**Ptosis attributed to prior craniotomy for unrelated illness. Ptosis not seen by neuro-ophthalmologist.

In total, 126 non-serious AEs have occurred to date in PUFs. Non-serious adverse events are shown in Table 3-15. Table 3-16, Table 3-17 and Table 3-18 show breakdowns by follow-up interval, status and relatedness to device, procedure or underlying disease. 6 events were probably or definitely related to PED, 15 were probably or definitely related to the PED placement procedure, and 18 were probably or definitely related to an underlying condition. Most events resolved completely.

Table 3-15. Summary of non-serious adverse events to date.

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

Table 3-16. Non-serious adverse events to date by interval.

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

Table 3-17. Status of non-serious events to date.

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

*Example: Headache improved but not completely resolved.

Table 3-18. Level of relatedness to Pipeline device, placement procedure or pre-existing condition for non-serious adverse events to date.

Level of Relatedness	Relatedness to...		
	PED	PED Placement Procedure	Preexisting Condition
Not available	2 (1.6%)	1 (0.8%)	1 (0.8%)
Unrelated	71 (56.3%)	57 (45.2%)	80 (63.5%)
Unlikely	15 (11.9%)	13 (10.3%)	1 (0.8%)
Possibly	32 (25.4%)	40 (31.7%)	25 (19.8%)
Probably	6 (4.8%)	11 (8.7%)	11 (8.7%)
Definitely	0 (0%)	4 (3.2%)	7 (5.6%)
Total	126 (100%)	126 (100%)	126 (100%)

Summary of serious and non-serious adverse events. The SAE rate after PED placement was low given the complexity of cases. SAEs occurred primarily in the peri-procedural setting. No SAEs occurred between Day 180 and 1 Year. Non-serious AEs were also rare between Day 180 and 1 Year and were typically unrelated to PED.

3.2.13 Protocol Deviations

Protocol deviations were described in Section 12.5.12 of Module 3. Monitoring of the study continues, and 11 additional minor protocol deviations have been reported (**Table 3-19**). No additional major deviations (deviation from eligibility criteria, informed consent problem or unauthorized device use) were discovered since submission of Module 3. An updated deviation table is provided in **Table 3-20**. In summary, protocol deviations were generally minor and did not affect the scientific validity of the study or its conclusions.

Table 3-19. Additional minor protocol deviations reported since PMA submission.

Deviation Type	Deviation Subtype	N
Missed visit	NR*	2
Test/visit outside of window	NR	5
Test not done acc to protocol	Sensory examination in complete	1
	Visual acuity exam incomplete	2
Required med not given/stopped early	Preoperative aspirin incorrect	1
	Total	11

*NR = not relevant

Table 3-20. Summary of protocol deviations to date.

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

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

3.3 **Additional Published Articles**

No additional articles or studies regarding PED have been published since May 2010.

3.4 **Discussion**

PUFS is an ongoing multicenter international clinical trial of PED for the treatment of large or giant IAs that were either untreatable by coils alone, failed prior coil treatment, or had a very low expected rate of complete occlusion based on information published in the medical literature. Large and giant IAs are an important clinical problem in that patients with large and giant IAs face a high risk of spontaneous, potentially fatal IA rupture and many patients with large and giant IAs have debilitating neurologic symptoms due to mass effect from the IA.

Information presented in this 90-day update support the long-term safety and effectiveness of PED. Specifically:

- **Clinical follow-up was excellent.** Compared to the published literature, the degree of long-term follow-up available in this study, including 1-year angiograms, is very high.
- One-year angiograms showed that once complete IA occlusion occurred at 180 days, **there was no recurrence at 1 year.**
- One-year angiograms also showed **no increase in stenosis** and **no new cases of stenosis.** In 1 case, stenosis present at 180 days was improved at 1 year.
- **Additional treatments for the target IA were rare** (only 1 case to date). In contrast, additional treatments are very common in patients with large or giant IAs who undergo coil embolization. For example, in Hauck et al, of 15 patients with large or giant IAs treated with coil embolization, 12 patients underwent 16 retreatments.⁷
- **Device-related adverse events** between 180 days and 1 year **were rare.**
- **Protocol deviations between 180 days and 1 year were rare.** In general, protocol deviations did not affect study validity.

3.5 **Conclusion**

PUFS provides strong evidence that PED is highly effective in the treatment of large and giant IAs. The posterior probability that the study met its effectiveness success goal was 0.999999. This main contribution of this report is long-term follow-up at 1 year; data show that **once cured, a PED-treated aneurysm remains cured.** This is not surprising given the proposed mechanism of action: endothelial cells grow on the implant mesh and permanently seal the aneurysm neck. PUFS also provides strong evidence to support a reasonable safety profile in this difficult-to-treat aneurysm population. The study met its pre-trial safety threshold with a posterior probability of 0.999979. The level of evidence for safety also appeared to meet or exceed that of other devices approved via the HDE

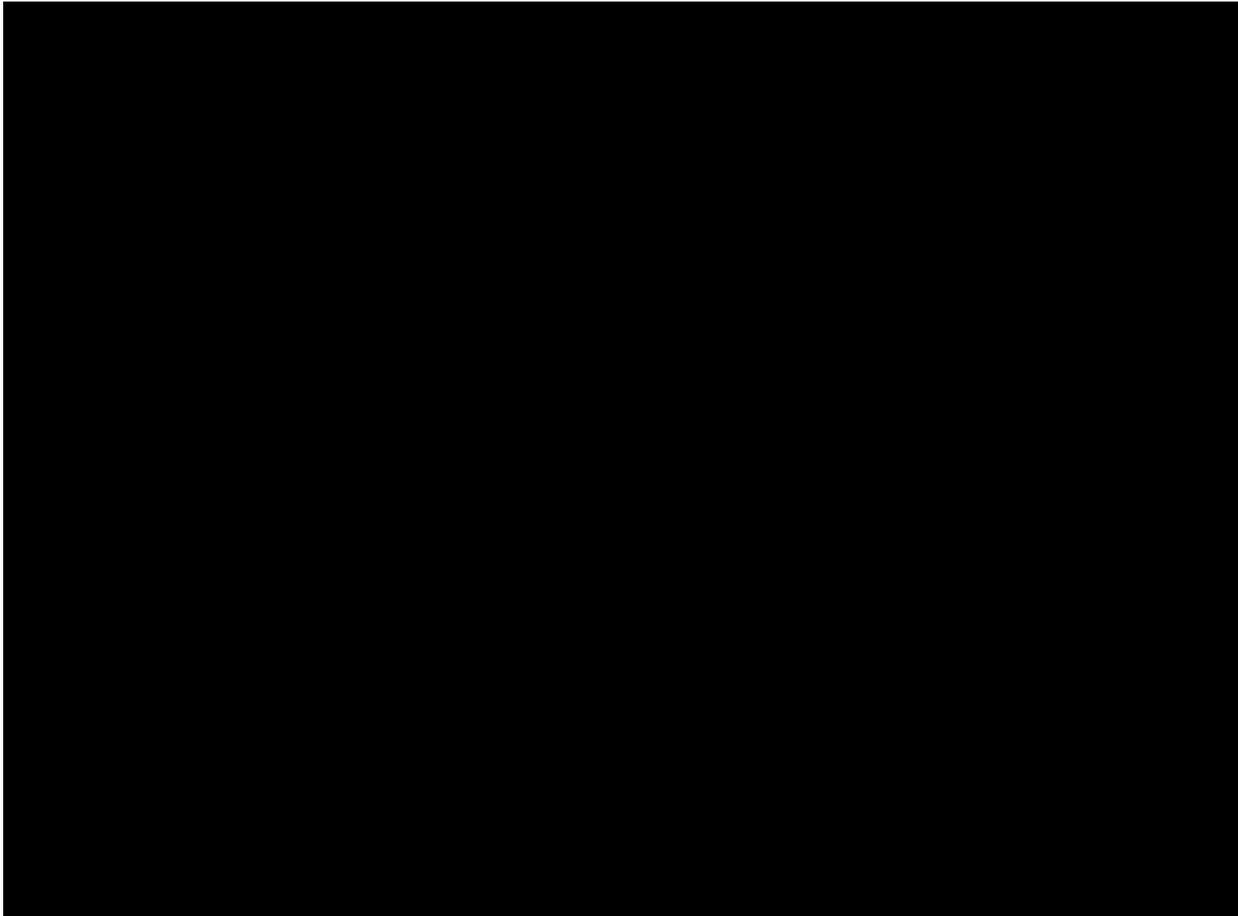
route. Late follow-up of PUFs patients has shown no additional PED-related adverse events of note. Overall, the risks of PED use in the intended patient population appear to be strongly outweighed by the benefits.

In conclusion, **PED is a breakthrough medical innovation.** The PUFs study constitutes *valid scientific evidence* (21 CFR 860.7) and provides *reasonable assurance that the device is safe and effective for its intended use* (21 CFR 814.20).

APPENDICES

Appendix 1. Radiographic Images from All PUFs Cases

The attached DVD contains angiographic images collected to date for all PUFs patients. Images from 1-year angiograms are available for the following patients:



Appendix 2. Supporting Letters from Physicians and Patients

Chestnut submitted several letters from physicians and patients in support of PED in Module 3. Since this submission, Chestnut has received additional letters from patients, which are provided on the following pages.

June 21, 2010

New York University Medical Center
Department of Radiology and Neurosurgery
Tisch Hospital, 2-HE-208
550 First Avenue
New York, NY 10026

On January 14th 2007, while working in Florida, I was suddenly struck with Double Vision and pain behind my left eye. My life was thrown into chaos. I went to the emergency room of Florida Hospital Medical Center a CT scan and and MRI showed a large mass which was later identified by attending Neuroradiologist, Dr. Frank Hellinger, as an unusually shaped large aneurysm behind my left eye.

On the advice of Dr. Hellinger, I returned home to New York City with several recommendations for the best doctors to perform the necessary angiogram and subsequent surgery or treatment for my condition. The physician he described as the best for this particular delicate and difficult to treat affliction was Dr Peter Kim Nelson. My first appointment from the recommendation list was with the clinical Director of Neruoendovascular Surgery, Dr Philip M Myers, at NY Presbyterian Neurological Institute. I begin to get a clearer picture of the unique problem my type of anuerysm posed. Dr. Myers echoed that I should see Dr. Nelson who he explained is developing and using a new device with success on patients with similar cases.

Dr. Nelson performed the angiogram which revealed a Jumbo Aneurysm that displaced Supraclinoid Carotid Artery, which in turn displaced the left side of the optic chiasm superiorly. Dr. Nelson and his team helped me understand every aspect of my condition, the current options available, the possible outcomes etc. I decided to wait for FDA approval for "Pipeline Embolization Device".

Finally, after two long and stressful years, On January 15, 2009 I underwent treatment with the experimental "Pipeline Embolization Device" (PED). Dr. Nelson and his team were able to successfully treat me with this Chestnut Medical device. After a carefully watched and painful recovery of about 90 days, I was finally completely pain free and with perfect vision! A follow up angiogram at 6 and 12 months post surgery show the aneurysm has been completely deflated! I now celebrate each day I am without pain and worry.

I want to express my heartfelt gratitude to Dr. Peter Kim Nelson, Dr Tibor Besche, Dr. Kathleen Mc Connell, Dr Mo Foulandvand, (Neuro-Ophthalmologist) and the rest of the team working in the Neurosurgery Department at NYU. Dr. Nelson is a brilliant pioneer without whom this this amazing advancement would not have been possible and many lives, perhaps mine would have been lost.

Sincerely,



From: [REDACTED]@aol.com
Sent: Wednesday, June 16, 2010 3:37 PM
To: Kelly, Cheryl - SJHMC
Subject: For Ch [REDACTED] Pad [REDACTED] by Kimberly Carter

[REDACTED]
27095 Antelope Dr
Pioneer CA 95666
(209) 295-3383 or (209) 217-6537

June 8, 2010

Dear Dr. McDougall,

On behalf of myself and my family I would like to express my heartfelt appreciation as a recipient of the pipeline surgery procedure. On May 2, 2009 I was transferred from Sutter Amador Hospital to Sutter Roseville Hospital in critical condition. While in the Intensive Care Unit at Sutter Roseville Hospital I was diagnosed with a brain aneurysm, I was in such dire condition I went into cardiac arrest on two different occasions. Within two days at Sutter Roseville I was approved for this trial procedure and flown by the air ambulance from California to St. Joseph's Hospital in Phoenix Arizona. While at St. Joseph's I was taken into surgery and received the Pipeline Embolization Device by Dr Fiorella and the surgery staff, soon after the first pipeline surgery procedure I was diagnosed with a splenic artery aneurysm in my abdominal area and was taken back into surgery to place a coil on the artery. Since the last procedure my disease was diagnosed as Fibromuscular Dysplasia, without these procedures I believe without a doubt I would not be alive today. I'm so thankful for another chance at life. On May [REDACTED] later I was able to experience and celebrate the birth of my granddaughter Elle Ann Marie into this world. By the grace of God and medical science I was given the greatest gift that could ever be given "life".

I also want to give credit where credit is due to Dr. David Fiorella and the hospital staff, which had shown extreme competence, sensitivity and the highest standard of care to both myself and my family. Dr. Fiorella's calming and soothing bedside manner helped me get through a very traumatic event in my life. I'm so very thankful that I was blessed with a doctor of such great stature and skill.

It is my hope and prayers that other individuals that are stricken by this debilitating disease will have the same chance and opportunity at life and a future that I have been given. I am living proof that this procedure works and should be available to everyone that is need of a life saving miracle.

Sincerely,

[REDACTED]

[REDACTED]

Appendix 3. References

1. Yang X, Wu Z, Mu S, Li Y, Lv M. Endovascular treatment of giant and large intracranial aneurysms using the neuroform stent-assisted coil placement. *Neurol Res* 2008;30:598-602.
2. Yahia AM, Gordon V, Whapham J, Malek A, Steel J, Fessler RD. Complications of Neuroform stent in endovascular treatment of intracranial aneurysms. *Neurocritical care* 2008;8:19-30.
3. Ansari SA, Lassig JP, Nicol E, Thompson BG, Gemmete JJ, Gandhi D. Thrombosis of a fusiform intracranial aneurysm induced by overlapping neuroform stents: case report. *Neurosurgery* 2007;60:E950-1; discussion E-1.
4. Lubicz B, Francois O, Levivier M, Brotchi J, Baleriaux D. Preliminary experience with the enterprise stent for endovascular treatment of complex intracranial aneurysms: potential advantages and limiting characteristics. *Neurosurgery* 2008;62:1063-9; discussion 9-70.
5. Rodriguez GJ, Maud A, Taylor RA. Another delayed migration of an enterprise stent. *Ajnr* 2009;30:E57.
6. Kelly ME, Turner RD, Moskowitz SI, Gonugunta V, Hussain MS, Fiorella D. Delayed migration of a self-expanding intracranial microstent. *Ajnr* 2008;29:1959-60.
7. Hauck EF, Welch BG, White JA, et al. Stent/coil treatment of very large and giant unruptured ophthalmic and cavernous aneurysms. *Surg Neurol* 2009;71:19-24; discussion