Appendix 3 – PMA Amendment 3: Response to FDA Questions

Chestnut Medical

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Document Mail Center
Center for Devices and Radiological Health
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10903 New Hampshire Avenue
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Silver Spring, MD 20993-0002

11-2-2010 dd.

Subject: PMA Number P100018/~~A2~~ AmdmTT #3 per FDA
Responses to PMA Deficiency Letter
Original PMA for Pipeline™ Embolization Device (PED)

Attn: Joseph Hutter, Ph.D.

Dear Dr. Hutter,

Chestnut Medical submitted Module 3, the final clinical module, of the above-referenced PMA on [redacted]. On [redacted], FDA notified Chestnut that the PMA was suitable for filing, with a filing date of [redacted]. This letter also noted that the PMA was granted expedited review. FDA requested a 90-day update, which was submitted on [redacted]. On [redacted] FDA sent Chestnut Medical a deficiency letter regarding this PMA. Please find below our replies to the deficiency letter. The text of FDA's deficiency questions is shown in bold italics. Our responses are in plain text.

We look forward to continuing to work interactively with FDA on this PMA application.

Sincerely,

Daniel Cher

Daniel Cher, MD
Vice President of Clinical and Regulatory Affairs
[redacted]

Major Deficiencies

1. ***You have provided a clinical study report for the Pipeline for Uncoilable or Failed Aneurysms (PUFS) study in Section 12. Based on a review of the Case Report Forms (CRFs) and an initial review of this section, we found that you have not provided all of the data collected during this study. Specifically,***

    a. ***Your protocol specifies follow-up evaluation at time points of 30, 90 and 180 days, and 1, 3, 4 and 5 years. You, however, have not consistently reported your results at all these time points.***
    b. ***There are data in your CRFs which you have not reported. For example, when a stroke occurred, you did not identify stroke location, major versus minor stroke, the National Institutes of Health Stroke Score (NIHSS), etc.***

In order for us to assess the results of this pivotal study, you will need to provide a new set of tables that presents all of the data. Please include the findings at each follow-up time point specified in your protocol for the particular parameter, up to the closure date for your 90-day PMA update. For your reference, we have enclosed sample Tables 1-11 as an attachment to illustrate the preferred format.

Response to # 1a

Appendix 1 provides the additional analyses requested. The Appendix also includes selected tables requested separately by FDA's Dr. Larry Rodichok in an email to me dated September 29, 2010. Please note that at the time of submission of the 90-day update (July 2010), no subject had yet reached 2-year follow-up, so analysis of 2-year data could not be performed.

Response to #1b

Eight PUFS subjects experienced stroke, 5 of which were classified as major stroke by the Clinical Events Committee. Locations and grading are shown in **Table 1**. All strokes were ipsilateral to the target aneurysm.

Table 1. Stroke location/severity in PUFS.

Subject ID	Stroke Location	Timing	Stroke Severity	NIH Stroke Scale Score after Stroke
[redacted]	Left subdural hemorrhage and left posterior frontal lobe intraparenchymal hematoma	Postoperative day (POD) #14	Dead	ND*
[redacted]	Left anterior cerebral artery territory infarction	Immediately postop	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 mo postop	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. Score likely zero at 7 days after minor stroke.
[redacted]	Left caudate head and lateral ventrical 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.

2. ***You have provided adverse event data for the PUFS study and for compassionate/emergency use cases in Section 12 and Appendix 18 and for the PITA (Pipeline for Intracranial Treatment of Aneurysms) study in Sections 11 and Appendix 1. However, these adverse event data are in the form of narratives rather than succinct, standardized terminology such as MedDRA (Medical Dictionary for Regulatory Activities) or SNOMED CT (Systematized Nomenclature of Medicine - Clinical Terms; http://www.ihtsdo.org/). Please review each adverse event, determine the standardized terminology that best describes it, and provide new tables using the standardized terminology (see also the adverse event sample Tables 3 and 4 that we have enclosed with this letter). Data elements that should be included in an adverse event table are identified in sample Table 4.***

Response to # 2

MEDRA was used to reclassify adverse events. Listings for the requested adverse event types in PUFS are provided in **Table 2** – **Table 4**. Percentages listed in the tables show

the number of events divided by the number of subjects treated (107). **Table 5** shows adverse events in PITA after classification with MEDRA.

Table 2. Serious adverse events by MEDRA body system and term (N=107 subjects). Each entry indicates that event occurred at or before the assessment period.

MEDRA Category	MEDRA Term	Index Proc	Immed Post-Proc	Prior to Disch	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%)

Table 3. Non-serious adverse events by MEDRA body system and term (N=107 subjects). Each entry indicates that event occurred at or before the assessment period.

MEDRA Category	MEDRA 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 disorders	Headache	0 (0%)	1 (0.9%)	11 (10.3%)	4 (3.7%)	2 (1.9%)	0 (0%)	18 (16.8%)
	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%)

MEDRA Category	MEDRA Term	Immed Post-Proc	Prior to Disch	Day 30	Day 90	Day 180	1 Year	Cum to 180 Days
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%)

Table 4. Adverse events judged probably or definitely related to PED by MEDRA body system and term (N=107). Each entry indicates that event occurred at or before the assessment period.

MEDRA Category	MEDRA Term	Immed Post-Proc	Prior to Disch	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%)	1 (0.9%)	0 (0%)
Central nervous system vascular disorders	Ischemic stroke	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	2 (1.9%)	0 (0%)	3 (2.8%)
	Thrombotic stroke	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Gastrointestinal signs and symptoms	Nausea	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)
Nervous system disorders	Amaurosis fugax	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	2 (1.9%)	2 (1.9%)	3 (2.8%)
	Headache	0 (0%)	0 (0%)	3 (2.8%)	0 (0%)	2 (1.9%)	0 (0%)	5 (4.7%)
Procedural and device related injuries and complications NEC	Procedural headache	0 (0%)	2 (1.9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.9%)
Vascular disorders NEC	Arteriovenous fistula	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	0 (0%)	1 (0.9%)
Vision disorders	Diplopia	0 (0%)	0 (0%)	2 (1.9%)	0 (0%)	0 (0%)	0 (0%)	2 (1.9%)
Total		1 (0.9%)	2 (1.9%)	7 (6.5%)	1 (0.9%)	7 (6.5%)	3 (2.8%)	18 (16.8%)

Table 5. All adverse events in PITA classified using MEDRA body system and term.

MEDRA category	MEDRA term	Event Description	Number of Subjects (%) N=31	Time of Occurrence		
				Procedure-Discharge	1-30 Days	1-6 Months
Headaches NEC	Headache	Headache	3 (9.7%)	3	0	0
Allergic conditions NEC	Immediate post-injection reaction	Allergic Reaction	2 (6.5%)	2	0	0
Central nervous system haemorrhages and cerebrovascular accidents	Ischemic stroke	Stroke	2 (6.5%)	2	0	0
Nausea and vomiting	Procedural vomiting	Vomiting	2 (6.5%)	2	0	0
Musculoskeletal and connective tissue pain and discomfort	Back pain	Back Pain	1 (3.2%)	1	0	0
Neurological signs and symptoms NEC	Dizziness	Dizziness	1 (3.2%)	1	0	0
Disorder characterized by fever	Postoperative fever	Fever	1 (3.2%)	1	0	0
Alopecias	Application site alopecia	Hair Loss	1 (3.2%)	0	1	0
Vascular hypertensive disorders NEC	Procedural hypertension	Hypertension	1 (3.2%)	1	0	0
Vascular hypotensive disorders	Procedural hypotension	Hypotension	1 (3.2%)	1	0	0
Nausea and vomiting	Procedural nausea	Nausea	1 (3.2%)	1	0	0
Pain and discomfort NEC	Discomfort	Postural Pain	1 (3.2%)	1	0	0
Haemorrhages NEC	Vessel puncture site hemorrhage	Puncture Site Injury	1 (3.2%)	1	0	0
Nausea and vomiting	Procedural vomiting	Total	18 (100%)	17	1	0

3. ***You have provided data regarding the use of concomitant medications for the PUFS study in Section 12 and for the PITA study in Appendix 1. However, these data are also not in an analyzable format. Please place these data in standardized format such as the World Health Organization (WHO) drug dictionary. Data elements that should be included in a concomitant medication table are identified in sample Table 5.***

Response to #3

Concomitant medication reported at baseline was recoded using the WHO system and is summarized in **Table 6**.

Table 6. Baseline medications in effectiveness cohort by descending frequency.

Code	Drug	Total
B01AC06	acetylsalicylic acid	37
B01AC04	clopidogrel	33
C09AA03	lisinopril	11
C07AB02	metoprolol	9
UNK	Could not read	8
H03AA01	levothyroxine sodium	8
C08CA01	amlodipine	7
A02BC01	omeprazole	6
C03AA03	hydrochlorothiazide	6
C10AA05	atorvastatin	5
N05BA12	alprazolam	5
A01AD05	acetylsalicylic acid	4
A11A	MULTIVITAMINS, COMBINATIONS	4
C09CA01	losartan	4
N03AE01	clonazepam	4
N06AB10	escitalopram	4
C09CA03	valsartan	3
H02AB07	prednisone	3
N06AB06	sertraline	3
N06AX12	bupropion	3
R03BB04	tiotropium bromide	3
A02AC01	calcium carbonate	2
A02BC03	lansoprazole	2
A02BC05	esomeprazole	2
A12BA02	potassium citrate	2
C01DA02	glyceryl trinitrate	2
C01EB15	trimetazidine	2
C03DB02	triamterene	2
C07AB03	atenolol	2
C07AG02	carvedilol	2
C08DA01	verapamil	2
C09AA04	perindopril	2
C09CA08	olmesartan medoxomil	2
C10AA01	simvastatin	2
C10AA07	rosuvastatin	2

Code	Drug	Total
G03CA57	conjugated estrogens	2
G04BD07	tolterodine	2
N03AB02	phenytoin	2
N06AB03	fluoxetine	2
N06AB04	citalopram	2
N06AB05	paroxetine	2
N06AX05	trazodone	2
N06AX11	mirtazapine	2
N06AX21	duloxetine	2
R03AK04	salbutamol	2
R03BA05	fluticasone	2
R05DA03	hydrocodone	2
R05DA03	hydrocodone	2
A02BA03	famotidine	1
A02BC02	pantoprazole	1
A06A	Laxatives	1
A07EA02	hydrocortisone	1
A10BA02	metformin	1
B03BB01	folic acid	1
B03BB51	folic acid, combinations	1
C01AA05	digoxin	1
C02AC01	clonidine	1
C03DA01	spironolactone	1
C03DB01	amiloride	1
C07AB52	metoprolol, combinations	1
C07AG01	labetalol	1
C07BB03	atenolol and thiazides	1
C08CA06	nimodipine	1
C08CA15	benidipine	1
C08DB01	diltiazem	1
C09AA07	benazepril	1
C09BA02	enalapril and diuretics	1
C09BA03	lisinopril and diuretics	1
C09CA06	candesartan	1
C09CA07	telmisartan	1
C09DA03	valsartan and diuretics	1
C10AA02	lovastatin	1
C10AA03	pravastatin	1
C10AA04	fluvastatin	1
C10AB04	gemfibrozil	1
C10AB05	fenofibrate	1
C10AX09	ezetimibe	1
D11AX11	hydroquinone	1
J01FA01	erythromycin	1
M01AB05	diclofenac	1
M01AE02	naproxen	1
M01AX05	glucosamine	1
M03BX08	cyclobenzaprine	1
M05BA04	alendronic acid	1
N02AA05	oxycodone	1

Code	Drug	Total
N02AA55	oxycodone, combinations	1
N02AC54	dextropropoxyphene, comb. excl. psycholeptics	1
N02BA11	diflunisal	1
N02BE01	paracetamol	1
N02CC03	zolmitriptan	1
N03AG01	valproic acid	1
N03AX09	lamotrigine	1
N03AX12	gabapentin	1
N03AX15	zonisamide	1
N03AX16	pregabalin	1
N04BC04	ropinirole	1
N04BD02	rasagiline	1
N05BA01	diazepam	1
N05CA07	talbutal	1
N05CD07	temazepam	1
N05CF02	zolpidem	1
N06AA04	clomipramine	1
N06AA10	nortriptyline	1
N06AX16	venlafaxine	1
N06AX23	desvenlafaxine	1
N06BC01	caffeine	1
NA	NA	1
R03BA03	flunisolide	1
R03DC03	montelukast	1
R06AE05	meclozine	1
S01ED01	timolol	1
S01EE01	latanoprost	1
Total		288

Early in the study, Chestnut told sites to document concomitant medication use at subsequent visits only as it related to use of antithrombotic agents or other agents that could affect blood clotting. We did not expect that PED placement would have any effect on medications used to treat other illnesses, and therefore did not collect this information. In addition, we did not expect that concomitant use of medications at baseline would affect Pipeline placement or success rates, except for use of agents that could affect coagulation or platelets (e.g., Coumadin). In two cases, concomitant medication was highly likely to have played a role in an adverse event, as described in **Table 7**.

Table 7. Subjects in which concomitant medication was likely to have played a role in adverse event.

Subject ID	Description
[redacted]	Subject had Factor V Leiden, a genetic deficiency of coagulation factors that increases the risk for spontaneous venous thrombosis. Subject was taking Coumadin on a daily basis. The investigator discussed the use of perioperative Coumadin with two consulting hematologists prior to enrollment and believed that PED treatment was in the patient's best interest and that the subject could be treated safely despite being on three agents affecting blood clotting (aspirin, clopidogrel and Coumadin). The patient was enrolled in PUFS as a protocol deviation. Coumadin was withheld perioperatively but restarted on postoperative day #1. On POD #4 the subject had intracranial hemorrhage. At the time of hemorrhage, the prothrombin time was elevated. Subject's stroke was graded as minor. This case was described in detail in original PMA on p. 123 and p. 1507.
[redacted]	Subject awoke from a long procedure with possible dysphasia. On POD #1 subject was treated with IV tirofiban, an antiplatelet antibody. Subject subsequently had intracranial hemorrhage. This case was described in detail in the original PMA on pp. 102, 104 and 1512.

In PUFS, 325 mg of daily aspirin was required for at least 2 days prior to the protocol and for at least 6 months after PED placement. 75 mg of clopidogrel was required for 1 week prior to the procedure (or a 600 mg loading dose 1 day prior to the procedure) and the same dose daily for at least 3 months after PED placement. **Table 8** shows antiplatelet agent use by study visit. All subjects received aspirin and clopidogrel prior to the placement procedure; in >90% of cases, dosing was according to the protocol. At Day 30, 96% of subjects were taking aspirin and 96% of subjects were taking clopidogrel. At Day 90, 96% of subjects were taking aspirin and 92% of subjects were taking clopidogrel. At Day 180, >94% of subjects were taking aspirin. Clopidogrel was not required at Day 180 (it was required only until 3 months) but was being taken by 64% of subjects. In most cases when aspirin or clopidogrel was stopped, stopping was for clinically relevant reasons (e.g., excessive bleeding). Overall, compliance with study-related medications was very high.

Table 8. Medications by study visit.

Medication	Dosing	Procedure N=108	Day 30 N=103	Day 90 N=103	Day 180 N=102
Aspirin	325 mg or 300 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%)[#]	6 (5.9%)[§§]
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%)	0 (0%)
	Not taking or dose unknown	0 (0%)	4 (3.9%)[§]	8 (7.8%)[##]	37 (36.3%)

[*]Not taking aspirin because of bleeding in 4 cases, unknown in 1.
[§]Recent bleeding in 2, over-anticoagulated by laboratory exam in 1, unknown in 1.
[#]Recent bleeding in 2, medication non-compliance in 1, unknown in 1.
[##]Non-compliant in 1, recent bleeding in 1, unknown in 6.
[§§]Non-compliant in 1, recent bleeding in 2, unknown in 3.
[£]Not required per protocol

Minor Deficiencies

4. ***You have presented analyses for a number of populations and subgroups. For each population or subgroup, please first provide a table summarizing its demographics. Next, provide the analyses (summary tables and narrative discussions) pre-specified in the Statistical Analysis Plan (SAP) for the cohort and include justification for any analysis that deviates from the definition in the SAP. Follow the SAP-defined analyses with the additional analyses for the same population and explanations for how they support the marketing application.***

Response to # 4

To date, all analyses provided in PUFS were based on the following 3 cohorts:

- **Enrolled subjects**, which includes all subjects who were enrolled.
- **Safety cohort**, comprising the enrolled subject cohort after excluding one subject [redacted] because PED placement was not possible in this subject and no Chestnut product was inserted into the body.
- **Effectiveness cohort**, comprising the enrolled subject cohort after excluding 4 subjects because their target aneurysms did not qualify or because of inability to catheterize the distal parent artery.

Demographic characteristics of the 3 cohorts are shown in **Table 9**. In informal email communication with Chestnut on September 29, 2010 FDA also requested tables showing demographics for various subgroups, such as gender and aneurysm size. **Table 10 – Table 14** provide summaries of baseline characteristics by various subgroups, including the 4 subgroups that were pre-specified. These tables use the

effectiveness cohort. Baseline characteristics were divided into four categories: demographics, neurology/aneurysm history, other medical history, and laboratory values. P-values for **Table 9** are not reported since the cohorts displayed are substantially overlapping. Nonetheless, there were no important differences in baseline characteristics of the 3 cohorts. Interpretation of observed differences in baseline characteristics across subgroups is questionable and subject to multiplicity concerns because of the the large number of p-values calculated.

Table 9. Demographic characteristics of PUFS subjects by analysis cohort.

Characteristic Mean (SD) Range or N (%)	Enrolled Subjects N=108	Safety Cohort N=107	Effectiveness Cohort N=104
Demographics			
Age	57.0 (11.3) 30.2-75.0	56.9 (11.3) 30.2-75.0	56.8 (11.5) 30.2-75.0
Female gender	96 (88.9%)	95 (88.8%)	94 (90.4%)
Race			
NR	3 (2.8%)	2 (1.9%)	2 (1.9%)
Black	5 (4.5%)	6 (5.6%)	6 (5.8%)
White	99 (91.7%)	99 (92.5%)	96 (92.3%)
Hispanic or Latino ethnicity	6 (5.6%)	6 (5.6%)	5 (4.8%)
Neurology/Aneurysm History			
SAH	8 (7.4%)	7 (6.5%)	6 (5.8%)
History of stroke	7 (6.5%)	5 (%)	7 (%)
Previous interventions for target IA	6 (5.6%)	5 (4.7%)	4 (3.8%)
Coiling	1 (0.9%)	1 (0.9%)	1 (1.0%)
Surgical wrapping	1 (0.9%)	1 (0.9%)	1 (1.0%)
Surgical clipping			
History of aneurysm in 1st degree relative	10 (9.3%)	9 (8.4%)	9 (8.5%)
NIH Stroke Scale Score	0.5 (1.3) 0 – 10	0.5 (1.3) 0 – 10	0.4 (0.9) 0 – 6
Modified Rankin Score	0.6 (0.8) 0 – 4	0.6 (0.8) 0 – 4	0.5 (0.7) 0 – 3
Other Medical History			
History of hypertension	60 (55.6%)	59 (55.1%)	58 (55.8%)
Smoking			
Current	31 (28.7%)	31 (29.0%)	30 (28.8%)
Previous	31 (28.7%)	31 (29.0%)	31 (29.8%)
Never	46 (42.6%)	45 (42.1%)	43 (41.3%)
Coronary artery disease	6 (5.6%)	6 (5.6%)	6 (5.7%)
History of myocardial infarction	2 (1.9%)	2 (1.9%)	2 (1.9%)
Diabetes	7 (6.5%)	7 (6.5%)	7 (6.6%)
Current/previous cocaine use *	1 (0.9%)	1 (0.9%)	1 (0.9%)
Laboratory Values			
Hematocrit	39.3 (4.9) 13.8-56.3	39.3 (4.9) 13.8-56.3	39.3 (4.9) 13.8-56.3
Platelet count	263.1 (72.7) 104-544	263.5 (72.9) 104-544	266.0 (72.4) 104-544
Creatinine	0.8 (0.2) 0.5-2.1	0.8 (0.2) 0.5-2.1	0.8 (0.2) 0.5-2.1

*Last reported use of cocaine in this single subject was in 1970. Current cocaine use was an exclusion criterion.

Table 10. Demographic characteristics of PUFS subjects by gender (effectiveness cohort, n=104).

Characteristic Mean (SD) Range or N (%)	Subgroup		
	Men **N=10**	**Women** **N=94**	**P-value**
Demographics			
Age	50.8 (13.1) 32.2-72.5	57.4 (11.2) 30.2-75.0	0.0808
Race NR Black White	 0 (0%) 0 (0%) 10 (100%)	 2 (2.1%) 6 (6.4%) 86 (91.5%)	0.6348
Hispanic or Latino ethnicity	0 (0%)	5 (5.3%)	1.0000
Neurology/Aneurysm History			
Subarachnoid hemorrhage	1 (10%)	5 (5.3%)	1.0000
Stroke	1 (10%)	4 (4.3%)	0.4634
Previous interventions for target aneurysm	2 (20%)	5 (5.3%)	0.2201
Aneurysm in 1st degree relative	2 (20%)	7 (7.4%)	0.2648
NIH Stroke Scale Score	0.4 (0.7) 0 – 2	0.4 (0.9) 0 – 6	0.9006
Modified Rankin Score	0.3 (0.5) 0-1	0.6 (0.7) 0-3	0.2555
Other Medical History			
History of hypertension	5 (50%)	53 (56.4%)	0.7469
Smoking Current Previous Never	 2 (20%) 3 (30%) 5 (50%)	 28 (29.8%) 28 (29.8%) 38 (40.4%)	0.9137
Coronary artery disease	0 (0%)	6 (6.4%)	0.6383
Myocardial infarction	0 (0%)	2 (2.1%)	1.0000
Diabetes	1 (10%)	6 (6.4%)	1.0000
Laboratory Values			
Hematocrit	42.3 (2.8) 37-47	38.9 (5.0) 13.8-56.3	0.0416
Platelet count	242.4 (59.7) 114 – 321	268.6 (73.4) 104-544	0.2793
Creatinine	1.0 (0.2) 0.7 – 1.4	0.8 (0.2) 0.5-2.1	0.0388

Table 11. Demographic characteristics of PUFS subjects by aneurysm size, effectiveness cohort.

Characteristic Mean (SD) Range or N (%)	Aneurysm Size, mm		
	<25 mm N=82	**≥25 mm N=22**	**P-value**
Demographics			
Age	56.6 (11.5) 30.2 – 75	57.2 (11.5) 30.3-75.0	0.8313
Female gender	73 (89.0%)	21 (95.5%)	0.4603
Race NR Black White	 1 (1.2%) 4 (4.9%) 77 (93.9%)	 1 (4.5%) 2 (9.1%) 19 (86.4%)	0.6004
Hispanic or Latino ethnicity	3 (3.7%)	2 (9.1%)	0.5805
Neurology/Aneurysm History			
Subarachnoid hemorrhage	6 (7.3%)	0 (0%)	0.3381
Stroke	4 (4.9%)	1 (4.5%)	1.0000
Previous surgical or neurovascular interventions for target aneurysm	5 (6.1%)	2 (9.1%)	0.7159
Aneurysm in 1st degree relative	8 (9.8%)	1 (4.5%)	0.5603
NIH Stroke Scale Score	0.3 (0.7) 0 – 5	0.8 (1.4) 0-6	0.0215
Modified Rankin Score	0.4 (0.6) 0 – 2	1.1 (0.9) 0 – 3	<.0001
Other Medical History			
History of hypertension	43 (52.4%)	15 (68.2%)	0.2308
Smoking Current Previous Never	 25 (30.5%) 24 (29.3%) 33 (40.2%)	 5 (22.7%) 7 (31.8%) 10 (45.5%)	0.8267
Coronary artery disease	3 (3.7%)	3 (13.6%)	0.1074
Myocardial infarction	1 (1.2%)	1 (4.5%)	0.5635
Diabetes	4 (4.9%)	3 (13.6%)	0.3420
Laboratory Values			
Hematocrit	39.3 (4.6) 13.8 – 48.6	39.2 (6.0) 27.1-56.3	0.9516
Platelet count	270.5 (70.6) 114 – 544	248.4 (78.3) 104-475	0.2132
Creatinine	0.8 (0.2) 0.5 – 2.1	0.8 (0.3) 0.5-1.7	0.7936

Table 12. Demographic characteristics of PUFS subjects by aneurysm neck size, effectiveness cohort.

Characteristic Mean (SD) Range or N (%)	Aneurysm Neck Size, mm		
	<6 mm N=20	≥6 mm N=84	P-value
Demographics			
Age	57.1 (12.4) 34.1 – 72.5	56.7 (11.3) 30.2 – 75.0	0.8930
Female gender	19 (95.0%)	75 (89.3%)	0.6827
Race NR Black White	 0 (0%) 2 (10%) 18 (90%)	 2 (2.4%) 4 (4.8%) 78 (92.9%)	0.5947
Hispanic or Latino ethnicity	1 (5%)	4 (4.8%)	1.0000
Neurology/Aneurysm History			
Subarachnoid hemorrhage	1 (5%)	5 (6.0%)	1.0000
Stroke	0 (0%)	5 (6.0%)	0.1514
Previous surgical or neurovascular interventions for target aneurysm	1 (5%)	6 (7.1%)	1.0000
Aneurysm in 1st degree relative	4 (20%)	5 (6.0%)	0.0925
NIH Stroke Scale Score	0.1 (0.3) 0 – 1	0.4 (1.0) 0 – 6	0.1575
Modified Rankin Score	0.4 (0.5) 0 – 1	0.6 (0.8) 0 – 3	0.2312
Other Medical History			
History of hypertension	8 (40%)	50 (59.5%)	0.1371
Smoking Current Previous Never	 6 (30%) 5 (25%) 9 (45%)	 24 (28.6%) 26 (31.0%) 34 (40.5%)	0.9040
Coronary artery disease	0 (0%)	6 (7.1%)	0.3515
Myocardial infarction	0 (0%)	2 (2.4%)	1.0000
Diabetes	2 (10%)	5 (6.0%)	0.1378
Laboratory Values			
Hematocrit	39.1 (3.0) 34.9 – 44.4	39.3 (5.3) 13.8 – 56.3	0.8477
Platelet count	264.3 (70.4) 143 – 391	266.4 (73.2) 104 – 544	0.9059
Creatinine	0.8 (0.2) 0.5 – 1.3	0.8 (0.2) 0.5 – 2.1	0.6721

Table 13. Demographic characteristics of PUFS subjects by smoking status, effectiveness cohort.

Characteristic Mean (SD) Range or N (%)	Current or Former Smoker		
	No N=43	Yes N=61	P-value
Demographics			
Age	56.1 (12.1) 30.2 – 75	57.3 (11.0) 30.3 – 75	0.5952
Female gender	38 (88.4%)	56 (91.8%)	0.7375
Race NR Black White	 0 (0%) 2 (4.7%) 38 (88.4%)	 2 (3.3%) 4 (6.6%) 55 (90.2%)	0.7021
Hispanic or Latino ethnicity	3 (7.0%)	2 (3.3%)	0.6476
Neurology/Aneurysm History			
Subarachnoid hemorrhage	2 (4.7%)	4 (6.6%)	1.0000
Stroke	2 (4.7%)	3 (4.9%)	1.0000
Previous interventions for target aneurysm	2 (4.7%)	5 (8.2%)	0.4258
Aneurysm in 1st degree relative	6 (14.0%)	3 (4.9%)	0.1242
NIH Stroke Scale Score	0.5 (1.1) 0 – 6	0.3 (0.7) 0 – 5	0.2241
Modified Rankin Score	0.5 (0.7) 0 – 2	0.6 (0.8) 0 – 3	0.7709
Other Medical History			
History of hypertension	25 (58.1%)	33 (54.1%)	0.6943
Coronary artery disease	2 (4.7%)	4 (6.6%)	1.0000
Myocardial infarction	0 (0%)	2 (3.3%)	0.5008
Diabetes, n (%)	2 (4.7%)	5 (8.2%)	0.8219
Laboratory Values			
Hematocrit	39.3 (3.1) 33.9 – 47.0	39.2 (5.9) 13.8 – 56.3	0.9184
Platelet count	266.3 (65.8) 114 – 475	265.9 (77.3) 104 – 544	0.9765
Creatinine	0.8 (0.2) 0.5 – 1.1	0.9 (0.3) 0.6 – 2.1	0.0754

Table 14. Demographic characteristics of PUFS subjects by partial thrombosis of aneurysm at baseline, effectiveness cohort.

Characteristic Mean (SD) Range or N (%)	Target IA partially thrombosed at baseline?		
	No **N=88**	**Yes** **N=16**	**P-value**
Demographics			
Age	56.5 (11.5) 30.2 – 75.0	58.4 (11.2) 41.8 – 72.9	0.5373
Female gender	80 (90.9%)	16 (100%)	1.0000
Race NR Black White	 2 (2.3%) 6 (6.8%) 80 (90.9%)	 0 (0%) 0 (0%) 16 (100%)	0.5862
Hispanic or Latino ethnicity	4 (4.5%)	1 (6.3%)	1.0000
Neurology/Aneurysm History			
Subarachnoid hemorrhage	4 (4.5%)	2 (12.5%)	0.2298
Stroke, n (%)	2 (2.3%)	3 (18.8%)	0.0453
Previous interventions for target aneurysm	2 (2.3%)	5 (31.3%)	<.0001
Aneurysm in 1st degree relative	8 (9.1%)	1 (6.3%)	1.0000
NIH Stroke Scale Score	0.2 (0.4) 0 – 2	1.2 (1.8) 0 – 6	<.0001
Modified Rankin Score	0.5 (0.6) 0 – 3	0.9 (1.0) 0 – 3	0.0190
Other Medical History			
History of hypertension	39.4 (5.1) 13.8 – 56.3	38.6 (4.1) 32.0 – 47.0	0.1080
Smoking status Current Former Never	 28 (31.8%) 27 (30.7%) 33 (37.5%)	 2 (12.5%) 4 (25.0%) 10 (62.5%)	0.1562
Coronary artery disease	4 (4.5%)	2 (12.5%)	0.2298
Myocardial infarction	2 (2.3%)	0 (0%)	1.0000
Diabetes	6 (6.8%)	1 (6.3%)	1.0000
Laboratory Values			
Hematocrit	39.4 (5.1) 13.8 – 56.3	38.6 (4.1) 32.0 – 47.0	0.5767
Platelet count	266.5 (75.6) 104 – 544	263.6 (53.1) 156 - 339	0.8859
Creatinine	0.8 (0.2) 0.5 – 1.7	0.9 (0.4) 0.5 – 2.1	0.5781

5. ***You have alluded to the use of brain imaging techniques in various parts of the submission. Data from these imaging studies could provide important information on the occurrence of asymptomatic vascular events. Please clarify if these data were collected in a systematic fashion. If so, they should be provided.***

Response to #5

The PUFS protocol included angiograms at baseline, 180 days, 1 year, 3 years and 5 years. It did not include postoperative cross-sectional imaging. Such imaging was done when clinically relevant.

6. ***You report in volume 1, p. 47 that there were 5 cases out of 364 PEDs used where the physician experienced excessive friction when trying to pass the delivery wire through the microcatheter. You appear to have linked these reported problems with the Boston Scientific Renegade Hi-Flo Catheter. You, in response, developed your own Marksman Catheter with reinforcement features to retain its circular cross-section even in tortuous vasculature. You indicate that using this design has significantly reduced issues with friction of delivery wires for the PED. Therefore, please justify why the use of the PED should not be restricted to the use of the Marksman Catheter only, since it's possible that other neurovasculature-indicated catheters could also have these types of friction problems when used with your device.***

Response to #6

We will revise the PED labeling to note that PED should be delivered only using the Marksman catheter.

7. ***Please provide the complete study data in analysis-ready electronic form. This is necessary for FDA to verify your analyses and conduct our own data exploration. In addition to the datasets, please provide any programs (instruction sets) used to manipulate the data and conduct analyses.***

Response to #7

The dataset was provided to FDA via email on September 26, 2010. Data are organized according to **Table 15**. No manipulation is required – the datasets indicated in the table are relevant for the various analysis cohorts.

Table 15. Organization of SAS dataset provided to FDA.

Data Table	N Rows	Unique Identifier	Description
Patient	108	Rec_key or ptID	One row for each subject
Effectiveness	106	Rec_key or ptID	One row for each subject in effectiveness cohort
Safety	107	Rec_key or ptID	One row for each subject in safety cohort
Adverse	172	Rec_key or ptID||ae_seq	One row for each adverse event
Deviation	372	Rec_key or ptID||pd_seq	One row for each deviation
Device, Device2	356, 366	Key DeviceID	One row for each PED device opened during a PUFS case. Device2 has additional PEDs used in contralateral aneurysms.
Visit	955	Rec_key or ptID||visitID	One row for each subject visit, including baseline
Corelab	567	IRCratingID or ptID||memberID||visitID	One row for each core lab adjudication (3 ratings per subject per visit)
Malfunction	13	Rec_key	One row for each device malfunction
NontargetIA	2	Rec_key or ptID	One row for each non-target IA treated
Exit	9	Rec_key	One row for each subject who exited from study

8. ***You state in volume 1, p. 57, that "one patient was excluded from the safety analysis because the physician could not pass the micro-guide wire beyond the target aneurysm." Please be aware that we are still interested in safety outcomes for this subject as the procedure was attempted and could have resulted in an adverse event. Please provide a detailed narrative of the safety history of this subject.***

Response to # 8

This is subject [redacted], who was described on pages 90, 93, 94, 95, 97, 101, 107, 117 and 125 of the PMA. These pages are reproduced in **Appendix 3** of this letter.

In this case, the investigators could not gain access to the distal parent artery with the microguide wire. For this reason, PED was not inserted into the body and PED placement was not attempted. Instead, the subject underwent further coil packing of her aneurysm. She developed postoperative confusion and fever. CT scan showed hydrocephalus related to the aneurysm. She underwent lumbar puncture, which ameliorated symptoms. Her case demonstrates that further packing of a recurrent large/giant aneurysm with additional coils is associated with adverse events; in this case, the subject experienced an increase in mass effect with hydrocephalus.

In addition, the subject, who has a history of hypertension, was hospitalized briefly on POD #129 for a hypertensive crisis. This event was probably unrelated to use of coils. Hypertension is a known risk factor for intracranial aneurysm.

The subject was followed for safety but was not included in the safety cohort since PED

was not inserted into the body and the procedure she underwent was essentially a standard coil embolization. Also, the adverse events that she experienced were not due to the attempted procedure with the PED device.

9. Your accounting of subjects is incomplete. Please update this information with a table or a flow chart showing the number of subjects who were available at each follow-up time point and were evaluated. The time period for this report is from the start of the study up to the closure date for your 90-day PMA update.

Response to # 9

A full accounting was provided in the original PMA in Section 12.5.5 (p. 94-96, reproduced in **Table 16** below). An updated accounting was provided in the 90-day amendment in **Section 3.2.4**, p. 1866.

Table 16. Accounting for subjects to Day 180.

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

*Expected = theoretical – (deaths + failures)

10. You provide an analysis of the primary effectiveness endpoint for the four pre-defined subgroups in Section 12.5.8. Please provide additional safety and effectiveness analyses for the following subgroups: female, male, aneurysm location, specific age range, previous medical conditions such as hypertension, concomitant medication use, United States (US) subjects, and outside U.S. (OUS) subjects. Please further stratify these subgroups by female and male, and provide the respective safety and effectiveness analyses. These subgroup analyses are necessary to ensure that their safety and effectiveness profile does not differ greatly from the overall results. Note that we will also consider multiplicity if any subgroups are nominally significant.

Response to #10

The requested analyses are shown in **Table 17** and **Table 18.** The tables list 74 p-values. **Table 19** shows ordered p-values from the subgroup analyses provided in **Table 17** and **Table 18** as well as the Holm* adjusted comparators. **Figure 1** plots the

* As reviewed in a teleconference with FDA in late September 2010, FDA's requests for multiple analyses lead to a substantial multiplicity issue. Chestnut originally proposed a total of 8 subgroup

ordered observed p-values and Holm cutoffs. Of note, 3 of 74 (4.1%) values are below the 0.05 cutoff; the observed rate of "p<.05" p-values (4.1%) is consistent with the Type 1 error rate (i.e., rate due to chance alone: 5%). All of the observed p-values are more than 10-fold above the relevant Holm cutoffs. According to the Holm adjustment, none of the subgroup hypotheses are rejected.

The 3 p-values < .05 involved two primary comparisons:

1. Effectiveness as a function of age group, showing a lower effectiveness rate in the middle (55-65) age subgroup as compared to the younger and older age range subgroups.

2. Safety as a function of age group amongst males, showing no strokes in the two younger age groups among men and 2 strokes in older age group among men.

Regarding the first comparison, the result does not trend with age and is thus biologically implausible. Regarding the second comparison, the analysis of the primary safety endpoint by age group considering both men and women together showed a p-value of 0.4430. It is only when men are looked at separately the p-value goes below 0.05; moreover, this p-value is based only only 2 events. The biological plausibility of a difference in response to PED relevant to safety concerns between men and women is unknown. Whether the difference was due to confounders is not known. We believe the observation is spurious and is the result of multiple hypothesis testing. We conclude that no statistically relevant differences in safety or effectiveness across subgroups are found.

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analyses in the protocol. To address multiplicity, FDA asked Chestnut to apply an adjustment. Chestnut and FDA agreed to use the Holm method. The Holm method (described in IDE supplement [redacted] states that the *k* observed p-values (ordered lowest to highest) should be compared with the Holm cutoffs, such that we reject all hypotheses 1 through *i* where

$$p_i \leq \frac{\alpha}{k-(i-1)}.$$

The issue of multiplicity was discussed in teleconferences with Drs. Larry Rodichok and Joe Hutter on September 16, 2010 and with Pablo Bonangelino (FDA statistician) on September 17, 2010. In addition to the analyses shown in the tables, Dr. Rodichok also separately requested (email dated September 29, 2010) tables showing baseline medical characteristics of subjects and aneurysm characteristics by various subgroups, greatly increasing the number of unplanned comparisons. Chestnut believes that these analyses are exploratory only and that p-values are questionable due to multiplicity.

Table 17. Subgroup analysis for 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%)	0.4501	NA		NA	
Female	72/96 (75%)					
Aneurysm location						
Cavernous	33/47 (70.2%)	0.7137	31/44 (70%)	0.5903	2/3 (67%)	1.0
Ophthalmic	29/37 (78.4%)		26/32 (81%)		3/5 (60%)	
Supraclinoid	16/22 (72.7%)		14/20 (75%)		1/2 (50%)	
Aneurysm size						
>25 mm	15/22 (68%)	0.5891	15/21 (71%)	0.7764	0/1 (0%)	0.4000
<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 (87.8%)	0.0131	31/35 (88.6%)	.0144	5/6 (83%)	0.3333
55-65 yo	21/36 (58.3%)		20/34 (58.8%)		1/2 (50%)	
>65 yo	21/29 (72.4%)		21/27 (77.8%)		0/2 (0%)	
History of hypertension						
No	37/47 (78.7%)	0.3759	33/42 (78.6%)	0.6353	2/5 (40%)	0.5238
Yes	41/59 (69.5%)		39/45 (72.2%)		4/5 (80%)	

	Overall		Women		Men	
Subgroup	**Results**	**P-value**	**Results**	**P-value**	**Results**	**P-value**
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 (60%)	
Clinical study site						
Site 01	2/3 (67%)		2/3 (67%)		0/0	
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%)	0.8287	14/17 (82%)	0.6516	1/2 (50%)	1.0
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						
Becske	19/29 (66%)		18/27 (67%)		1/2 (50%)	
Cekirge	6/8 (75%)		5/7 (71%)		1/1 (100%)	
Fiorella	16/20 (80%)		15/18 (83%)		1/2 (50%)	
Geyik	0/1 (0%)		0/1 (0%)		0	
Grobelny	1/1 (100%)		1/1 (100%)		0	
Kallmes	4/6 (67%)		4/6 (67%)		0	
Levy	5/5 (100%)	0.5833	5/5 (100%)	0.3879	0	0.7968
Lopes	1/2 (50%)		1/2 (50%)		0	
Moran	2/4 (50%)		1/3 (33%)		1/1 (100%)	
Saatci	4/6 (67%)		2/2 (100%)		2/4 (50%)	
Siddiqui	1/1 (50%)		1/2 (50%)		0	
Szikora	13/15 (87%)		13/15 (87%)		0	
Woo	3/4 (75%)		3/4 (75%)		0	
Yavuz	3/3 (100%)		3/3 (100%)		0	

0

Table 18. Subgroup analyses for primary safety endpoint, showing the proportion of subjects in a subgroup who met the primary safety endpoint definition (major stroke or neurologic death as judged by the study's CEC). Shaded boxes represent previously reported, pre-specified subgroup analyses.

	Overall		Women N=95		Men N=12	
Subgroup	**Results**	**P-value**	**Results**	**P-value**	**Results**	**P-value**
Gender						
Male	2/12 (16.7%)	0.1344	NA		NA	
Female	4/95 (4.2%)					
Aneurysm location						
Cavernous	1/49 (2.0%)	0.3375	1/44 (2.3%)	0.3369	0/5 (0%)	0.3182
Ophthalmic	3/36 (8.3%)		1/31 (3.2%)		2/5 (40%)	
Supraclinoid	2/22 (9.1%)		2/20 (10.0%)		0/2 (0%)	
Aneurysm size						
<25 mm	6/85 (7.1%)	0.3419	4/74 (5.4%)	0.5724	2/11 (18%)	1.0
>25 mm	0/22 (0%)		0/21 (0%)		0/1 (0%)	
Neck size						
<6 mm	1/22 (4.6%)	1.0	1/20 (5.0%)	1.0	0/2 (0%)	1.0
>6 mm	5/85 (5.9%)		3/75 (4.0%)		2/10 (20%)	
Current/former smoker						
No	4/45 (8.9%)	0.2363	3/38 (7.9%)	0.2983	1/7 (14.3%)	1.0
Yes	2/62 (3.2%)		1/57 (1.8%)		1/5 (20%)	
IA partially thrombosed						
No	6/90 (6.7%)	0.5866	4/80 (5.0%)	1.0	2/10 (20%)	1.0
Yes	0/17 (0%)		0/15 (0%)		0/2 (0%)	
Age range						
<55 yo	1/40 (2.5%)	0.4430	1/34 (2.9%)	1.0	0/6 (0%)	0.0152
55-65 yo	2/39 (5.1%)		2/35 (5.7%)		0/4 (0%)	
>65 yo	3/28 (10.7%)		1/26 (3.9%)		2/2 (100%)	
History of hypertension						
No	0/47 (0%)	0.0869	0/41 (0%)	0.1311	0/6 (0%)	0.3182
Yes	6/59 (10.2%)		4/54 (7.4%)		2/5 (40%)	
Unknown	0/1 (0%)		0/0 (0%)		0/1 (0%)	

	Overall		Women N=95		Men N=12	
Subgroup	**Results**	**P-value**	**Results**	**P-value**	**Results**	**P-value**
Site geography						
US	4/75 (5.3%)	1.0	2/68 (2.9%)	0.3191	2/7 (28.6%)	0.4697
OUS	2/32 (6.3%)		2/27 (7.4%)		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 (6.9%)		1/27 (3.7%)		1/2 (50%)	
Site 05	2/20 (10%)		1/17 (5.9%)		1/3 (33.3%)	
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 (15.4%)		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						
Becske	2/29 (6.9%)		1/27 (3.7%)		1/2 (50%)	
Cekirge	2/8 (25%)		2/7 (28.6%)		0/1 (0%)	
Fiorella	2/21 (9.5%)		1/18 (5.6%)		1/3 (33%)	
Geyik	0/1 (0%)		0/1 (0%)		0	
Grobelny	0/1 (0%)		0/1 (0%)		0	
Kallmes	0/6 (0%)		0/6 (0%)		0	
Levy	0/5 (0%)	0.6481	0/5 (0%)	0.4451	0	0.6970
Lopes	0/2 (0%)		0/2 (0%)		0	
Moran	0/4 (0%)		0/3 (0%)		0/1 (0%)	
Saatci	0/6 (0%)		0/2 (0%)		0/4 (0%)	
Shownkeen	0/1 (0%)		0		0/1 (0%)	
Siddiqui	0/2 (0%)		0/2 (0%)		0	
Szikora	0/14 (0%)		0/14 (0%)		0	
Woo	0/4 (0%)		0/4 (0%)		0	
Yavuz	0/3 (0%)		0/3 (0%)		0	

	Overall		Women N=95		Men N=12	
Subgroup	**Results**	**P-value**	**Results**	**P-value**	**Results**	**P-value**
Number of PEDs used						
1 or 2	2/36 (5.6%)	1.0	1/34 (2.9%)	0.4581	1/2 (50%)	0.3636
3 or 4	3/62 (4.8%)		2/55 (3.6%)		1/7 (14.3%)	
5 or more	1/9 (11.1%)		1/6 (16.7%)		0/3 (0%)	
Mean length of PEDs used						
10-15	1/38 (2.6%)	0.4191	1/36 (2.8%)	1.0	0/2 (0%)	1.0
16-20	5/69 (7.3%)		3/59 (5.1%)		2/10 (20%)	
Mean diameter of PEDs used						
<4.0	2/53 (3.8%)	0.7057	2/52 (3.9%)	1.0	0/1 (0%)	1.0
4.0-<4.5	3/44 (6.8%)		2/37 (5.4%)		1/7 (14.3)	
4.5-5.0	1/10 (10%)		0/6 (0%)		1/4 (25%)	
Procedure duration						
<2 hrs	3/55 (5.5%)	0.4141	2/48 (4.2%)	0.1992	1/7 (14.3%)	1.0
2-4 hrs	2/47 (4.3%)		1/43 (2.3%)		1/4 (25%)	
>4 hrs	1/5 (20%)		1/4 (25%)		0/1 (0%)	

Table 19. Ordered P-values from Table 17 and Table 18 compared to Holm threshold.

Index	Observed P-Value	Holm Cutoff
1	0.0131	0.000676
2	0.0144	0.000685
3	0.0152	0.000694
4	0.0869	0.000704
5	0.1311	0.000714
6	0.1344	0.000725
7	0.1992	0.000735
8	0.2363	0.000746
9	0.2677	0.000758
10	0.2983	0.000769
11	0.3182	0.000781
12	0.3182	0.000794
13	0.3191	0.000806
14	0.3291	0.00082
15	0.3333	0.000833
16	0.3369	0.000847
17	0.3375	0.000862
18	0.3419	0.000877
19	0.3636	0.000893
20	0.3759	0.000909
21	0.3844	0.000926
22	0.3879	0.000943
23	0.4	0.000962
24	0.4141	0.00098
25	0.4191	0.001
26	0.4373	0.00102
27	0.443	0.001042
28	0.4451	0.001064
29	0.4501	0.001087
30	0.4581	0.001111
31	0.4667	0.001136
32	0.4697	0.001163
33	0.4697	0.00119
34	0.4807	0.00122
35	0.482	0.00125
36	0.5238	0.001282
37	0.5238	0.001316
38	0.5724	0.001351
39	0.5833	0.001389
40	0.5866	0.001429
41	0.5891	0.001471
42	0.5903	0.001515
43	0.6353	0.001563
44	0.6368	0.001613
45	0.6481	0.001667
46	0.6516	0.001724

Index	Observed P-Value	Holm Cutoff
47	0.697	0.001786
48	0.7057	0.001852
49	0.7137	0.001923
50	0.7588	0.002
51	0.7764	0.002083
52	0.7968	0.002174
53	0.8245	0.002273
54	0.8287	0.002381
55	0.8871	0.0025
56	1	0.002632
57	1	0.002778
58	1	0.002941
59	1	0.003125
60	1	0.003333
61	1	0.003571
62	1	0.003846
63	1	0.004167
64	1	0.004545
65	1	0.005
66	1	0.005556
67	1	0.00625
68	1	0.007143
69	1	0.008333
70	1	0.01
71	1	0.0125
72	1	0.016667
73	1	0.025
74	1	0.05

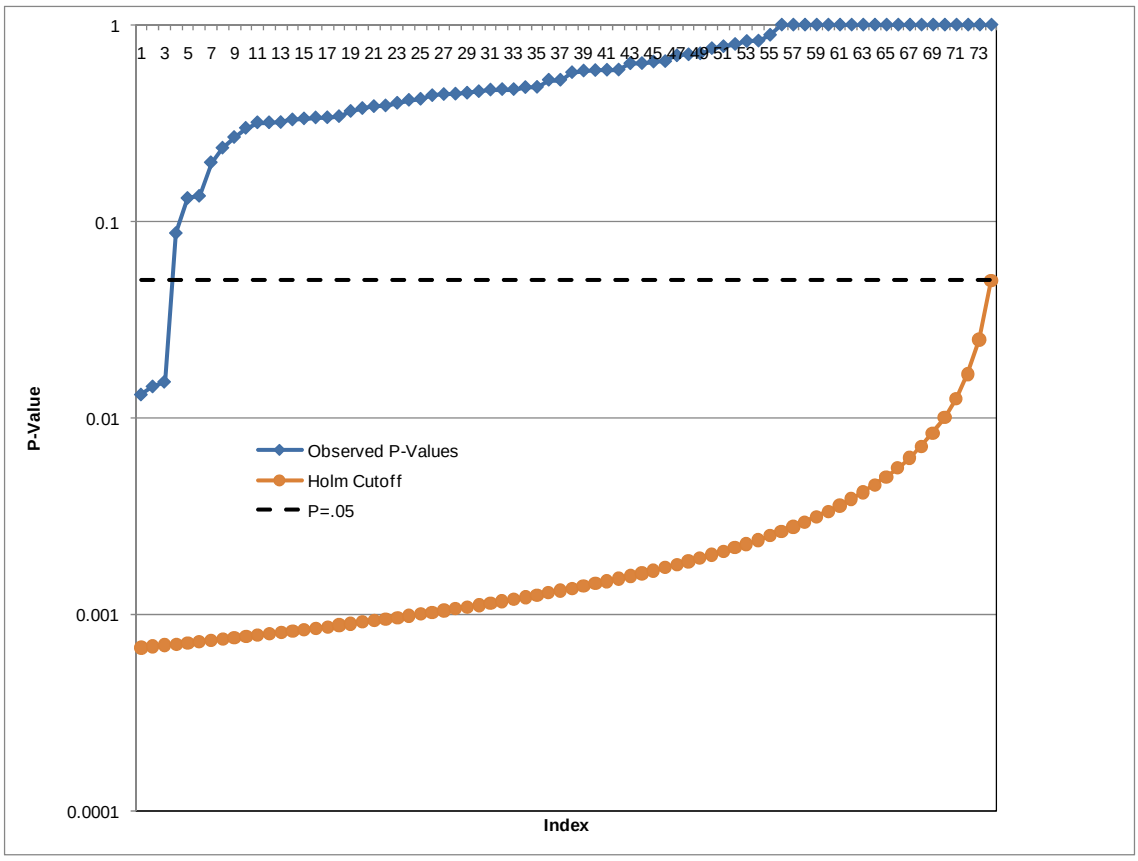

Figure 1. Observed p-values for subgroup analyses and related Holm cutoffs. The dotted line shows p=0.05.

11. ***Specific to hypertension, 55.6% of study subjects were noted to have preexisting hypertension. A literature review and systematic review of the coincidence of intracranial aneurysm and hypertension revealed that approximately 46.6% of those with intracranial aneurysms had preexisting hypertension. The potential for hypertension to impact outcome should be evaluated; hence, please stratify the results of this study based on those who had hypertension at baseline compared with those who did not.***

<u>Response to #11</u>

55.6% of study subjects reported a history of pre-existing hypertension. The literature review identified by FDA (not provided to Chestnut) showed that hypertension can be seen in 46.6% of subjects with aneurysm. Note that the observed rate of 55.6% is not statistically different from the presumed population rate (46.6%, p = 0.077).* Indeed, the figures are remarkably similar, suggesting that the recruited population in PUFS is similar in many ways to that reported in the literature.

* R code: `prop.test(60,108, p=0.466,alternative=c("two.sided"))`

If hypertension is causal in aneurysms, it is perhaps not surprising that hypertension in the PUFS subject population, all of whom have large/giant aneurysms, is somewhat more prevalent than when considering the aneurysm population as a whole. As noted as part of our response to Deficiency #10, hypertension did not appear to affect the likelihood of effectiveness success or safety failure.

12. ***For all of the subgroup analyses please provide 95% credible intervals for the difference in safety and effectiveness rates between levels of a subgroup. This will give some indication of the statistical power of the subgroup results.***

Response to #12

Table 20 shows exact risk differences and 95% confidence intervals for dichotomous effectiveness comparisons shown in **Table 17**. **Table 21** shows exact risk differences and confidence intervals for dichotomous safety comparisons shown in **Table 18**. None of the 95% confidence limits in these tables excluded 0. Moreover, given the large number of hypotheses FDA has requested, reporting a 95% interval markedly understates true degree of uncertainty for these parameters. Our conclusion from **Table 20** and **Table 21** is that none of the subgroup analyses showed statistically meaningful differences.

Table 20. Subgroup analysis for primary effectiveness endpoint with risk differences and confidence intervals for dichotomous variables shown in bold. Shaded boxes represent previously reported pre-specified subgroup analyses.

	Overall		Women		Men	
Subgroup	**Results**	**P-value**	**Results**	**P-value**	**Results**	**P-value**
Gender Male Female **RD (95% CI)**	 6/10 (60%) 72/96 (75%) -15% (-47.6-17.5%)	0.4501	NA	NA	NA	NA
Aneurysm size >25 mm <25 mm **RD (95% CI)**	 15/22 (68%) 63/84 (75%) -6.8% (-30.1-16.5%)	0.5891	 15/21 (71%) 57/75 (76%) -4.6% (-28.3-19.8%)	0.7764	 0/1 (0%) 6/9 (67%) -66.7% (-97.5-40.4%)	0.4000
Neck size <6 mm >6 mm **RD (95% CI)**	 18/21 (86%) 60/85 (71%) 15.1% (-8.5-38.3%)	0.2677	 17/20 (85%) 55/76 (72%) 12.6% (-12.2-36.8%)	0.3844	 1/1 (100%) 5/9 (56%) 44.4% (-61.0-97.5%)	1.0
Current/former smoker No Yes **RD (95% CI)**	 31/43 (72%) 47/63 (75%) -2.5% (-21.6-16.9%)	0.8245	 27/38 (71%) 45/58 (78%) -6.5% (-26.5-13.8%)	0.4807	 4/5 (80%) 2/5 (40%) 40% (-30.5-86.7%)	0.5238
IA partially thrombosed No Yes **RD (95% CI)**	 67/90 (74%) 11/16 (69%) 5.7% (-20.9-32.2%)	0.7588	 63/82 (77%) 9/14 (64%) 12.5% (-16.0-40.6%)	0.3291	 4/8 (50%) 2/2 (100%) -50% (-98.7-35.9%)	0.4667
History of hypertension No Yes **RD (95% CI)**	 37/47 (79%) 41/59 (69%) 9.2% (-9.8-28.0%)	0.3759	 33/42 (79%) 39/45 (72%) -8.1% (-29.0-13.3%)	0.6353	 2/5 (40%) 4/5 (80%) -40% (-86.7-30.5%)	0.5238
Site geography US OUS **RD (95% CI)**	 52/73 (71%) 26/33 (79%) -7.6% (-27.7-13.0%)	0.4820	 49/68 (72%) 23/28 (82%) -10.1% (-31.5-12.1%)	0.4373	 3/5 (60%) 3/6 (50%) 10% (-50.1-65.3%)	1.0

Table 21. Subgroup analysis for primary safety endpoint with risk differences and confidence intervals for dichotomous variables shown in bold.
Shaded boxes represent previously reported pre-specified subgroup analyses.

	Overall		Women N=95		Men N=12	
Subgroup	**Results**	**P-value**	**Results**	**P-value**	**Results**	**P-value**
Gender						
Male	2/12 (16.7%)	0.1344	NA		NA	
Female	4/95 (4.2%)					
RD (95% CI)	12.5% (-17.6-42.2%)					
Aneurysm size						
<25 mm	6/85 (7.1%)	0.3419	4/74 (5.4%)	0.5724	2/11 (18%)	1.0
>25 mm	0/22 (0%)		0/21 (0%)		0/1 (0%)	
RD (95% CI)	7.1% (-16.5-30.3%)		5.4%(-18.6-29.2%)		18.2% (-81.8-97.5%)	
Neck size						
<6 mm	1/22 (4.6%)	1.0	1/20 (5.0%)	1.0	0/2 (0%)	1.0
>6 mm	5/85 (5.9%)		3/75 (4.0%)		2/10 (20%)	
RD (95% CI)	-1.3% (-24.7-22.1%)		1% (-23.7-25.5%)		-20% (-84.2-61.6%)	
Current/former smoker						
No	4/45 (8.9%)	0.2363	3/38 (7.9%)	0.2983	1/7 (14.3%)	1.0
Yes	2/62 (3.2%)		1/57 (1.8%)		1/5 (20%)	
RD (95% CI)	5.7% (-13.4-24.5%)		6.1% (-14.7-26.6%)		-5.7% (-58.7-47.8%)	
IA partially thrombosed						
No	6/90 (6.7%)	0.5866	4/80 (5.0%)	1.0	2/10 (20%)	1.0
Yes	0/17 (0%)		0/15 (0%)		0/2 (0%)	
RD (95% CI)	6.7% (-19.2-32.2%)		5% (-22.8-32.5%)		20% (-61.6-84.2%)	
History of hypertension						
No	0/47 (0%)	0.0869	0/41 (0%)	0.1311	0/6 (0%)	0.3182
Yes	6/59 (10.2%)		4/54 (7.4%)		2/5 (40%)	
RD (95% CI)	-10.2% (-28.8-9.0%)		-7.4% (-27.3-12.7%)		-40% (-85.3-22.6%)	
Site geography						
US	4/75 (5.3%)	1.0	2/68 (2.9%)	0.3191	2/7 (28.6%)	0.4697
OUS	2/32 (6.3%)		2/27 (7.4%)		0/5 (0%)	
RD (95% CI)	-0.9% (-21.3-19.6%)		-4.5% (-26.3-17.7%)		28.6% (-29.6-74.4%)	
Mean length of PEDs used						
10-15	1/38 (2.6%)	0.4191	1/36 (2.8%)	1.0	0/2 (0%)	1.0
16-20	5/69 (7.3%)		3/59 (5.1%)		2/10 (20%)	
RD (95% CI)	-4.6% (-24.1-15.0%)		-2.3% (-22.8-18.4%)		-20% (-84.2-61.6%)	

13. You have not provided a poolability analysis, or safety and effectiveness results stratified by investigator. These analyses are important to demonstrate that results can be generalized across different investigators. Please provide an analysis of data pooling by investigator to FDA.

Response to Deficiency #13

Poolability for safety and effectiveness by investigator is based on the following considerations:

- The patient population was very clearly defined
- All investigators used the same protocol
- All investigators completed the same standardized CRFs
- All investigators used devices manufactured in the same location under the same quality system
- All investigators submitted equivalent imaging
- All adverse events were judged by the same CEC
- All aneurysm occlusions were judged by the same independent radiology core lab
- All CRFs were carefully monitored and source verified
- A p-value for a chi-squared test of effectiveness success by site was reported on p. 98 of the PMA report. The values corresponding to this table are in **Table 17** of this letter. **Table 18** of this letter shows a tabulation of the primary safety endpoint by study site. Corresponding p-values for these two tables are 0.8287 and 0.8871. P-values for a chi-squared test of effectiveness and safety success by primary operator are provided in **Table 17 and Table 18**. There was **no statistically significant effect modification b**y investigator.

There is no evidence to suggest that data cannot be pooled by clinical site.

14. In the PUFS study, there were a number of subjects from OUS. Please provide a table which shows the demographic (age, race, sex, etc.) information for US versus OUS subjects, and justify the pooling of the two groups.

Response to #14

In PUFS, 76 subjects were from the US and 32 were from outside of the US (OUS). As shown in our response to deficiency #12, **Table 20** and **Table 21** show no interaction between the primary effectiveness or safety endpoints and study site geography (i.e., US vs. OUS), either as a whole population or amongst men or women as subgroups. **Table 22** shows baseline characteristics by geographic location. Subjects in the US were slightly older than subjects outside the US (p=0.0044); otherwise, the two populations were remarkably similar. Interpretation of comparisons shown in **Table 22** is questionable given the large number of comparisons and p-values FDA has asked us to calculate. The justification for pooling across geographic locations is identical to that for pooling across sites (see response to #13).

Table 22. Demographic characteristics of PUFS subjects by geographic location, all enrolled subjects.

Characteristic Mean (SD) Range or N (%)	Geographic Location		
	US N=76	OUS N=32	P-value
Age	58.9 (10.6) 30.3-75.0	52.2 (11.7) 30.2-75.0	0.0044
Hematocrit	39.3 (5.4) 13.8-56.3	39.1 (3.4) 32.0-47.0	0.8466
Platelet count	263.6 (76.6) 104-544	262.1 (63.6) 169-475	0.9253
Creatinine	0.8 (0.2) 0.5-1.7	0.9 (0.3) 0.5-2.1	0.6607
NIH Stroke Scale Score	0.5 (1.3) 0-10	0.4 (1.2) 0-6	0.8323
Modified Rankin Score	0.6 (0.9) 0-4	0.4 (0.1) 0-1	0.2156
Female gender	69 (90.8%)	27 (84.4%)	0.5035
Race NR Black White	 3 (3.9%) 6 (7.9%) 67 (88.2%)	 0 (0%) 0 (0%) 32 (100%)	0.1742
Hispanic or Latino ethnicity	6 (7.9%)	0 (0%)	0.1748
History of hypertension	44 (57.9%)	16 (50%)	0.6649
Smoking Current Previous	 24 (31.6%) 22 (28.9%)	 7 (21.9%) 9 (28.1%)	0.5343

Table 23. Aneurysm characteristics of PUFS subjects by geographic location, all enrolled subjects.

Characteristic Mean (SD) Range or N (%)	Geographic Location		
	US N=76	OUS N=32	P-value
Aneurysm size	18.3 (6.4) 6.2-32.1	18.0 (6.7) 10.1-30.0	0.8034
Neck size	10.7 (6.9) 4.3-30.4	8.8 (4.6) 4.6-30.4	0.9468
Aneurysm location			
Petrous	3 (3.9%)	1 (3.1%)	
Cavernous	34 (44.7%)	11 (34.4%)	
Carotid cave	2 (2.6%)	0 (0%)	
Superior hypophyseal	3 (3.9%)	7 (21.9%)	0.1383
Lateral clinoidal	2 (2.6%)	0 (0%)	
Paraophthalmic	25 (32.9%)	10 (31.3%)	
Supraclinoid	6 (7.9%)	3 (9.4%)	
Poster comm	1 (1.3%)	0 (0%)	

15. You have not provided an analysis to identify possible risk factors for failure in the primary effectiveness or safety endpoints. In order to provide all analysis of risk, the characteristics of the population that experienced failure should be compared to the population with a successful outcome. Differences in demographics and baseline disease characteristics should be discussed. In addition, it would be possible to do a logistic regression with factors such as (continuous) size of the aneurysm, (continuous) neck size of the aneurysm, (categorical) location of the aneurysm, (categorical) sex, etc. These factors could be modeled one at a time in a logistic regression to identify variables which are predictive of outcome. There are also sufficient events to model the risk factors for failure taken up to three at a time. These analyses are necessary to more fully characterize the functioning of your device and when it may fail. Please provide them.

Response to #15

In deficiency #10, FDA asked for subgroup analyses by a number of characteristics. These analyses are shown in **Table 17** (effectiveness) and **Table 18** (safety) of this letter. In our response to #10, we included the factors for safety analyses listed in this deficiency, namely: demographic characteristics (age, gender, etc.), baseline disease characteristics (primarily a history of hypertension), aneurysm size, neck size and location. None of these analyses were statistically significant.

As suggested, we used multivariate logistic regression and stepwise forward variable selection for the primary effectiveness and safety endpoints. Variables evaluated in the model were:

- Continuous variables: age, aneurysm size, aneurysm neck size
- Categorical variables: gender, race, aneurysm location, smoker (current/former vs. never), partial thrombosis of the aneurysm, hypertension, baseline MRS score, baseline

NIHSS score

Additional models were run with just the continuous variables, as suggested by FDA. No model showed a statistically significant predictive effect for either the primary effectiveness or safety outcome.

16. You report on changes in visual acuity as an "Additional Endpoint." Specifically, you state that 8 subjects had improvement in visual acuity by 2 or more lines at 180 days, and 5 subjects had worsened visual acuity by 2 or more lines at 180 days compared to baseline. However, you do not specify how many total subjects had a visual acuity assessment by an ophthalmologist. This information is important to assess the number of subjects without significant change in visual acuity. Please update your report with this information.

Response to #16

Visual acuity assessment was performed in 102 cases at baseline and in 93 cases at 180 days. All visual exams but two were performed by an ophthalmologist. One was performed by a study investigator and one by an optometrist. The optometrist carefully documented the subject's improvement in visual function from the time of Pipeline placement.

17. Your literature review of surgical treatment of giant aneurysms shows "Excellent/Good" outcomes occurring as often as in 89% of cases (vol. 2, appendix 4, p. 106). In light of this finding, please discuss how the risk/benefit profile of your device compares with standard surgical treatment.

Response to #17

The articles cited described case series of surgical treatment of giant aneurysms in very general terms. The definition of excellent/good is not provided by these articles and the articles take a very generic approach to outcomes. It is likely the case that if the subject survived the procedure without major stroke, this was called "excellent." By this definition, the "excellent" rate in PUFS is 103/107 (96%).* The articles do not refer to angiographic outcomes.

We believe that a balanced interpretation of the outcomes reported in these articles would include equal consideration of the other columns in these tables, with poor outcomes ranging from 3 to 38% and death ranging from 6 to 25%. In comparison to PUFS, these poor outcome rates are exceedingly high. The articles do not report late outcomes (as we did in PUFS). Moreover, the means by which subjects were included in these case series are not reported; it is possible that surgeons refused to operate on the hardest cases (indeed, our experience is that several surgeons and radiologists across the country referred their difficult cases to PUFS study centers for treatment in PUFS), and the resultant reported cohort of "easier" giant aneurysm cases underestimates the true risk of surgery in this population.

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* 3 perioperative deaths ([redacted]) and 1 perioperative major stroke [redacted].

18. You report only descriptive results for the 28 compassionate use cases in the U.S. Please provide a summary of the safety experience of the PED for each of the two compassionate subgroups (ICA and posterior circulation) and for the compassionate group as a whole (see also #2 above for the format of this summary). Similarly, please provide the same summary for the 55 subjects treated as "Canada Special Access Cases." The data from these groups, while not part of the pivotal data to support safety of your device, may be considered in our assessment of the overall safety of the PED.

Response to #18

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 patients were seriously ill and did not have other reasonable alternative treatments.

US Compassionate Use Cases

A total of 23 patients with IAs of the ICA and 14 patients with IAs of the posterior circulation have undergone PED placement (or attempted placement) as compassionate use cases. An updated chart describing these patients is shown in **Table 27**. Our experience with PED in the anterior and posterior circulation is reported separately because of the very different underlying illnesses.

Anterior Circulation Cases

23 patients with anterior circulation lesions were treated. 21 of the ICA cases were large/giant and wide-necked, i.e., similar in many ways to subjects in PUFS. Of these 21, 7 adverse events occurred in 6 patients (**Table 24**). Follow-up has ranged from <3 months (for 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 also successfully treated without adverse events.

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. The safety experience in the anterior circulation was excellent, and compared very favorably to that observed in PUFS. The effectiveness of aneurysm occlusion with PED in these cases was very high.

Table 24. Summary of adverse events in 21 compassionate use cases of PED use in wide-necked large/giant IAs of the internal carotid artery.

Event (MEDRA)	Frequency	Patient Name Code	Status
Headache	2	[redacted]	Resolved in 1, ongoing in other*
Gastrointestinal and hepatobiliary procedural complications	1	[redacted]L	Resolved
Headache and optic neuropathy	1	[redacted]	Resolved
Epistaxis	1	[redacted]	Resolved
Ear pain (trigeminal neuropathy)	1	[redacted]	Ongoing
Minor stroke	1	[redacted]	Resolved

*Cause of headache not known but thought by physician not to be due to aneurysm

Posterior Circulation

14 patients with posterior circulation lesions have undergone PED placement or attempted placement. In these 14 patients there were 13 adverse events (**Table 25**).

Compassionate use cases in the posterior circulation were patients with complex vascular disease referred from other medical centers by neurosurgeons and neuroradiologists in whom no other feasible treatment was available. The complex nature of these cases is discussed in **Table 26**.

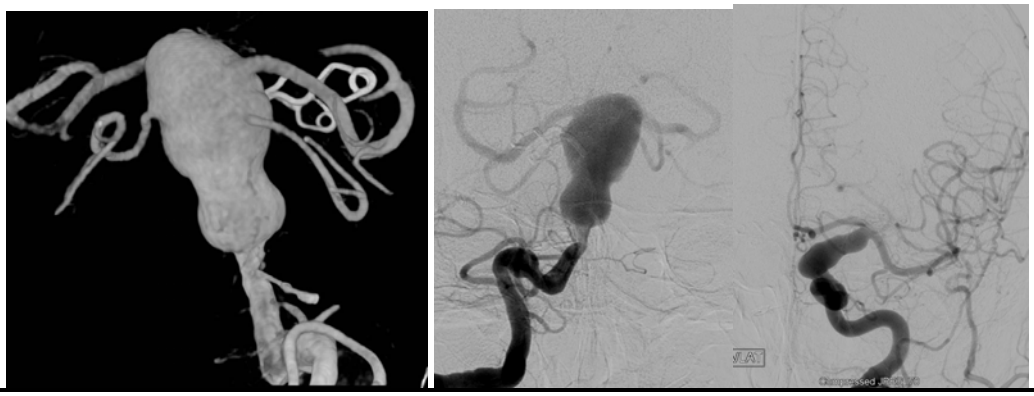
In a small number of posterior circulation cases, the patients were treated on an emergency basis. In all other cases, Chestnut submitted a written request to ask for permission to perform the case. In some cases, the very high-risk nature of any treatment was discussed by telephone with FDA to ensure that FDA understood the desperate nature of these cases. For example, patient [redacted], who had a postoperative stroke, was discussed with FDA in a teleconference in December 2008 and the high-risk nature of the case was detailed in an email to FDA on January 23, 2009. Comparing the experience of these complex and "no-option" posterior circulation cases to that in PUFS would be inappropriate since the underlying illnesses were in many cases markedly different.

Table 25. Summary of adverse events in 14 compassionate use cases of PED use in the posterior circulation.

Event (MEDRA)	Frequency	Patient Initials or Name Code
Basilar artery thrombosis	2	[redacted]
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 MEDRA

Table 26. Further information on adverse events in posterior circulation PED cases.

Patient Name Code	Explanation
[redacted]	Patient had history of stroke due to spontaneous occlusion of the vertebral artery prior to treatment. Patient had excellent angiographic response to PED. Around 2 years after treatment, patient had stroke due to inadvertent termination of aspirin treatment on the advice of a physician not familiar with the patient's history of spontaneous arterial thrombosis. Case history of this patient recently published (Neurosurgery 2010;3;E313).
[redacted]	Marked atherosclerosis of the basilar artery near giant aneurysm (see below). CTA at 1 month showed near-complete occlusion of aneurysm and patent basilar artery. Progressive symptoms at 2 months. Patient hospitalized, underwent lung nodule biopsy, told had probable lung cancer. Patient died in the hospital, possibly from a stroke. Autopsy was not performed.
[redacted]	55-year-old with markedly abnormal basilar artery (left below) plus bilateral carotid disease (right below). The patient had already undergone two surgeries by Dr. Robert Spetzler (Barrow Neurologic Institute), which failed to control aneurysm growth. Patient had experienced stroke prior to PED treatment. Aneurysm was progressively dilating and involved both posterior cerebral arteries and both posterior inferior cerebellar arteries. Chestnut reviewed the extremely high-risk nature of this case with FDA by teleconference (December 2008) before sending its request for compassionate use. We told FDA that treatment of this aneurysm with <u>any device</u> was likely to have a bad result, but we felt obliged to try PED. The patient, who was a physician, understood that PED was a last-ditch attempt to save his life. PED placement resulted in marked improvement of flow out of aneurysm, but the patient's underlying disease was too severe to be adequately addressed by PED. The patient had a perioperative stroke. He eventually died of sepsis several months later. 

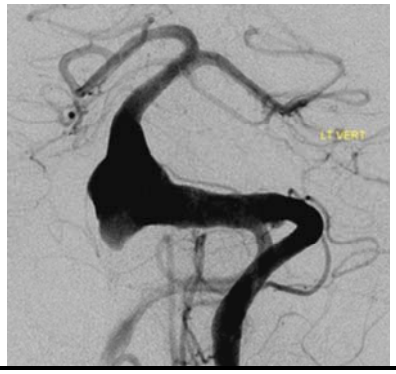
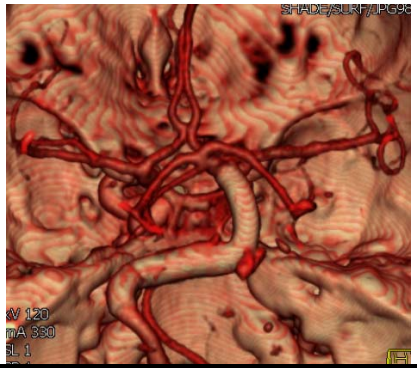
Patient Name Code	Explanation
[redacted]	Iatrogenic rupture of the PCOMM with a microcatheter before any Chestnut product opened.
[redacted]	Postoperative medullary infarct attributed by treating physician to use of other products during the case. (Note that Onyx HD500 and coils were used to occlude the contralateral vertebral artery.) Not attributed to PED.
[redacted]	Patient presented with sudden deterioration and mental status changes due to brainstem mass effect resulting from giant aneurysm (brainstem compression clearly evident in MRI shown below), suggesting that rupture was impending. Developed postoperative hydrocephalus and sepsis, eventually resulting patient's death.
[redacted]	Presented with acute worsening of chronic headache resulting from intramural dissection from a fusiform basilar artery aneurysm (left below). Transferred emergently to NYU for salvage treatment with PED. The treating physician believed that re-rupture was iminent. Although PED placement went well, the patient had subarachnoid hemorrhage near the dissection site on POD #3. CTA on POD #3 (right below) clearly showed that basilar artery and branch vessels were patent.  

Table 27. PED Compassionate use cases in US. IAs that are similar to PUFS (i.e., located in the ICA and large/giant with wide necks) are shown as shaded rows.

#	Initials/ Name Code	Age	Proc date	Location Physician	Aneurysm location	Neck size, mm	Maximum fundus diameter, mm	Symptoms	Adverse event	Device malfunction?	Follow-Up	FDA Request/Approval/Notification
1	[redacted]	50	1/11/2007	[redacted]	Vertebral V4	Fusiform	12	Headache, neck pain	None	No	Complete occlusion @1 yr, no symptoms. Continued asymptomatic at 1.5 years.	Request: December 19, 2006 Approval: December 28, 2006
2	[redacted]	57	2/5/2007	[redacted]	Vertebral V4	Fusiform	14	Stroke, recurrent paresthesias	None	No	Complete occlusion @1yr, death from medication error and progressive disease @2 yrs	Request: January 22, 2007 Approval: February 2, 2007
3	[redacted]	13	4/11/2008	[redacted]	Basilar trunk	Fusiform	28.9	Headache, nystagmus	None	No	Complete occlusion @7 mo, reduced aneurysm size, all symptoms resolved	Request: April 2, 2008 Approval: April 10, 2008
4	[redacted]	51	6/26/2008	[redacted]	ICA cavernous	Fusiform	20	Ptosis, diplopia	Headache	No	Complete occlusion @7 mo, reduced headaches, ophthalmoplegia resolved	Request: S1 Approval: 6/19/08
5	[redacted]	87	11/18/2008	[redacted]	ICA paraophthalmic * Could not complete case as could not catheterize parent vessel	15	36	Intractable retroorbital pain	No	No	Could not complete case as could not catheterize parent vessel	Request: S11 Approval: 12/15/08
6	[redacted]	36	12/9/2008	[redacted]	ICA paraophthalmic and fusiform distal ICA	SHA area was fusiform. Paraophthalmic aneurysm neck was 13 mm	25	Headache, vision loss due to optic nerve compression	None	No	Complete occlusion @4 mo. Headaches resolved, blurry vision much improved	Request: S12 Approval: 12/8/08
7	[redacted]	56	1/9/2009	[redacted]	Basilar artery	Dolichoectatic	20 x 33 x 24	Headache, vertigo, disequilibrium	None	No	Near complete occlusion @1mo. However, progressive aneurysm symptoms occurred, patient eventually died of stroke	Request: S13 Approval: 12/15/08
8	[redacted]	55	2/2/2009	[redacted]	Basilar artery involving PCA, SCA AICA and bilateral carotid aneurysms	Dolichoectatic	>30mm	Headache, weakness	Stroke	No	Progressive occlusion of aneurysm, slow recovery from stroke. Died of multiorgan failure about 6 mo after PED treatment	Request: S19 Approval: 1/29/09
9	[redacted]	42	2/19/2009	[redacted]	Basilar trunk	10-15 mm	~20mm	Dizziness, perioral numbness, difficulty swallowing	Artery (not aneurysm) rupture	No	Patient died during catheterization. No Chestnut products used	Request: S20 Approval: 2/6/09
10	[redacted]	54	1/25/2009	[redacted]	ICA paraophthalmic	~4 mm	~8 mm	Unknown	None	No	Angiogram @5 months showed complete occlusion. Angiogram @17 mo showed complete occlusion.	Notification: S26
11	[redacted]	65	5/11/09	[redacted]	ICA, iatrogenic pseudoaneurysm	~1.5 mm	~2.5 mm	None	None	No	Angiogram @6 months showed complete occlusion. Patient doing well clinically	Notification: S26
12	[redacted]	61	6/22/2009	[redacted]	ICA, iatrogenic pseudoaneurysm after brain tumor surgery	<4	7	None	Seizure @7 mo due to residual tumor	No	Angiogram @7 mo showed complete occlusion.	Request: S28 Approval: 6/30/09 Notification: S30 (case was done emergently)
13	[redacted]	52	8/25/2009	[redacted]	Supraclinoid ICA	Fusiform/multilobulated	12	Incidental	None	No	Angiogram @4.6 mo showed complete occlusion	Request: S33 Approval: 8/10/09
14	[redacted]	24	8/25/2009	[redacted]	Basilar trunk	Fusiform	20	Headache	None	No	Headache resolved @30 d. Angiogram @3 mo showed tiny residual, but otherwise perfect reconstruction	Request: S33 Approval: 8/10/09
15	[redacted]	34	8/25/2009	[redacted]	Basilar	Fusiform	NS		Retroperitoneal hematoma & medial medullary infarct with pain syndrome, possibly due to use of Onyx/coils to occlude the contralateral vertebral artery	No	Improving symptoms related to medullary infarct. Angiogram @6 months and @12 mo showed complete occlusion. Patient also had cavernous aneurysm treated in PUFS-CA at Mayo Clinic 6/15/10	Request: S33 Approval: 8/10/09
16	[redacted]	57	8/20/2009	[redacted]	Supraclinoid ICA	Fusiform	20	Headache, crescendo symptoms suggesting impending rupture	None	No	Headaches resolved, angiogram @day 6 showed complete occlusion (previously we reported "near-complete")	Request: S34 Approval: 9/15/09 Notification: S37 (case treated emergently)
17	[redacted]	26	8/21/2009	[redacted]	Vertebral artery	Fusiform	15	Headache	Headache/n/v 1mo after procedure, resolved	No	Angiogram @6 mo showed complete occlusion. Marked reduction in headaches.	Request: S34 Approval: 9/15/09 Notification: S37 (case treated emergently)

#	Initials/ Name Code	Age	Proc date	Location Physician	Aneurysm location	Neck size, mm	Maximum fundus diameter, mm	Symptoms	Adverse event	Device malfunction?	Follow-Up	FDA Request/Approval/Notification
18		63	9/1/2009		Basilar trunk	NR	35	Sudden deterioration, mental status changes	None	No	Post op course complicated by hydrocephalus and sepsis. Expired @3 months from hemorrhagic transformation of infarct	Notification: S37
19		61	9/29/2009		Basilar	~10 mm	25	Headache, neck pain, dizziness, gait instability	None	No	Angiogram @3 mo showed complete occlusion Angiogram @12 mo showed complete occlusion. MRI showed reduction of aneurysm size.	Notification: S39
20		66	11/19/09		Vertebrobasilar	Fusiform	38	Gait instability, slurred speech, aspiration, behavioral/cognitive changes	Hydrocephalus requiring placement of a VP shunt	No	Stabilization of neurologic status. Angiogram @4 mo showed complete occlusion	Request: S41 Approval: 11/2/09
21		63	11/24/09		Paraophthalmic	N/A	~30	Progressive visual loss	None	No	Near complete occlusion at 4 mo by angiogram. Vision stable.	Request: S38 Approval: 10/23/09
22		61	12/2/09		Cavernous carotid	Fusiform	14 mm	Diplopia and abducens palsy	None	No	Clinically improving. Recent angiogram showed complete occlusion	Request: S42 Approval: 11/20/09
23		86	11/6/09		Paraophthalmic	N/A	~20 mm	Aneurysm recurrence with progressive contralateral blindness due to aneurysm despite two prior coiling procedures	Esophageal injury due to orogastric tube placed as part of anesthesia	No	Angiogram @3 mo showed complete occlusion. Clinically improved, but formal visual field testing pending	Request: S43 Notification: S44 (case was done emergently)
24		56	11/19/09		Supraclinoid carotid	>10 mm	20 mm	Headache and visual loss	Transient worsening of symptoms, since resolved.	No	Transient worsening of symptoms, now back to baseline. CTA showed complete occlusion. Angiogram @8 mo shows complete occlusion and mild transient intimal hyperplasia.	Notification: S46
25		61	11/23/09		Basilar	Fusiform	~40 mm	Headache	Post-operative aneurysmal hemorrhage	No	Fatal SAH 3 days after PED placement	Notification: S47
26		48	12/28/09		Cavernous carotid	Fusiform	16 mm	Headache	Persistent head/ear pain	No	Angiogram @6 mo shows complete occlusion	Request: S45 Approval: 12/1/09
27		18	1/5/10		Cavernous carotid	N/A	N/A	Headaches, diplopia with abducens palsy	Epistaxis on POD#3, easily controlled. Patient has history of nosebleeds.	No	At hospital discharge, decreased diplopia. Patient is back in school full time, headaches and nosebleeds have resolved. Angiogram @6 mo shows complete occlusion.	Notification: S50
28		45	1/14/10		Cavernous carotid	N/A	29.3	Nausea, retro-orbital pain, abducens palsy	Readmitted on POD3 for headache, nausea and ptosis. No AEs since then.	No	Dramatic improvement in clinical status since placement. MRA @6 mo showed small residual flow in aneurysm.	Notification: S51
29		38	5/17/10		Paraophthalmic	~5 mm	~12 mm	None	None	No	Follow-up pending	Notification: S56
30		50	6/11/10		Bilateral cavernous sinus IAs (only LICA treated)	NA	25	Headache, trigeminal neuralgia	Postoperative right arm weakness, emergency angiogram performed with mechanical/chemical thrombectomy of acute thrombosis in PED. Had minor stroke.	No	Follow-up pending	Request: S53 Approval: 5/6/10
31		22	6/22/10		Soldier w long, asymptomatic petrous segment IA	fusiform	40	Left temporal headaches.	None	No	Follow-up pending	Request: S53 Approved: 5/6/10
32		52	6/23/10		Fusiform supraclinoid IA	NA, multilobulated	14	HA, lightheadedness, occ blurry vision, increased tearing, dizziness	None	No	Follow-up pending	Request: S54 Approval: 5/27/10
33		58	6/23/10		Enlarging multilobulated IA	NA, multilobulated	10	Hemiparesis, facial droop (MCA territory stroke, no SAH)	None	No	Progressive enlargement of his ventricles indicative of hydrocephalus for which he had placement of a VP shunt. Neurological exam has stabilized. Some cognitive improvement and is starting to walk.	Request: S54 Approval: 5/27/10
34		64	7/9/10		Supraclinoid IA w residual after Neuroform + coil	NA	20	None	None	No	Follow-up pending	Request: S52 Approval: 2/25/10

#	Initials/ Name Code	Age	Proc date	Location Physician	Aneurysm location	Neck size, mm	Maximum fundus diameter, mm	Symptoms	Adverse event	Device malfunction?	Follow-Up	FDA Request/Approval/Notification
35	[redacted]	63	8/2/10	[redacted]	PICA + atherosclerotic disease			Diplopia (abducens palsy), vertigo, difficulty with balance	None	No	Follow-up pending	Request: S59 Approval: 8/18/10 Notification S60
36	[redacted]	66	8/4/10	[redacted]	Cavernous carotid	NA	34	Dizziness	None	No	Follow-up pending	Request: S52 Approval: 2/25/10
37	[redacted]	35	9/25/10	[redacted]	Cavernous carotid		27	Blindness acutely worsening after coil embolization a few weeks earlier	None	No	Pending	Notification: S64

Canadian Experience

By Canadian regulations, physicians make their own, independent requests for use of an unapproved medical device to Health Canada (HC). HC granted Chestnut the right to send devices to Canada for use at the physician's discretion. A small number of Canadian physicians used PED in the pre-market setting to treat subjects. Physicians from University of Toronto provided us with a summary of adverse events, reported in Appendix 22 of the original PMA. In cases performed by Drs. Weill and Kelly, no adverse events were reported (see p. 141 of original PMA). Summary letters from Canadian physicians were provided in Appendix 24 of the original PMA (see pages 1606, 1609, 1612, 1617).

PED has been approved in Canada for commercial sale by Health Canada.

19. You report that, "PED was used in a single-center series of cases in Buenos Aires, Argentina by Dr. Pedro Lylyk. To date, PED has been used in 180 cases. .." You further state that, "Clinical experience in the first 53 cases … with a total of 63 IA's has been published and is described below." However, you present data on only 28 aneurysms followed out to 6 months. Please provide all available information on the Argentina case series. These data, while not part of the pivotal data to support device safety, may be considered in our assessment of the overall safety of the PED.

Response to #19

Dr. Lylyk's experience with PED was reported to FDA in two parts:

- **Part 1, published article**: Dr. Lylyk published his early experience with PED. The article was included in **Appendix 27**, pp. 1819-1830. At the time this article was published, 53 subjects had been treated and 180-day follow-up was available in 28 subjects.

- **Part 2, further experience**: Since publishing this experience, Dr. Lylyk has treated many more subjects. He summarized his experience for us in a letter (**Appendix 24** of original submission, p. 1621) and a PowerPoint presentation (p. 1625-1739). In this presentation, Dr. Lylyk noted that 180-day follow-up in 64 subjects showed a complete aneurysm occlusion rate of 79% (see p. 1662), a figure remarkably similar to that observed in PUFS. He reported 1-year follow-up in 46 cases with a complete occlusion rate of 93%. Some patients now have follow-up to 4 years.

As shown in **Figure 2** below, Dr. Lylyk reported use of PED in 180 patients (217 aneurysms). Half of these cases were large/giant aneurysms, 81% were unruptured and 84% were located in the ICA. Transient intimal hyperplasia* occurred in 7 patients (3.9%) and was asymptomatic. Safety outcomes were as follows:

* Transient intimal hyperplasia of the parent artery may be a more appropriate term than "stenosis" since aneurysms are not known to be associated with stenotic vascular disease. Moreover, in many cases, TIH resolves spontaneously, which is different from stenosis, which is usually progressive.

- 1 acute thrombosis of the parent artery
- 2 perforator infarcts (in patients with basilar artery aneurysms)
- 3 thromboembolic events
- 4 intracranial hemorrhages

In total, 4 of 180 (2.2%) died after PED treatment in this case series of difficult-to-treat aneurysms and 5.4% total experienced major morbidity or mortality. These data were presented on p. 1729 of the originally submitted PMA. According to Dr. Lylyk, one of the world's experts in aneurysm treatment, the 5.4% morbidity/mortality rate compares very favorably with expected morbidity/mortality had patients undergone surgical or other endovascular treatment.

Figure 2. Excerpt from Dr. Lylyk's letter to Chestnut regarding his experience with Pipeline Embolization Device. EVRT refers to "ENERI Vascular Reconstruction Trial", a single-center study in Argentina.

I would like to take this opportunity to update you on the progress of EVRT. As of December 2009 we have treated 217 aneurysms in 180 patients using 301 PEDs. EVRT patients are those with difficult-to-treat aneurysms that, in most cases, are not well-treated by currently available techniques, such as other stents, coils, or open surgery. I have used PED for aneurysms of all sizes and locations. Half of my cases were large or giant, as in PUFS, 81% were unruptured, and 84% were located on the internal carotid artery. 21% of my cases had failed previous attempts at treatment. In 78% of our cases, PED was used alone, while in the other 22%, PED was used in combination with coils. Adjunctive use of coils was mostly in cases that had recently ruptured. In patients presenting with mass effect (55%) we preferred to treat with PED alone, as was done in the PUFS study. In nearly 70% of these patients, the symptoms of mass effect resolved on follow up and we have documented involution of the aneurysm fundus with cross-sectional imaging. Simultaneous occlusion of the aneurysm with PED, preservation of the parent artery and resolution of neurologic symptoms (since the aneurysm fundus itself is not filled with a coil mass) is a tremendous and revolutionary benefit for these patients; the symptoms increased in only 6 patients, but this was controlled with corticosteroids in one month.

In terms of efficacy, the results with PED have been remarkable: at six-month follow up 79% of the patients had complete occlusion of their aneurysms. I understand this value is very similar to what was observed in PUFS. By one-year follow-up the aneurysm occlusion rate increased to 93%. The few patients that did not have complete occlusion by one year usually had been previously treated with other intracranial stents. In the 14 patients who have follow-up to two years or more, 100% of the aneurysms were occluded. I have never had a single case yet of an aneurysm recurrence after successful treatment with PED. As you are aware, this is in sharp distinction to the treatment of aneurysms with coils, where recurrence is common, especially in patients with large and giant aneurysms.

In-stent stenosis has not been a problem: we have had 7 patients who have had a transient intimal hyperplasia with no clinical symptoms, and all resolved angiographically without treatment by one year.

In terms of acute safety, we have had 10 clinically significant incidents, resulting in four deaths. We had one case of acute in-stent thrombosis. Despite commonly covering multiple perforators and branch vessels, only two patients had acute infarcts related to perforators and both of these were in dysplastic basilar arteries. We have had three thromboembolic events and four intracranial hemorrhages. The procedure-related rate of major neurologic morbidity and mortality of 5.4% compares quite favorably to the published literature for other treatments of these complex intracranial aneurysms. It should be recalled that many of my patients simply could not be reasonably treated with any other techniques. Although, there are possibilities for more improvements.

The introduction of the PED represents a quantum advance for this field. I am pleased to say that our center has performed the most PED cases in the world, and our experience represents nearly one-quarter of the total worldwide experience with PED. We are honored to have introduced this technology to the world and believe that it offers physicians an important tool in the treatment of these complex and difficult intracranial aneurysms.

I encourage US FDA to approve the device so that physicians in the US have access to this remarkable new technology.

Sincerely,

Pedro Lylyk, MD

20. Subjects in the PITA trial were allowed to be treated with the PED alone or with the combined PED and coiling; however, results were not stratified by those who did or did not have coiling. Coils were used in 48% of the cases. Please provide an analysis of the results of the trial by those who used PED alone vs. those who used PED and coiling.

Response to #20

PITA was performed in 2007-2008, before we understood that PED could be used alone without coils. Coils were used in 16 of 31 cases of which aneurysm occlusion could be judged in 15. The complete occlusion rate when coils were used was 100%; the rate when coils were not used was 86.7% (**Table 28**). Coil use did not appear to affect the likelihood of complete occlusion (exact chi-squared p-value 0.4828).

Table 28. Complete occlusion rate by use of coils with PED in PITA study.

Coils Used	Complete Aneurysm Occlusion Rate
Yes	15/15 (100%)
No	13/15 (86.7%)
Total	28/30 (93.3%)

21. Each attempted deployment of the PED device presents a risk of adverse events. In the PUFS study, a large majority of subjects were treated with 3 or more PEDs (66%). Please provide analyses that evaluate safety in relationship to aspects of the procedure required to deploy the device such as the number and size of PEDs used, duration of the procedure, total length of artery stented, etc.

Response to #21

The factors FDA has requested (number of PEDs used, size of PEDs used, duration of procedure) were added to the subgroup analyses presented in our response to deficiency #10 above (see p. 28 of this letter). These factors were not predictive of the major safety endpoint. The IDE-approved protocol did not include measurement of the length of the treated artery, so this information is not available. However, length of the treated artery is roughly proportional the length of the aneurysm neck since PED is placed from normal artery distal to the aneurysm to normal artery proximal to the aneurysm. The distance separating normal artery segments is roughly the neck size. Neck size was not predictive of the major safety endpoint (see original PMA, p. 105).

22. The PMA does not include a discussion of post-approval plans or a Post-Approval Study (PAS) protocol. If your application is approved, FDA may require you to conduct a post-approval study as a condition of approval. It is important to evaluate the long term safety and effectiveness use of the PED system in the United States. Your current protocol includes follow-up visits with angiography at 1, 3, and 5 years, and telephone evaluations at 2 and 4 years. Please provide a protocol for a post-approval study which addresses the following primary objectives:

a. The panel will be asked if angiography should be done at 2 years rather than 3 years to further evaluate the effectiveness of the device. For example, what is the proportion of subjects with complete occlusion of the target intracranial aneurysm and $\leq$ 50% stenosis of the parent artery at the target location at 24 months post-procedure? The goal of the study should be >50% of subjects, i.e., Pr(p>0.50 | Trial Data) > 0.975.

b. ***What is the safety of the device at 2 years post-procedure? For example, what is proportion of subjects who experience either death due to neurologic reasons or***

major ipsilateral stroke at 24 months post-procedure? The goal of the study should be <20% of subjects, (i.e. Pr(p<0.20 | Trial Data) > 0.975).

OSB Division of Epidemiology, in consultation with the Clinical Reviewer, the Lead Reviewer and other members of the review team will work interactively with you to develop the PAS protocol. Please contact Dr. Kristen Van Dole at 301-796-6334 or kristen.vandole@fda.hhs.gov to start the interactive development of your PAS protocol. An outline detailing the elements you should include in the post-approval study protocol is provided below.

[Remainder of question omitted for brevity]

Response to #22a

During the week of October 4, FDA informed Chestnut that Dr. Kristen Van Dole (the OSB contact referred to in the text above) no longer works at FDA. By telephone, Dr. Hutter told Chestnut he would find the appropriate person in OSB/Division of Epidemiology with whom to discuss a post-market study. On October 7, Chestnut sent FDA by email a short summary of why PUFS itself will address FDA's concerns regarding long-term follow-up. This summary is repeated below. FDA has not yet responded to this summary or provided a contact in OSB with whom to discuss a PAS.

FDA notes that the panel may be asked about 2-year angiograms. The IDE-approved PUFS protocol is a 5-year study that includes angiograms at baseline, 180 days, 1 year, 3 years and 5 years, but not 2 years. Since PUFS enrollment started in November 2008, two-year follow-up visits in PUFS will begin in about two weeks. At this point, the date of the panel meeting is unclear; however, it is likely that by the time the panel meets, most subjects will have already passed the 2-year follow-up time point. Moreover, a change to the protocol involving angiography would require local IRB/EC review and re-negotiation of clinical contrast, which would likely introduce many months of delay.

PUFS was designed as a 5-year study. When we designed the study with FDA's Dr. Peter Hudson, it was clear to all that much of the very long-term follow-up in PUFS would be done in the post-market setting. The primary endpoints of PUFS are at 180 days. As noted above, PUFS also includes 1-, 3- and 5-year angiograms and clinic visits as well as telephone visits at 2 and 4 years. The primary purpose of these exams/visits is to determine very long-term angiographic and clinical follow-up. These assessments will meet FDA's goals as stated in the deficiency.

PUFS will have adequate statistical power to address FDA's questions. PUFS enrolled and treated 108 subjects, of which 107 underwent PED placement. Of these 107, the effectiveness cohort consists of 104 subjects. Of these 104, 99 underwent angiography at 180 days and 89 have thus far undergone angiography at 1 year. Amongst subjects undergoing angiography at both 180 days and 1 year, 73 (83.0%) and 74 (84.1%) had complete occlusion of the target angiogram, respectively. The correlation between angiographic results at 180 days and 1 year was extremely high, with only 1 subject showing worse results at 1 year and 4 subjects showing

improved results (i.e., residual aneurysm/neck at 180 days → complete occlusion at 1 year).

We can use the following standard methods to predict very long-term PUFS outcomes under two scenarios:

- **Scenario 1**, perfect correlation. In this scenario we assume that 1-year outcomes perfectly predict 3-year or 5-year outcomes. Under this assumption, the 3-year complete occlusion rate will be approximately 84%, and the LCL of the 3-year rate will be >50% (FDA's stated target) even if only a small number of subjects are evaluated.

- **Scenario 2**, no correlation. In this extremely conservative scenario we assume that 1-year outcomes are uncorrelated with 3-year outcomes, but the 3-year effectiveness rate remains 84%. Based on what we know, this assumption is clearly incorrect, but it is very conservative. A beta-binomial can be used to calculate the predictive distribution of the 3-year success rate.[*] Predictive distributions are an accepted Bayesian method for trial planning.[†] Despite the fact that the spread of a predictive distribution is typically quite wide, the chance that the predicted 3-year effectiveness rate will exceed 50% (FDA's desired target) is >99% provided that at least 50 subjects are evaluated at 3 years. Loss to follow-up and/or withdrawal in PUFS from 90 1-year subjects to 50 3-year subjects seems unlikely.

Note that the above methods assume that no subject has progressive thrombosis of the target aneurysm, i.e., goes from residual neck/aneurysm at one angiogram to complete occlusion at a subsequent angiogram. However, we have seen this improvement in 4 of 10 subjects to date.

In summary, PUFS has high power to show effectiveness rates >50% in the very long term (3 years) because:

1. The 180-day and 1-year effectiveness rates were high,

2. The 180-day and 1-year outcomes were highly correlated, and

3. Subject loss to follow-up to date has been low.

Response to #22b

A similar argument can be made from the safety perspective. The primary safety endpoint of PUFS was major ipsilateral stroke and/or neurologic death. Risk for device-related stroke/death appears to be restricted to the perioperative time period. (Of course, PUFS subjects remain at risk for stroke due to "standard" causes associated with old age, hypertension and other risk

---

[*] R code:

```
sims=100000
n=50
s=rbinom(sims,n,.84)
q=qbeta(.025, 1+s, 1+n-s)
mean(q>.5)
```

[†] Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials, see http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071072.htm, Section 5.4.

factors.) The primary safety endpoint rate by 3 years is likely to remain low and statistically <20%. PUFS likely has high statistical power to show that the 3-year major safety endpoint rate is <20%.

Appendix 1. Additional Analysis

This appendix provides additional information requested by FDA in its deficiency #1.

Angiographic Findings

Table 29 shows **Sample Table 1** requested by FDA. Note that aneurysm occlusion ranking was not assessed pre-procedure since all aneurysms were unoccluded. Aneurysm occlusion was also not assessed immediately postoperatively since PED is not intended to immediately occlude an aneurysm. Of subjects who had angiograms at both time points, 83% showed complete occlusion at 180 days and 84% showed complete occlusion at 1 year. Similarly, 85% showed minimal (<25%) stenosis at 6 months and 90% showed minimal stenosis at 1 year.

Table 29. Angiogram data by follow-up visits for subjects who had an angiogram at all visits (n=88).

	Occlusion Ranking	180 Days	1 Year
Occlusion Ranking	Complete occlusion	73 (83.0%)	74 (84.1%)
	Residual neck	8 (9.1%)	5 (5.7%)
	Residual aneurysm	6 (6.8%)	4 (4.5%)
	Other	1* (1.2%)	2** (2.3%)
	Not yet read	0 (0%)	3 (3.4%)
Percent stenosis	0 – ≤25%	75 (85.2%)	79 (89.8%)
	25 – ≤50%	10 (11.4%)	1 (1.1%)
	50 – ≤75%	0 (0%)	1 (1.1%)
	75 – 100%	2 (2.3%)	1 (1.1%)
	Other	1[#](1.1%)	6[§](4.7%)

*1 case of carotid occlusion; **2 cases of carotid occlusion; [#]1 case of carotid occlusion; [§]2 cases of carotid occlusion and 4 cases not yet read by core lab.

Table 30 shows angiogram data by follow-up visit for all subjects who had an angiogram at the listed visit. Of the 99 subjects with angiograms at 180 days, 81.8% showed complete occlusion and 85% showed minimal stenosis. Of the 89 who underwent angiogram at 1 year, 85% showed complete occlusion and 90% showed minimal stenosis.

Table 30. Angiogram data by follow-up visits for subjects who had an angiogram at the listed visit.

Angiographic reads		180 Days N=99	1 Year N=89
Occlusion Ranking	Complete occlusion	81 (81.8%)	75 (84.3%)
	Residual neck	8 (8.1%)	4 (4.5%)
	Residual aneurysm	6 (6.1%)	4 (4.5%)
	Other	4* (4.0%)	2** (2.2%)
	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 (2.0%)	1 (1.1%)
	Other	3[#] (3.0%)	2[§](2.3%)
Not yet read		0 (0%)	4 (4.6%)

*1 case of carotid-cavernous fistula and 3 cases of carotid occlusion
**2 cases of carotid occlusion
[#]3 cases of carotid occlusion
[§]2 cases of carotid occlusion

Medications

The MEDRA dictionary was used to encode all adverse events in PUFS. MEDRA terms describing each adverse event were identical in many cases. When terms were different, the differences were minor (see **Table 31**).

Table 31. Examples of MEDRA terms that differed from previously reported AE terms.

MEDRA Term	Previously Reported Term
Arteriovenous fistula	Carotid cavernous fistula
Breast cancer recurrent	Breast cancer recurrence
Carotid artery occlusion	Carotid occlusion
Cerebral haematoma	Intracranial hemorrhage
Colitis (excl infective)	Colitis
Compartment syndrome	Non-neuro bleeding: compartment syndrome
Confusion postoperative	Confusion, fever
Conjunctival haemorrhage	Subconjunctival hemorrhage

Table 2 (p. 5 of this letter) shows MEDRA categories and terms for all serious adverse events (**Sample Table 3**). **Table 3** of this letter (p. 6) shows the same information for non-serious adverse events. **Table 4** (p. 8) shows the same information for all events judged as probably or definitely related to PED. In addition, in late September 2010 we sent FDA by email this information in Excel format in the file "Adverse Events Sample Table 4.xls," which is sortable and filterable.

Modified Rankin Scale

Table 32 shows modified Rankin Scale score by study visit. One subject, in whom PED was not placed, was followed for safety only; this subject is excluded from the table. Most subjects had MRS 0 or 1 throughout the study. Large MRS increases were due to stroke or neurologic death (outcomes described in detail in original PMA). Small increases in MRS were primarily due to postoperative headache, stroke or neurologic death.

Table 32. Modified Rankin Scale score by study visit.

MRS	Prior to PED Placement N=107	Discharge N=107	Day 30 N=106	Day 180 N=105
0	58 (54.2%)	54 (50.5%)	57 (53.8%)	63 (60.0%)
1	35 (32.7%)	39 (36.4%)	30 (28.3%)	31 (29.5%)
2	9 (8.4%)	6 (5.6%)	10 (9.4%)	4 (3.8%)
3	2 (1.9%)	1 (0.9%)	2 (1.9%)	0 (0%)
4	1 (0.9%)	2 (1.9%)	1 (0.9%)	1 (1.0%)
5	0 (0%)	0 (0%)	0 (0%)	0 (0%)
6	0 (0%)	1 (0.9%)	3 (2.8%)	3 (2.9%)
ND	2 (1.9%)	4 (3.7%)	3 (2.8%)	3 (2.9%)

Table 33. Change in Modified Rankin Scale score from baseline to discharge (n=107).

	Score at Discharge							
Score at Baseline	**ND**	**0**	**1**	**2**	**3**	**4**	**5**	**6**
ND	2	0	0	0	0	0	0	0
0	1	47	8	0	1	0	0	1
1	0	6	29	0	0	0	0	0
2	1	1	2	5	0	0	0	0
3	0	0	0	1	0	1	0	0
4	0	0	0	0	0	1	0	0
5	0	0	0	0	0	0	0	0
Total	4	54	39	6	1	2	0	1

Table 34. Change in Modified Rankin Scale score from baseline to day 30 (n=106).

	Score at Day 30*							
Score at Baseline	**ND**	**0**	**1**	**2**	**3**	**4**	**5**	**6**
ND	0	1	0	0	0	0	0	1
0	1	48	5	2	0	0	0	1
1	1	8	22	2	1	0	0	1
2	1	0	3	4	1	0	0	0
3	0	0	0	2	0	0	0	0
4	0	0	0	0	0	1	0	0
5	0	0	0	0	0	0	0	0
Total	3	57	30	10	2	1	0	3

Table 35. Change in MRS from baseline to day 180 (n=105).

	Score at Day 180*							
Score at Baseline	**ND**	**0**	**1**	**2**	**3**	**4**	**5**	**6**
ND	0	1	0	0	0	0	0	1
0	1	48	5	1	0	0	0	1
1	1	12	20	1	0	0	0	1
2	1	2	5	1	0	0	0	0
3	0	0	1	1	0	0	0	0
4	0	0	0	0	0	1	0	0
5	0	0	0	0	0	0	0	0
Total	3	63	31	4	0	1	0	3

Neurologic Findings by Visit

Table 36 provides the table representing FDA's Sample Table #8. **Table 37** shows abnormal findings as reported by the neuro-ophthalmologist at baseline and 180 days.

Table 36. Abnormal neurologic findings by study visit.

Assessment	Baseline	Discharge	Day 30	Day 180
Mental status abnormal	0/108 (0%)	2/107 (1.9%)	0/101 (0%)	0/99 (0%)
Optic nerve (II)	22/107 (20.6%)	20/106 (18.9%)	17/101 (16.8%)	16/99 (16.2%)
Oculomotor nerve (III)	24/107 (22.4%)	21/106 (19.8%)	24/101 (23.8%)	15/99 (15.2%)
Trochlear nerve (IV)	4/107 (3.7%)	4/105 (3.8%)	7/101 (6.9%)	1/99 (1.0%)
Trigeminal nerve (V)	9/107 (8.4%)	4/106 (3.8%)	5/101 (5.0%)	3/99 (3.0%)
Abducens nerve (VI)	21/107 (19.6%)	19/106 (17.9%)	26/101 (25.7%)	12/99 (12.1%)
Facial nerve (VII)	2/107 (1.9%)	1/106 (0.9%)	1/101 (1.0%)	1/99 (1.0%)
Vestibulocochlear nerve (VIII)	4/107 (3.7%)	3/106 (2.8%)	2/101 (2.0%)	2/99 (2.0%)
Glossopharyngeal nerve (IX)	2/107 (1.9%)	1/106 (0.9%)	0/101 (0%)	1/99 (1.0%)
Vagus nerve (X)	1/107 (0.9%)	1/106 (0.9%)	1/101 (1.0%)	0/99 (0%)
Spinal accessory nerve (XI)	1/107 (0.9%)	1/106 (0.9%)	0/100 (0%)	1/99 (1.0%)
Hypoglossal nerve (XII)	2/107 (1.9%)	0/106 (0%)	1/101 (1.0%)	0/99 (0%)
Muscle appearance	2/107 (1.9%)	1/102 (1.0%)	4/101 (4.0%)	0/99 (0%)
Muscle tone	2/107 (1.9%)	3/102 (2.9%)	2/101 (2.0%)	1/99 (1.0%)
Muscle strength	4/107 (3.7%)	2/104 (1.9%)	3/101 (3.0%)	1/99 (1.0%)
Gait				
Spastic	0/107 (0%)	0/106 (0%)	0/101 (0%)	0/99 (0%)
Parkinsonian	0/107 (0%)	0/106 (0%)	0/101 (0%)	0/99 (0%)
Ataxic	0/107 (0%)	0/106 (0%)	0/101 (0%)	0/99 (0%)
Antalgic	1/107 (0.9%)	0/106 (0%)	1/101 (1.0%)	1/99 (1.0%)
Abnormal	3/107 (2.8%)	1/106 (0.9%)	1/101 (1.0%)	0/99 (0%)
Coordination	4/108 (3.7%)	2/107 (1.9%)	4/101 (4.0%)	0.99 (0%)
Sensory examination	6/108 (5.6%)	3/107 (2.8%)	7/101 (6.9%)	4/99 (4.0%)
Deep tendon reflex	7/108 (6.5%)	4/107 (3.7%)	5/101 (5.0%)	6/99 (6.1%)
Other reflexes	1/108 (0.9%)	1/107 (0.9%)	2/101 (2.0%)	2/99 (2.0%)

Table 37. Abnormal visual examination by neuro-ophthalmologist by study visit, effectiveness cohort.

Assessment			Baseline	180 Days
OD Snellen, denominator > 22			52 (50%)	48 (46.2%)
OS Snellen, denominator > 22			46 (44.2%)	35 (33.7%)
OD reactive to light			5 (4.8%)	2 (1.9%)
OS reactive to light			6 (5.8%)	4 (3.8%)
OD reactive to accommodation			4 (3.8%)	1 (1.0%)
OS reactive to accommodation			5 (4.8%)	5 (4.8%)
OD relative afferent pupillary deficit			11 (1.6%)	9 (8.7%)
OS relative afferent pupillary deficit			7 (6.7%)	7 (6.7%)
OD other significant pupillary findings			2 (1.9%)	0 (0%)
OS other significant pupillary findings			3 (2.9%)	0 (0%)
OD corneal reflex			6 (5.8%)	3 (2.9%)
OS corneal reflex			1 (1.0%)	1 (1.0%)
OD eye movement up			10 (9.6%)	6 (5.8%)
OD eye movement down			6 (5.8%)	4 (3.8%)
OD eye movement left			5 (4.8%)	4 (3.8%)
OD eye movement right			12 (11.5%)	11 (10.6%)
OS eye movement up			7 (6.7%)	6 (5.8%)
OS eye movement down			3 (2.9%)	2 (1.9%)
OS eye movement left			7 (6.7%)	3 (2.9%)
OS eye movement right			3 (2.9%)	2 (1.9%)
Right gaze alignment >4 diopters heterophoria			14 (13.5%)	16 (15.4%)
Right gaze alignment >4 diopters hypertropia			2 (1.9%)	0 (0%)
Primary gaze alignment >4 diopters heterophoria			21 (20.2%)	14 (13.5%)
Primary gaze alignment >4 diopters hypertropia			2 (1.9%)	1 (1.0%)
Left gaze alignment >4 diopters heterophoria			16 (15.4%)	14 (13.5%)
Left gaze alignment >4 diopters hypertropia			2 (1.9%)	1 (1.0%)
			Mean (SD)	Mean (SD)
OD, mean deviation index			-3.09 (5.46)	-3.15 (6.46)
OS, mean deviation index			-2.95 (6.68)	-2.19 (6.03)
OD, pattern SD			3.71 (9.0)	2.84 (2.48)
OS, pattern SD			3.25 (3.62)	2.85 (2.65)
OD, foveal sens			32.25 (8.46)	30.77 (10.30)
OS, foveal sens			33.03 (6.0)	32.25 (7.42)
Ophthalmologist Summary of CN Function				
CN II	OD	Abnormal	14 (13.5%)	13 (12.5%)
		Prob/def related	6 (5.8%)	NRPP*
	OS	Abnormal	18 (17.3%)	13 (12.5%)
		Prob/def related	8 (7.7%)	NRPP
CN III	OD	Abnormal	8 (7.7%)	5 (4.8%)
		Prob/def related	5 (4.8%)	NRPP
	OS	Abnormal	8 (7.7%)	6 (5.8%)
		Prob/def related	5 (4.8%)	NRPP
CN IV	OD	Abnormal	2 (1.9%)	0 (0%)
		Prob/def related	2 (1.9%)	NRPP
	OS	Abnormal	0 (0%)	2 (1.9%)
		Prob/def related	0 (0%)	NRPP
CN V	OD	Abnormal	5 (4.8%)	2 (1.9%)
		Prob/def related	1 (1.0%)	NRPP
	OS	Abnormal	0 (0%)	1 (1.0%)

Assessment			Baseline	180 Days
		Prob/def related	0 (0%)	NRPP
CN VI	OD	Abnormal	15 (14.4%)	13 (12.5%)
		Prob/def related	10 (9.6%)	NRPP
	OS	Abnormal	10 (9.6%)	8 (7.7%)
		Prob/def related	5 (4.8%)	NRPP

*NRPP = not required per protocol

For Sample Table 9, entitled "new neurologic findings since pre-implant by visit", change from baseline was not asked in the discharge or Day 30 form. A neurologic examination was not done at Day 90. Due to a typographical error, the Day 180 form asked for a comparison to last visit (i.e., Day 30) but did not ask for a comparison to baseline. (This was corrected in subsequent electronic CRFs to be used in PUFS-CA.) At each study visit, the assessor was asked to assess change in symptoms related to the target aneurysm since the last study visit.

To address the change in neurologic function over time after PED placement, two assessments were done:

1. **Assessment by medical monitor**. The medical monitor for the study reviewed the neurologic course of each individual subject, including the reported changes in physical examination by the investigator and by the neuro-ophthalmologist as well as the reported changes in aneurysm-related symptoms. Each individual subject had to be examined separately because of the complexity of many of the subject's neurologic findings. Some subjects had marked abnormalities at baseline, some of which were due to the target aneurysm and some due to other pathology (e.g., prior aneurysm in another location, head trauma, etc.). Some subjects exhibited mixed changes, with improvement in one neurologic area and worsening of another (e.g., headache resolved but new transient cranial neuropathy). We therefore reported neurologic changes on a global scale and by individual cranial nerve (see p. 106-109 and Appendix 14 of the previously submitted PMA).

2. **Assessment by consulting neuro-ophthalmologist**. As noted above, some of the subjects had complex neurologic findings. For example, one subject had esotropia due to blindness. Malalignment of the eyes is usually due to an oculomotor problem; however, this subject had malalignment due to aneurysm-related blindness, an unusual cause. We therefore asked Dr. Mohammad Fouladvand, neuroophthalmologist at New York University, to review the clinical eye exam worksheets and VF measurements for all PUFS subjects at baseline and follow-up. He completed a one-page CRF for each subject on which he rated the subject's baseline neuro-ophthalmologic findings and change in findings for each subject. His analysis was in complete agreement with that performed by the medical monitor. His report is included as **Appendix 2** to this letter.

Baseline Laboratory Values

Table 38 shows baseline laboratory values for study subjects. The minimum baseline hematocrit value (13.8) is likely an error and is probably the hemoglobin measurement.

Table 38. Baseline laboratory values

	N	Mean	Std	Min	Max	P50
Hematocrit	108	39.28	4.89	13.80	56.30	39.25
Platelet count	107	263.14	72.68	104	544	255
Serum creatinine	108	0.84	0.23	0.46	2.07	0.80

Appendix 2. Analysis Performed by Dr. Mohammad Fouladvand of All PUFS Subjects

Chestnut asked Dr. Mohammad Fouladvand, neuroopthalmologist at NYU, to review the eye findings from all PUFS subjects. Dr. Fouladvand was the study ophthalmologist for 29 PUFS subjects enrolled and treated at NYU. The following pages show his letter to Chestnut regarding his analysis, as well as the analysis of his data that Chestnut completed.

NYU Langone Medical Center

Mo Fouladvand, MD
Neuro-Ophthalmology
Associate Professor of Neurology and Ophthalmology

Daniel Cher, MD
Vice President of Clinical and Regulatory Affairs
Chestnut Medical Technologies
173 Jefferson Drive
Menlo Park, CA 94025

August 26, 2010

Re: neuro-ophthalmology analysis

Dear Daniel,

Thank you for the opportunity to review the eye exams in the PUFS study. As you know, I am a clinical associate professor of neuro-ophthalmology at New York University (NYU). I participated in PUFS as the neuro-ophthalmologist associated with NYU where I personally examined nearly 30 PUFS patients both before,and 180 days after treatment with the Pipeline Embolization Device (PED).

I also reviewed all available baseline and 180-day eye exam worksheets from all PUFS patients enrolled in the PUFS study. You created a case report form (CRF) for my analysis, and I completed a CRF for each patient. You entered the data into an online system and trained me on its use, and I used this system to respond to a small number of your queries.

I have reviewed your analysis and believe it to be accurate. As a practicing neuro-ophthalmologist, I often see patients with aneurysm-related cranial neuropathies. In my experience, and in the published literature, treatment of these aneurysms with coil embolization does not reliably result in improvement in ophthalmic signs or symptoms. In fact, patients may even get worse after coil embolization due to increased mass effect from coil. In contrast, I am impressed with the large proportion of patients in PUFS who experienced improvement in cranial neuropathies after PED treatment. I would expect that some patients with long-standing neuropathies might not improve; nonetheless, there were some cases of dramatic improvement after PED.

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Comparing the number of patients who improved to the number who worsened, I conclude that it is clear that the likelihood of improvement of objective neurologic signs and symptoms far outweighs the likelihood of worsening.

Thank you for allowing me to participate in this project.

Sincerely,

Mo Fouladvand, MD
Associate Professor of Neurology and Ophthalmology
NYU Medical Center
333 E. 34th Street, Suite 1F
New York, NY, 10016
[redacted]

1952

NYU Langone Medical Center

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August 26, 2010

Mohammad Fouladvand, MD
333 E. 34th Street, Suite 1F
New York, NY, 10016
(212) 263-0973

Re: neuro-ophthalmology analysis

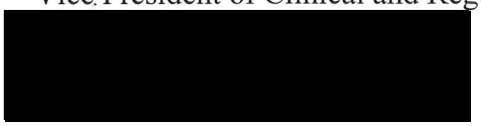
Dear Dr. Fouladvand,

Thank you for taking the time to review eye examination results in PUFS patients. You were the ophthalmologist at New York University (NYU) and personally examined about 30 PUFS cases at NYU. I sent you the eye examination worksheets from all the remaining PUFS patients. You reviewed these worksheets and completed a case report form on all patients. We reviewed the CRFs and entered the data into an electronic data capture tool (DataFax). You used DataFax to answer some of my queries.

I have statistical skills and am knowledgeable in SAS. I therefore created a number of tables describing PUFS patients, which you can review in the attached report. In creating these tables, I'm happy to report that your opinions regarding changes in eye function agreed substantially with my summary of these patients as submitted in our PMA application.

Sincerely,

Daniel Cher, MD
Vice President of Clinical and Regulatory Affairs



EYE EXAM ANALYSIS

1 Methods

1.1 Information Source

Raw data consisted of the eye exam worksheets for each PUFS patient completed by ophthalmologists at each PUFS site. Printed copies of eye exams were sent to Dr. Fouladvand. Some of the records contained printouts from visual field tests. Dr. Cher also provided Dr. Fouladvand with information that listed each patient and which side the aneurysm was located on (so that he could determine which side was "ipsilateral").

1.2 Case Report Form

Dr. Fouladvand completed a one-page case report form (**Appendix 1**) for each patient.

1.3 Data Entry

Dr. Fouladvand sent the completed CRF to Chestnut. Chestnut staff (Daniel Cher, Shira Stone) double data-entered information into a DataFax CRF that exactly mimicked the printed CRF (per standard DataFax routines). Daniel Cher reviewed information and created queries were relevant.

1.4 Query Resolution

Queries created by Dr. Cher were resolved by telephone with Dr. Fouladvand, who was trained in use of the DataFax system and corrected the queries.

1.5 Analysis

Data were exported and read into SAS. Dr. Cher created scripts for analysis. Analysis primarily consisted of tabulations.

2 Results

2.1 Patients

108 patients were treated in PUFS. For various reasons (**Table 1**), 10 patients were eliminated from analysis.

Table 1. Patients excluded from analysis by neuro-ophthalmologist.

Reason for Elimination from Analysis	N	Patients
Death	3	[redacted]
Refused 180-day examination	2	
Did not have 180-day examination	1	
Non-participatory	1	
Not treated with PED	1	
Withdrawal	1	
Loss to follow-up	1	
Total	10	

2.2 *Visual Fields*

At baseline, 68 patients had a normal ipsilateral VF examination (**Table 2**), 17 patients had a VF abnormality that was clearly related to the aneurysm, and 11 had a VF abnormality unrelated to the aneurysm (e.g., baseline glaucoma). At re-examination on 180 days, 81 were stable, 2 had worsened, 11 had moderately improved, 1 had highly improved, and 2 had complete resolution of VF abnormalities (**Table 3**). Some patients had baseline VF abnormalities not related to the target aneurysm. Of 17 patients with a VF abnormality related to the target aneurysm, 1 was highly improved, 7 were moderately improved, 7 were stable and 1 was markedly worse (**Table 4**). The patient who was highly improved [redacted]) had decreased OD VA, a bitemporal cut and APD related to an 18-mm right sided aneurysm. At 180 days, MDI improved from MDI -10 to -4.97. The patient who worsened [redacted]) had a 30 mm right-sided cavernous aneurysm that was partially thrombosed. She presented with abducens palsy. MDI worsened from -13.4 at baseline to -26.9 at 180 days. PSDs were high, indicating variability of sensitivity throughout the visual fields. (The other patient who worsened [redacted] had normal function at baseline but had a cilioretinal artery occlusion on POD #1.) Two patients were rated as having VF abnormalities not related to the target aneurysm [redacted] and [redacted]). However, these two patients showed complete resolution of VF abnormalities at 180 days.

Table 2. Ipsilateral VF at baseline.

Ipsilateral VF at Baseline	N (%)
Not available	1 (1%)
Abnormal, unclear relationship to aneurysm	1 (1%)
Abnormal, related to aneurysm	17 (17.3%)
Abnormal, unrelated to aneurysm	11 (11.2%)
Normal	68 (69.5%)
Total	98 (100%)

Table 3. Change in ipsilateral VF at 180 days.

Ipsilateral VF at 180 days	N (%)
Complete resolution	2 (2%)
Highly improved	1 (1%)
Moderately improved	11 (11.2%)
Markedly worse	2 (2%)
Stable	81 (82.7%)
Cannot tell	1 (1%)
Total	98 (100%)

Table 4. Change in VF by baseline amongst patients with VF abnormality at baseline

Baseline abnormality in ipsilateral VF	Ipsilateral VF at 180 Days	N
Related	Highly improved	1
	Moderately improved	8
	Markedly worse	1
	Stable	7
Not related	Complete resolution	2
	Moderately improved	2
	Stable	7
Total		28

Contralateral eye VFs were also examined. At baseline 5 patients had abnormal contralateral VF related to the aneurysm, 10 had abnormal VF unrelated to the aneurysm, 1 had abnormal VF of unclear relationship, and 81 were normal (**Table 5**). At 180 days, 1 had complete resolution, 1 was highly improved, 3 were moderately improved, 1 was unclear, and 92 were stable (**Table 6**); none worsened. Of those with baseline abnormalities in contralateral VF related to the target IA, 1 [redacted]) was highly improved, 1 was moderately improved ([redacted] and 3 were stable (**Table 7**). The two patients with improvement had very large or medially directed aneurysms that could theoretically affect contralateral VF by mass effect.

Table 5. Contralateral VF at baseline.

Contralateral VF at Baseline	N (%)
Not available	1 (1%)
Abnormal, unclear relationship to aneurysm	1 (1%)
Abnormal, related to aneurysm	5 (5.1%)
Abnormal, unrelated to aneurysm	10 (10.2%)
Normal	81 (82.7%)
Total	98 (100%)

Table 6. Change in contralateral VF at 180 days.

Ipsilateral VF at 180 days	N
Complete resolution	1
Highly improved	1
Moderately improved	3
Markedly worse	0
Stable	92
Cannot tell	1
Total	98

Table 7. Change in contralateral VF at 180 days among patients with contralateral VF abnormality at baseline by baseline abnormality.

Baseline Abnormality of Contralateral VF	Contralateral VF at 180 Days	N
Abnormal, unclear relationship	Moderately improved	1
Abnormal, related to aneurysm	Highly improved	1
	Moderately improved	1
	Stable	3
Abnormal, unrelated to aneurysm	Complete resolution	1
	Moderately improved	1
	Stable	8
Total		16

2.3 *Visual Acuity*

9 patients had visual acuity problems related to the target aneurysm at baseline and 3 patients had visual acuity problems unrelated to the target aneurysm (**Table 8**). At 180 days (**Table 9**), 3 were markedly improved, 3 were somewhat improved, 1 was somewhat worse [redacted], described above) and 1 was markedly worse ([redacted] cilioretinal artery occlusion). Amongst the 9 patients with baseline visual acuity abnormalities related to the target aneurysm, 3 were markedly improved, 2 were somewhat improved and 4 were about the same (**Table 10**).

Table 8. Ipsilateral visual acuity at baseline.

Baseline status	N (%)
Abnormal, related	9 (9.2%)
Abnormal, unrelated	3 (3.1%)
Normal	86 (87.8%)
Total	98 (100%)

Table 9. Change in ipsilateral visual acuity at 180 days.

Status at 180 days	N (%)
Markedly improved	3 (3.1%)
Somewhat improved	3 (3.1%)
About same	90 (91.8%)
Somewhat worse	1 (1.0%)
Markedly worse	1 (1.0%)
Total	98 (100%)

Table 10. Visual acuity at 180 days among patients with abnormal function at baseline.

Baseline Abnormality	180 Day Status	N
Abnormal, related	Markedly improved	3
	Somewhat improved	2
	About same	4
Abnormal, unrelated	About same	3
Total		12

2.4 Pupil Function

16 patients had ipsilateral pupil dysfunction (APD) related to the target aneurysm (**Table 11**). Of these, 2 showed complete resolution and 2 showed moderate improvement. One patient [redacted]), whose baseline function was normal, had cilioretinal artery embolism on POD #1, which caused optic atrophy and pupil dysfunction.

Table 11. Pupil function at baseline.

APD	N (%)
Absent	81 (82.7%)
Present, related to aneurysm	16 (16.3%)
Present, unrelated to aneurysm	1 (1.0%)
Total	98 (100%)

Table 12. Pupil function at 180 days.

APD	N (%)
Complete resolution	2 (2%)
Moderate improvement	2 (2%)
Stable	93 (94.9%)
Somewhat worse	1 (1%)
Total	98 (100%)

Table 13. Pupil function at 180 days among patients with abnormal function at baseline.

Baseline Abnormality	180-Day Status	N
Present, related	Complete resolution	2
	Moderate improvement	2
	Stable	12
Present, unrelated	Stable	1
Total		17

2.5 *Ipsilateral Ocular Motion Problem*

At baseline, ocular motion problems related to the target aneurysm were common, with 15 having CN3 abnormalities, 1 having CN4 abnormalities, and 20 having CN6 abnormalities (**Table 14**). Two patients had complete resolution or marked improvement of CN3 abnormalities and 7 patients had complete resolution or marked improvement of CN6 abnormalities (**Table 16**). 1 patient had worsened CN4 function ([redacted]) and 3 patients had worsened CN6 function at 180 days. Patient [redacted] had bilateral aneurysms. The 3 with worsened function [redacted] had normal exams at baseline.

Table 14. Baseline ipsilateral oculomotor problem and relationship to target aneurysm.

Oculomotor status at baseline	CN 3	CN4	CN6
Abnormal, related	15 (15.3%)	1 (1%)	20 (20.4%)
Abnormal, not related	0 (0%)	0 (0%)	1 (1%)
Normal	83 (84.7%)	97 (99%)	77 (78.6%)
Total	98 (100%)	98 (100%)	98 (100%)

Table 15. Overall change in ipsilateral oculomotor function at 180 days.

180-Day Status	CN 3	CN4	CN6
Complete resolution	1 (1%)	0	5 (5.1%)
Highly improved	1 (1%)	0	2 (2.0%)
Mod improved	6 (6.1%)	0	8 (8.2%)
Stable	90 (91.8%)	97 (99%)	80 (81.6%)
Somewhat worse	0	1 (1%)	3 (3.1%)
Markedly worse	0	0	0
Total	98 (100%)	98 (100%)	98 (100%)

Of 15 patients with baseline abnormalities of CN 3 related to the target aneurysm, 8 improved and 7 were stable (**Table 16**). Of 20 patients with baseline abnormalities of CN 6 function related to the target aneurysm, 5 were completely resolved at 180 days, 2 were highly improved, 7 were moderately improved, and 6 were stable (**Table 18**). One patient with CN6 abnormality not related to the target aneurysm also showed improvement ([redacted]). This patient had a history of strabismus surgery as a child.

Table 16. Change in CN 3 function among patients with baseline abnormality.

Abnormality at Baseline	Change at 180 days	N
Related	Complete resolution	1
	Highly improved	1
	Moderately improved	6
	Stable	7
Total		15

Table 17. Change in CN 4 function among patients with baseline abnormality.

Abnormality at Baseline	Change at 180 days	N
Abnormal, related	Stable	1

Table 18. Change in CN 6 function among patients with baseline abnormality.

Abnormality at Baseline	Change at 180 days	N
Abnormal, related	Complete resolution	5
	Highly improved	2
	Moderately improved	7
	Stable	6
Abnormal, unrelated	Moderately improved	1
Total		21

2.6 Facial Sensation

3 patients had abnormal facial sensation thought to be related to the target aneurysm (**Table 19**). Of these, 1 patient ([redacted]) had complete resolution of the facial sensation abnormality (**Table 21**).

Table 19. Ipsilateral facial sensation at baseline.

Baseline status	N (%)
Abnormal, related	3 (3.1%)
Normal	95 (96.9%)
Total	98 (100%)

Table 20. Change in ipsilateral facial sensation at 180 days.

Status at 180 days	N (%)
Complete resolution	1 (1%)
Stable	97 (99%)
Total	98 (100%)

Table 21. Facial sensation at 180 days among patients with abnormal function at baseline.

Baseline Abnormality	180 Day Status	N
Abnormal, related	Complete resolution	1
	Stable	2
Total		3

3 Summary

Compliance of patients to study-required baseline and 180-day ophthalmologic examinations was good. Of 104 patients who were enrolled and treated with PED and potentially available for 180-day follow-up, only 6 (5.8%) subjects did not have the long-term ophthalmologic follow-up visit.

Table 22 summarizes outcomes among patients with a neuro-ophthalmologic deficit related to the target aneurysm. In most categories, the preponderance of outcomes showed improvements. However, a small number of patients worsened, as summarized in **Table 23**.

Table 22. Outcomes among patients with baseline abnormality in neuro-ophthalmologic function related to the target aneurysm.

Neuro-Opthhalmologic Deficit Related to Aneurysm	Outcome
Visual field	2 improved, 3 stable
Visual acuity	5 improved, 4 same
Pupil function	2 complete resolution, 2 improved, 12 stable
Ocular motion, CN 3	1 complete resolution, 7 improved, 7 stable
Ocular motion, CN 4	1 stable
Ocular motion, CN 6	5 complete resolution, 9 improved, 6 stable
Facial sensation	1 complete resolution, 2 stable

Table 23. Patients with worsened neuro-ophthalmologic status at 180 days.

Patient ID	180-Day Outcome
[redacted]	Worsened VF, unknown cause
	Worsened VF, VA, pupil function due to cilioretinal artery occlusion
	New CN 4 neuropathy
	New CN 6 neuropathy
	New CN 6 neuropathy
	New CN 6 neuropathy

Appendix 1 – Case Report Form

The next pages show:

1. A completed case report form. Dr. Fouladvand used this CRF for each PUFS subject.
2. Sample eye exam worksheet completed by the site ophthalmologist.

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EXPERT REVIEW OF NEURO-OPHTHALMOLOGIC EXAMINATION

Patient name code: [redacted]

VISUAL FIELDS		
Ipsilateral	At baseline, visual fields **ipsilateral** to target aneurysm were:	AR (use code 1a)
	Compared to baseline, at 180 days visual fields **ipsilateral** to aneurysm were:	MI (use code 2)
Contralateral	At baseline, visual fields **contralateral** to target aneurysm were:	N (use code 1a)
	Compared to baseline, at 180 days visual fields **contralateral** to aneurysm were:	S (use code 2)
Comments:		

OCULAR MOTION AND ALIGNMENT		
At baseline, ocular motion ipsilateral to aneurysm was:	III – oculomotor: IV – trochlear: VI – abducens: (use code 1a)	AR N N
Compared to baseline, at 180 days ocular motion ipsilateral to aneurysm was:	III – oculomotor: IV – trochlear: VI – abducens: (use code 2)	S S S
Comments:		

PUPIL FUNCTION	
At baseline, ipsilateral APD was:	PR (use code 1b)
Compared to baseline, at 180 days ipsilateral APD was:	S (use code 2)
Comments:	

VISUAL ACUITY	
At baseline, visual acuity ipsilateral to aneurysm was:	N (use code 1a)
Compared to baseline, at 180 days visual acuity ipsilateral to aneurysm was:	AS (use code 3)
Comments:	

SENSORY	
At baseline, sensory component of ipsilateral trigeminal nerve was	N (use code 1a)
Compared to baseline, at 180 days sensory component of ipsilateral trigeminal nerve was:	S (use code 2)
Comments:	

Signed: [redacted]

Date evaluated: 6-1-10

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BASELINE VISUAL EXAMINATION

Site #: 0 0 4 Pt. Sequence #: 0 0 1 Name Code: [redacted]

This examination is performed by an ophthalmologist.

Date of visual examination	11/25/2008 (dd/mon/yyyy)
Last name of ophthalmologist	

Information to be collected below includes:

1. Fundus photograph
2. Visual acuity
3. Pupillary reflexes
4. Corneal reflex
5. Eye movement
6. Eye alignment
7. Visual fields
8. Summary of cranial nerve function

FUNDUS PHOTOGRAPH

At baseline only, take a fundus photograph and keep it in the patient's chart.

	OD	OS
Fundus photograph	● (1) Photo taken ○ (2) Photo not taken ○ (3) Photo not possible, Reason:	● (1) Photo taken ○ (2) Photo not taken ○ (3) Photo not possible, Reason:

BEST CORRECTED VISUAL ACUITY AT 20 FEET

Measure visual acuity with Snellen Chart. If patient wears glasses, ask patient to wear glasses during the assessment.

Note: If not done at 20 feet, indicate distance: _____ feet

	OD	OS
VA ● (1) SC ○ (2) CC	20/25 **If VA worse than 20/800:** ○ (1) CF at ____ ft ○ (2) HM ○ (3) LP ○ (4) NLP	20/30 **If VA worse than 20/800:** ○ (1) CF at ____ ft ○ (2) HM ○ (3) LP ○ (4) NLP
Ph	20/25 +1	20/25 +1
Near	20/20-1	20/20-1

+2.00

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BASELINE VISUAL EXAMINATION

Site #: 0 0 4 Pt. Sequence #: 0 0 1 Name Code: [redacted]

PUPIL FUNCTION

Complete pupil function examination before any use of eye dilation.

	OD		OS	
PUPILLARY REACTIONS	Yes	No	Yes	No
Reactive to light	●	○	●	○
Reactive to accommodation	●	○	●	○
Relative afferent pupillary defect (APD)?	○	●	●	○
Other significant pupillary findings?	○	●	○	●

If pupil exam abnormal, describe findings below.

OD	OS
Pupillary findings:	Pupillary findings:
nl	(L) trace APD (very sign APD)

CORNEAL SENSATION

Use cotton-tipped swab to test corneal blink reflex.

	OD		OS	
	Normal	Abnormal	Normal	Abnormal
Corneal blink reflex	●	○	●	○

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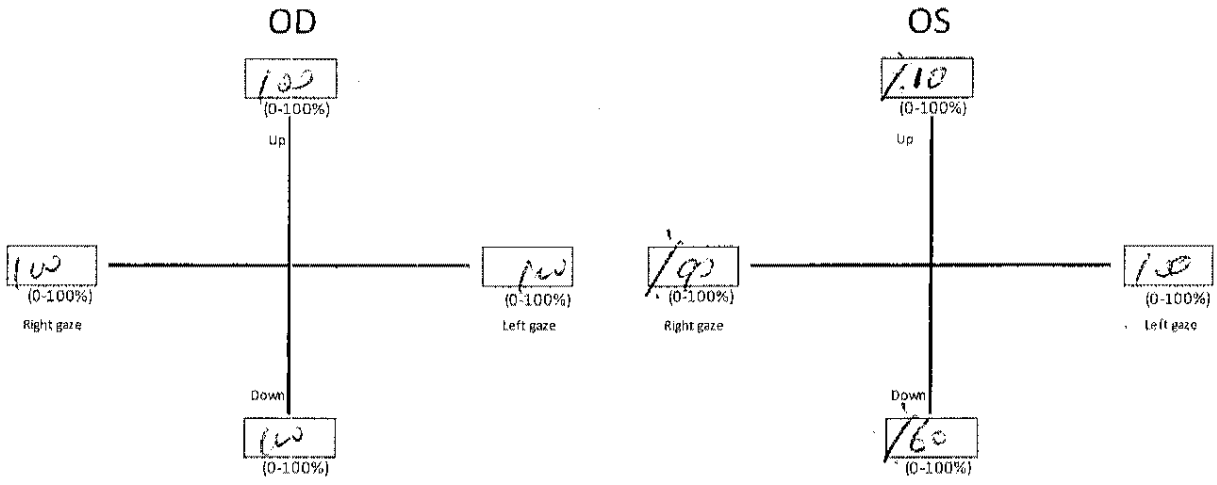
BASELINE VISUAL EXAMINATION

Site #: 0 0 4 Pt. Sequence #: 0 0 1 Name Code: [redacted]

EYE MOVEMENT

Rate eye movement on a 0-100% scale (in increments of 10%) for both eyes during right, left, upward and downward gaze.



NOTES:

hx pseudo-ptosis - observed regression of
(L) palpebral fissure during down gaze
in attempt to down gaze (R) eyelid get wider.

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BASELINE VISUAL EXAMINATION

Site #: 0 0 4 Pt. Sequence #: 0 0 1 Name Code: [redacted]

EYE ALIGNMENT: ALTERNATING COVER-UNCOVER TEST

Use the alternating cover-uncover test to assess eye alignment. Report number of **prism diopters required to correct vision** during center, left and right gazes. Fill in the box with a value for prism diopters and circle the relative alignment.

For example: 15 Δ X/XT E/ET

upgaze 12Δ D (L) hypertropia

Right gaze	Primary gaze	Left gaze
40 Δ X/XT 40 D XT Eso E/ET	0 Δ X/XT E/ET	0 Δ X/XT E/ET
2 D Δ H/HT	0 Δ H/HT	0 Δ H/HT

downgaze 6ΔD (L) hypertropia

Evidence of 4th nerve palsy?	(2) No (1) Yes If right 4th nerve palsy: Right head tilt: Δ HT Left head tilt: Δ HT

NOTES:
pt has limitation of (L) eye in supraduction & infraduction & also mild adduction deficit (for partial third nerve palsy) ptosis, has abnormal regeneration of (L) eyelid

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BASELINE VISUAL EXAMINATION

Site #: 0 0 4 Pt. Sequence #: 0 0 1 Name Code: [redacted]

VISUAL FIELD ANALYSIS

Use the Humphrey 24-2 Visual Field Analyzer to measure visual fields. Submit complete VFA output to the study Sponsor. Report only summary values here.

OD		Interpretation
Mean deviation index	-1.61 dB	Visual Field? ☐ (1) Normal ☐ (2) Abnormal ↓ ***Explain:*** _____
Pattern standard deviation	1.55 dB	
Foveal sensitivity	____ dB	
OS		
Mean deviation index	-3.41 dB	Visual Field? ☐ (1) Normal ☐ (2) Abnormal ↓ ***Explain:*** _____
Pattern standard deviation	9.99 dB	
Foveal sensitivity	____ dB	

NOTES:

hx wedge shape in [illegible] defl

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BASELINE VISUAL EXAMINATION

Site #: 004 Pt. Sequence #: 001 Name Code: [redacted]

SUMMARY OF EYE CRANIAL NERVE FUNCTION

Enter your summary of cranial nerve function regarding the eye. If any nerve function is abnormal, assess relatedness to target IA.

	OD			OS			
Cranial nerve	Normal	Abnormal	Related to target IA?	Normal	Abnormal	Related to target IA?	Comments (optional)
II – optic	●	○	○Unrel ○Unlik ○Poss ○Prob ○Defin	○	●	○Unrel ○Unlik ○Poss ○Prob ●Defin	mild (+) RAPD, Inferotemporal field defect optic disc pallor
III – oculomotor	●	○	○Unrel ○Unlik ○Poss ○Prob ○Defin	○	●	○Unrel ○Unlik ○Poss ○Prob ●Defin	partial third n palsy. chronic regeneration
IV – trochlear	●	○	○Unrel ○Unlik ○Poss ○Prob ○Defin	●	○	○Unrel ○Unlik ○Poss ○Prob ○Defin	
V – trigeminal	●	○	○Unrel ○Unlik ○Poss ○Prob ○Defin	●	○	○Unrel ○Unlik ○Poss ○Prob ○Defin	
VI - abducens	●	○	○Unrel ○Unlik ○Poss ○Prob ○Defin	●	○	○Unrel ○Unlik ○Poss ○Prob ○Defin	

Unrel	Unrelated to target IA
Unlik	Unlikely to be related to target IA
Poss	Possibly related to target IA
Prob	Probably related to target IA
Def	Definitely related to target IA

EXAM COMPLETED BY: [redacted] 11/25/08

SIGNATURE DATE

Chestnut Medical

DAY 180 VISUAL EXAMINATION

Site #: 1 0 4 Pt. Sequence #: 0 0 1 Name Code: [redacted]

Date of visual examination	6/15/09 (dd/mon/yyyy)
Last name of ophthalmologist	Foulderond

Information to be collected below includes:

1. Visual acuity
2. Pupillary reflexes
3. Corneal reflex
4. Eye movement
5. Eye alignment
6. Visual fields
7. Summary of cranial nerve function

BEST CORRECTED VISUAL ACUITY AT 20 FEET

Measure visual acuity with Snellen Chart. If patient wears glasses, ask patient to wear glasses during the assessment.

Note: If not done at 20 feet, indicate distance: _____ feet

	OD	OS
VA ⊗ (1) SC ○ (2) CC	20/25 **If VA worse than 20/800:** ○ (1) CF at ____ ft ○ (2) HM ○ (3) LP ○ (4) NLP	20/20-2 **If VA worse than 20/800:** ○ (1) CF at ____ ft ○ (2) HM ○ (3) LP ○ (4) NLP
Ph	____/____	____/____
Near	20/25	20/20
If visual acuity can be measured quantitatively, what is the change in VA from baseline?	○ (1) VA within two lines of baseline ○ (2) VA improved by 2 or more lines ○ (3) VA worsened by 2 or more lines	● (1) VA within two lines of baseline ○ (2) VA improved by 2 or more lines ○ (3) VA worsened by 2 or more lines
If VA can be measured only by CF, HM, LP or NLP, what is change in category from baseline?	○ (1) Same as baseline ○ (2) VA improved by 1 or more categories ○ (3) VA worsened by 1 or more categories	○ (1) Same as baseline ○ (2) VA improved by 1 or more categories ○ (3) VA worsened by 1 or more categories

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DAY 180 VISUAL EXAMINATION

Site #: 0 0 4 Pt. Sequence #: 0 0 1 Name Code [redacted]

PUPIL FUNCTION

Complete pupil function examination before any use of eye dilation.

	OD			OS		
PUPILLARY REACTIONS	Yes	No	Abnormal pupillary findings:	Yes	No	Abnormal pupillary findings:
Reactive to light	●	○		●	○	
Reactive to accommodation	●	○		●	○	
Relative afferent pupillary defect (APD)?	○	●		●	○	R APD + (B) #70
Change in pupillary reactions from baseline?	● Same ○ Better ○ Worse			● Same ○ Better ○ Worse		
Describe changes from baseline	no change			no chang		

CORNEAL SENSATION

Use cotton-tipped swab to test corneal blink reflex.

	OD		OS	
	Normal	Abnormal	Normal	Abnormal
Corneal blink reflex	●	○	●	○
Change from baseline	● Same ○ Better ○ Worse		● Same ○ Better ○ Worse	

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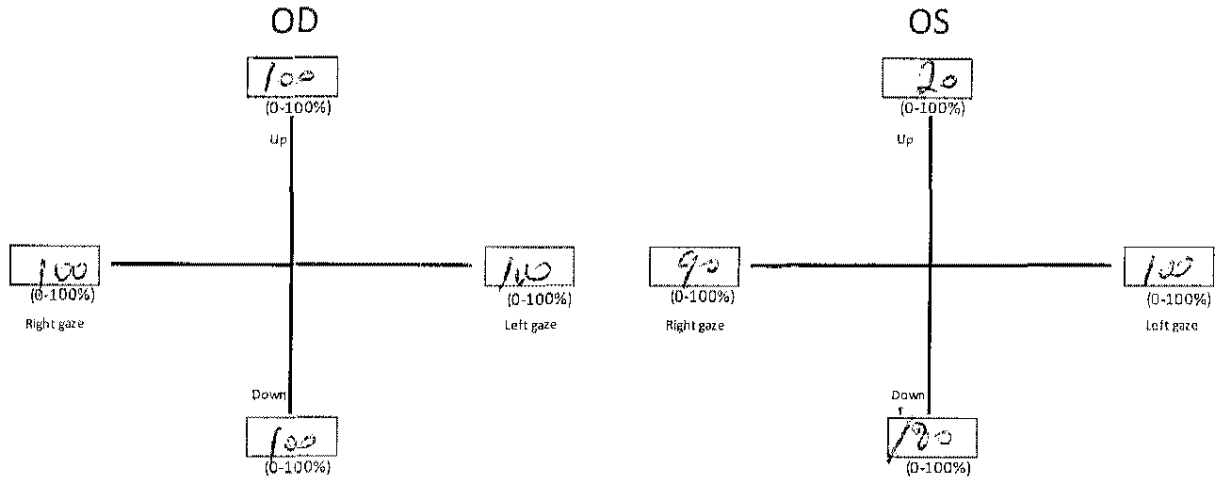
DAY 180 VISUAL EXAMINATION

Site #: 0 0 4 Pt. Sequence #: 0 0 1 Name Code: [redacted]

EYE MOVEMENT

Rate eye movement on a 0-100% scale (in increments of 10%) for both eyes during right, left, upward and downward gaze.



Compare eye movement to baseline function.

	OD	OS
	Change	Change
Compared to baseline, eye movement is:	☒ Same ○ Better ○ Worse	○ Same ☒ Better ○ Worse
If changed from baseline, describe:		slightly better in down gaze

NOTES:

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DAY 180 VISUAL EXAMINATION

Site #: 004 Pt. Sequence #: 001 Name Code: [redacted]

EYE ALIGNMENT: ALTERNATING COVER-UNCOVER TEST

Use the alternating cover-uncover test to assess eye alignment. Report number of **prism diopters required to correct vision** during center, left and right gazes. Fill in the box with a value for prism diopters and circle the relative alignment.

For example: 15Δ X/XT E/ET

	14Δ (2) hypo	
Right gaze	**Primary gaze**	**Left gaze**
4Δ X/XT Eot E/ET	0 Δ X/XT E/ET	0 Δ X/XT E/ET
2 Δ H/HT hypo	0 Δ H/HT	0 Δ H/HT
	4Δ (2) hyper	

still has (R) abducent regeneration of (2) rectus Right

Evidence of 4th nerve palsy?	☒ (2) No ○ (1) Yes If right 4th nerve palsy: Right head tilt: [ ] Δ HT Left head tilt: [ ] Δ HT

Compare eye alignment to baseline.

	Change
Compared to baseline, eye alignment is:	☒ Same ○ Better ○ Worse
If changed from baseline, describe:	not significant change

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DAY 180 VISUAL EXAMINATION

Site #: 004 Pt. Sequence #: 001 Name Code: [redacted]

VISUAL FIELD ANALYSIS

Use the Humphrey 24-2 Visual Field Analyzer to measure visual fields. Submit complete VFA output to the study Sponsor. Report only summary values here.

OD		Interpretation
Mean deviation index	-2.51 dB	Clinically significant change from baseline?
Pattern standard deviation	2.70 dB	☒ (1) Field same as baseline
Foveal sensitivity	____ dB	○ (2) Field improved from baseline
		○ (3) Field worsened from baseline
OS		
Mean deviation index	-0.18 dB	Clinically significant change from baseline?
Pattern standard deviation	1.52 dB	○ (1) Field same as baseline
Foveal sensitivity	____ dB	☒ (2) Field improved from baseline
		○ (3) Field worsened from baseline

NOTES:

Improvement of Infero temporal field
(↓ mal field defect

Chestnut Medical

DAY 180 VISUAL EXAMINATION

Site #: 004 Pt. Sequence #: 001 Name Code: [redacted]

SUMMARY OF EYE CRANIAL NERVE FUNCTION

Enter your summary of cranial nerve function regarding the eye and compare eye function to baseline. Explain any changes.

Cranial nerve	Function						
	OD			OS			
	Normal	Abnormal	Change	Normal	Abnormal	Change	Explain
II – optic	☒	○	☒ (1) Same ○ (2) Better ○ (3) Worse	○	☒	○ (1) Same ☒ (2) Better ○ (3) Worse	Improved temporal defect + VA
III – oculomotor	☒	○	☒ (1) Same ○ (2) Better ○ (3) Worse	○	☒	☒ (1) Same ○ (2) Better ○ (3) Worse	almost the same ↑ in inferior field
IV – trochlear	☒	○	○ (1) Same ○ (2) Better ○ (3) Worse	☒	○	○ (1) Same ○ (2) Better ○ (3) Worse	
V – trigeminal	☒	○	○ (1) Same ○ (2) Better ○ (3) Worse	☒	○	○ (1) Same ○ (2) Better ○ (3) Worse	
VI - abducens	☒	○	○ (1) Same ○ (2) Better ○ (3) Worse	☒	○	○ (1) Same ○ (2) Better ○ (3) Worse	

EXAM COMPLETED BY: [redacted]
SIGNATURE

06/18/07
DATE

Appendix 3. Adverse Event Description for Subject [redacted]

The following pages show excerpts from the original PMA describing subject [redacted] and her adverse event after coiling.

over the wire. The three longest procedures (295, 340 and 427 minutes) were in large or giant aneurysms that circumferentially encompassed most or all of the parent artery; these cases required substantial maneuvers to catheterize the parent artery distal to the target IA. Fluoroscopy time averaged 48.4 minutes (range 8 – 205.6). Although a direct comparison to coil embolization is not possible, Investigators noted that procedure/fluoroscopy times with PED were shorter than what they would typically expect in those cases in which IAs could potentially be treated with coils.

Table 12-14. Procedure and fluoroscopy time information.

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

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

12.5.4.1 PED Use

108 patients were enrolled and underwent attempted PED placement. PED was placed successfully in 107 (99.0%) patients. In one patient ([redacted]), the parent artery distal to the IA could not be catheterized and the Pipeline procedure was abandoned; the patient was treated with additional coils and had safety follow-up only. In the 107 patients in which PED was placed, 364 PEDs were used (**Table 12-15**). 2 patients underwent treatment of both the target IA and a contralateral IA; in these 2 patients, 8 additional PEDs were used for the contralateral IA. In total, 341 devices were implanted in the target IA in 107 patients. PEDs of all currently manufactured lengths were used (**Table 12-16**). On average, patients in PUFS had 3.1 PEDs placed per target IA (median 3, range 1-13, see **Table 12-17**).

Table 12-15. PED placement by target and device disposition.

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

*Described in **Section 12.5.4.2**.

510(k) marketing clearance in August 2009. Marksman received CE Mark (marketing clearance in EU) in August 2009. Investigators who used Marksman noted that Pipeline delivery was easier with Marksman than with other catheters. As noted above, PED delivery problems occurred occasionally with Renegade Hi-Flo but not with Marksman.

12.5.4.8 Other Device Use

Twenty-seven angioplasty balloons were used during 23 cases. Use of other devices was not a protocol deviation. Angioplasty balloons were used in all 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), and Sprinter (Medtronic, 2). 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 patient [redacted], overinflation of an angioplasty balloon just proximal to PED resulted in a small carotid tear causing carotid cavernous fistula. Two additional PEDs were placed over the CCF. The patient had mild postoperative confusion and right-sided drift that resolved over a few days. Postoperative CT scan showed a small subarachnoid hemorrhage as well as intraventricular hemorrhage. Repeat angiogram on postoperative day 1 showed that the CCF had resolved and the patient was discharged from the hospital a few days later.

12.5.4.9 Neck Coverage

The neck of the aneurysm was deemed to be covered by the investigator in all cases but 2 (1.9%). In 1 case [redacted]), PED could not be used because the physician could not pass the guidewire into the parent artery distal to the IA. The guidewire repeatedly became tangled in the coil-containing aneurysm fundus. PED placement was abandoned and the patient was treated with additional coils. In the other case ([redacted]I), the physician lost access to the parent artery distal to the aneurysm after placement of the first PED due to user error. The case was terminated after placement of only a single PED; the case was finished successfully in a subsequent procedure two weeks later, resulting in full coverage of the neck.

In one additional patient [redacted]), at the time of the procedure the investigator noted that the entire neck of the fusiform IA was covered with PED. However, review by the core laboratory suggested that the PED construct probably did not extend proximally enough to achieve complete neck coverage. Lack of coverage of the entire neck of this very long fusiform IA may have caused “endoleak”, which may explain why the IA was not completely occluded at 180 days. The patient underwent successful re-treatment on April 29, 2010 with placement of additional PEDs; follow-up angiography will be performed in 6-12 months.

12.5.4.10 Unwanted Thrombus

Unwanted thrombus on the end of the PED delivery wire was not seen in any case.

12.5.4.11 Non-Target Aneurysms

A non-target IA was treated in 5 cases as a protocol deviation. In 3 cases ([redacted], the patient had an additional IA that the investigator believed required simultaneous treatment; 2 were treated with PED and 1 with coils. In 1 case (P[redacted]), the patient had an IA that was located about 5 mm proximal to the target IA; PED was used to cover both the target IA and the more proximal IA. In 1 case ([redacted]), a contralateral IA that qualified for PUFS was treated 180 days after the initial IA was treated. All non-target IAs treated with PED were fully occluded at 180 days. Details regarding non-target IAs are provided in **Appendix 9**.

12.5.5 Clinical Follow-Up

Patient flow in PUFS was excellent and is described graphically in **Figure 12-4**. Patients who were lost to follow-up or withdrew are described in more detail in **Appendix 10**. In summary:

- Three patients were enrolled but did not undergo PED placement (see **Section 12.5.2**).
- 3 patients died during the first month after the procedure (see **Section 12.5.7**).
- One patient's [redacted] parent artery could not be catheterized distal to the target IA; this patient did not undergo PED placement but rather underwent repacking of the IA with coils. As per the protocol, she was deemed a "safety follow-up" patient only.
- One patient [redacted]) refused to attend the 30-day visit and subsequently withdrew from the study. She had normal neurologic status at last contact.
- One patient [redacted]) stopped actively participating in the study at approximately day 30, due primarily to social reasons (see **Table 17-7**, p. 132). She had two "house calls" from a study site physician in her home town in rural Northern Wisconsin, approximately 1,000 miles from the study center, primarily to assess safety outcomes. She was judged to have had a major stroke by the CEC, probably due to antiplatelet medication non-compliance.
- One patient [redacted] became lost to follow-up after the Day 30 visit when she moved and stopped responding to communication from the study center.
- One subject [redacted]) refused to participate further in the study after the 90-day phone call and did not undergo 180-day angiogram. By telephone follow-up with the patient, there were no obvious new neurologic problems.

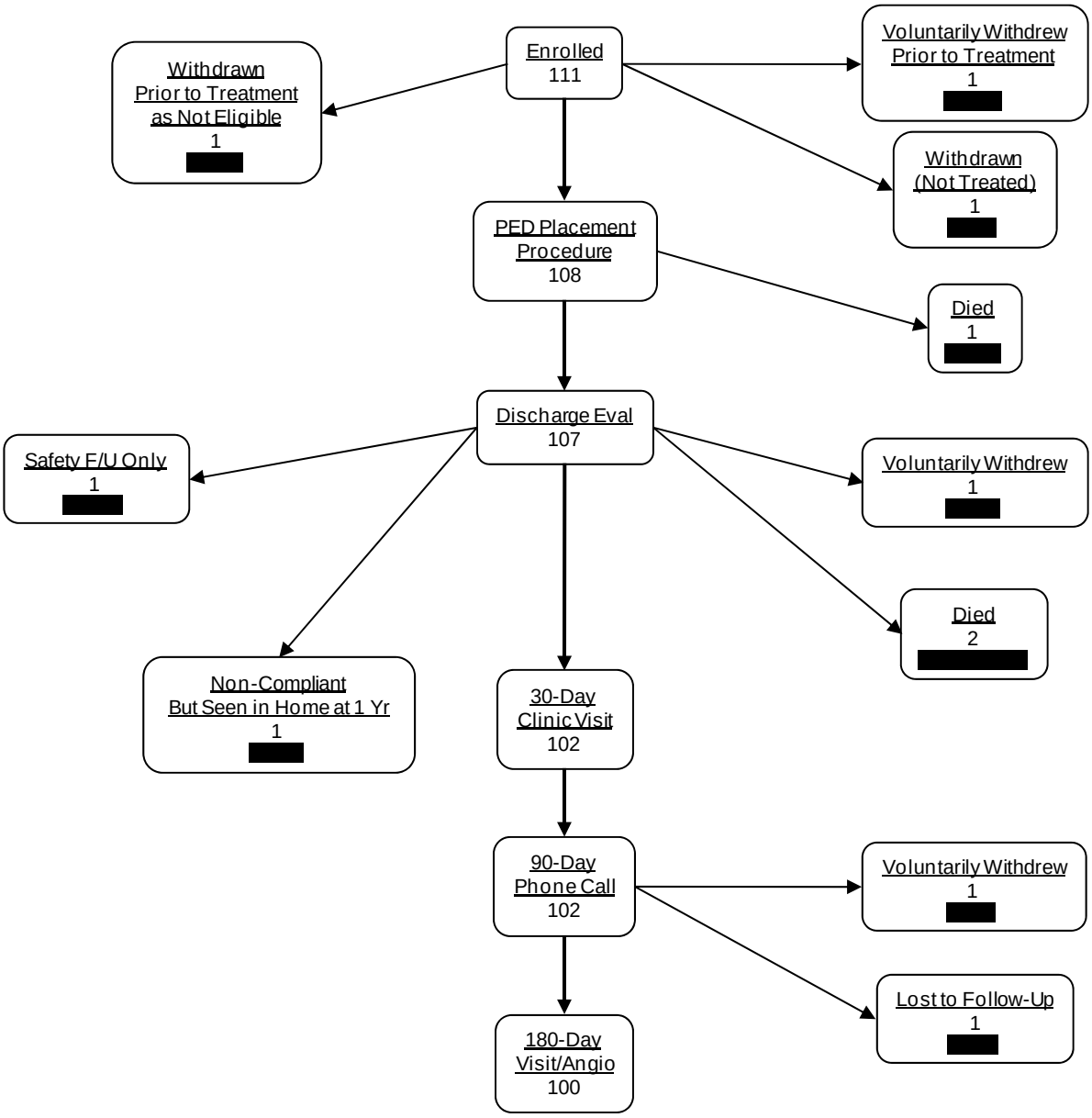

Figure 12-4. Patient flow in PUFS. Values in parentheses are patient name codes.

Table 12-19. Exclusions from effectiveness analysis.

Patient ID	Description	Status at 180 Days
[redacted]	The incorrect location of the patient's target IA was previously described.* Additionally, the patient had a previously unidentified Neuroform stent in place in the target aneurysm (exclusion criterion "i").	IA not occluded No SAE
	The investigator assured the Sponsor that the treated aneurysm was in the petrous segment of the internal carotid and the case proceeded. However, the aneurysm location was confirmed by the core laboratory to be in the cervical, not intracranial, portion of the carotid. Therefore, this case was excluded from the effectiveness cohort as it did not meet inclusion criteria "b1".	IA occluded* No SAE
	Patient's IA qualified for a prior revision of the PUFS protocol (revision B) but was not large enough to qualify for revision C (which required IA size to be ≥10 mm).	IA occluded* Minor stroke postoperatively (See **Section 12.5.11.1**)
	The investigator could not pass the micro-guidewire into the parent artery distal to the aneurysm. No PED was opened during this case. As per **Section 3.20.2** of the Clinical Protocol, this case was withdrawn from the effectiveness cohort.	Treated with coils Safety follow-up only SAE potentially related to placement of Cerecyte coils

met criteria for effectiveness success if included in analysis

Two additional IAs were included in the effectiveness cohort, bringing the total number of IAs treated with PED and included in the effectiveness analysis to 106. One patient [redacted]) underwent placement of PED in a single target aneurysm. At the 180-day visit, after angiogram of the target aneurysm was performed, she underwent treatment of a mirror-like contralateral IA whose size/shape characteristics qualified for PUFS (size 12.2 mm, neck 8.1 mm, dome 11.2 mm). A second patient [redacted]) had a qualifying contralateral IA (size 10.2 mm, neck 5.0 mm) that was treated simultaneously with treatment of the target IA.

An additional patient ([redacted]) underwent PED treatment of a previously treated contralateral IA simultaneous with treatment of the target IA, but the contralateral IA was not included in the effectiveness cohort. The contralateral IA had been previously treated with SILK (a permanent neurovascular implant manufactured by Balt, France, and available commercially in Europe and Turkey) but the IA had remained incompletely occluded. The physician believed it was in the best interest of the patient to undergo bilateral

* This case was described in detail in [redacted]) in response to FDA's comments regarding the [redacted] annual report. The patient presented in 2005 with SAH. Angiography showed multiple IAs. The left Pcomm IA was suspected as the source and it was embolized with coils. In a subsequent procedure, a small IA arising at the level of the anterior choroidal (distal to the Pcomm) was treated with stent-assisted coiling (Neuroform). Subsequently the patient had surgical clipping of both Acomm and right Pcomm IAs. The patient was referred to the site because of IA recurrence at the hypophyseal segment of the left ICA. Films available at referral were taken after the initial coiling but before the subsequent treatment with Neuroform. The correct location of the target aneurysm (Pcomm, which segment is immediately adjacent to the superior hypophyseal segment, a location allowed in PUFS), as well as its coverage by the proximal crowns of the implanted Neuroform stent, was established only at the time of PED. Given the patient's history of previous SAH, multiple IAs, and target IA recurrence after coiling, the investigator decided that the benefits of Pipeline treatment outweighed the other options: 1) doing no procedure and leaving the aneurysm untreated, 2) retreating the patient with coil embolization in the face of demonstrated failure of previous coiling and stenting or 3) direct surgery, which would be complicated by the operative complexities arising from the presence of both aneurysm coils and the indwelling Neuroform stent. In a letter to the Sponsor ([redacted] FDA suggested that the case be excluded.

Reason Why Non-Success	Freq	Patient ID Numbers
Coils used in fundus. Target IA was completely occluded and there was no stenosis.	1	[redacted]
Carotid-cavernous fistula	1	[redacted]
Total	**28**	

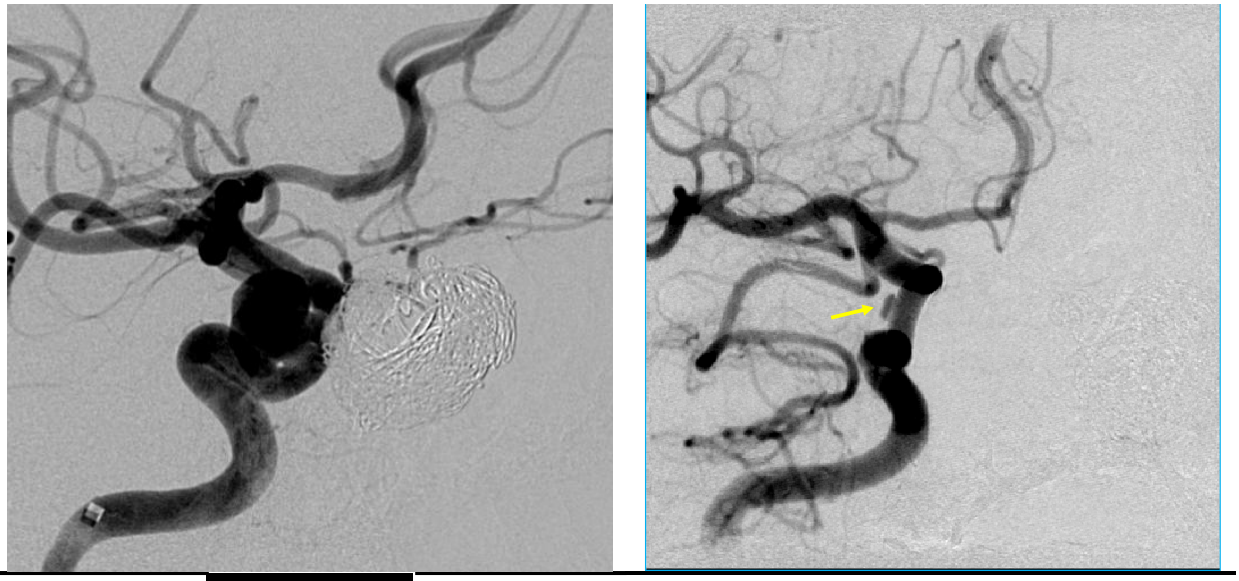

Figure 12-6. [redacted] Image at left shows angiogram prior to PED. (Coil mass is in the contralateral ICA.) Image at right shows angiogram at 180 days with tiny contrast residual.

12.5.6.1 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 IA occlusion and stenosis of ≤50% as adjudicated by the core radiology laboratory. Stenosis was judged according to the method of Samuels[26], which was used in the WASID study.[21] Two patients had stenosis (2/107, 1.9%). One case was symptomatic (stroke on postoperative day 62, see **Section 12.5.11.1**).

12.5.7 Primary Safety Endpoint Analysis

108 patients were enrolled and treated in PUFS. One patient ([redacted] 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 performed. The case was abandoned and the patient was re-treated with coils.[*] Therefore the safety cohort consists of 107 patients.

[*] The patient's target IA had been previously treated with coils and had recurred. Because the investigator could not place PED, he decided to fill the IA with more coils. Bioactive polymer-loaded Cerecyte coils (Micrus, San Jose, CA) were placed into the IA. Postoperatively, the patient

The primary safety endpoint (ipsilateral major stroke or neurologic death as adjudicated by the core laboratory) occurred in 6 patients (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.

Table 12-21 describes each event in detail. Four of the events occurred in the perioperative period before postoperative day (POD) 30, 1 occurred between POD 30 and POD 180 and 1 occurred at an unknown time. 3 events were ischemic, 2 were hemorrhagic and one was unknown. Extenuating circumstances were common in patients meeting the primary safety endpoint. Of the 3 patients with ischemic events, one ([redacted]) was not compliant with the study and with the required antiplatelet regimen, and one, who had stroke related to ipsilateral stenosis, showed stenosis of a contralateral IA treated with stent-coiling. Of the 2 patients with hemorrhagic events, one had a prolonged procedure due to an IA with a complex geometry requiring 13 PEDs [redacted]. The patient received tirofiban (Aggrastat, a glycoprotein IIb/IIIa inhibitor) postoperatively, which was probably directly related to the hemorrhage. The other patient [redacted]) had multiple risk factors for hemorrhage including: 1) hypertension with recent change in medication, 2) history of subarachnoid hemorrhage in same location 1 year earlier due to head trauma, 3) use of aspirin and clopidogrel as required by the protocol, 4) alcohol use,[27] and recent initiation of a selective serotonin reuptake inhibitor (sertraline HCl), which has been shown to reduce platelet serotonin content and increase bleeding time.[28, 29] In the remaining case ([redacted], adjudicated as probable neurologic death by the CEC, the patient had an extensive history of dilated cardiomyopathy, cardiac arrhythmia treated with an automated implantable cardiodefibrillator (AICD) and multiple medications for arrhythmia. The patient's death appeared typical for sudden cardiac death and treating physicians at the time of the event ordered neither a head CT nor a neurologist evaluation. Autopsy was refused. 3 of the events were considered probably or definitely PED-related.

Table 12-21. Description of events meeting primary safety endpoint.

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

developed fever and confusion. CT scan showed hydrocephalus unchanged from preoperative scans. The patient's confusion responded to lumbar puncture.

placement could notwas treated with Cerecyte coils, packing the

examination was incomplete. 24 patients (24%) had normal neurologic examinations at baseline and follow-up and had no symptoms related to the target IA (**Table 12-27**). 31 (31%) had neurologic signs associated with the target IA and showed improvement at 180 days compared to baseline. 3 (3%) improved due to unrelated reasons and 5 (5%) were possibly improved. 9 (9%) showed mixed findings (i.e., some aspects improved, some worsened), 19 (19%) showed no change, 8 (8%) were worse (in 2 cases unrelated to treatment of the target IA), and 1 (1%) showed unclear changes.

Table 12-26. Patients not included in analysis of change in neurologic signs/symptoms.

Comment	Freq	Patient ID
Dead	3	[redacted]
Voluntary withdrawal	3	
Not treated with PED	1	
Detailed eye exam not performed	1	

Table 12-27. Summary of changes in neurologic status.

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

Individual patients often had multiple cranial nerves affected simultaneously. **Table 12-28** lists the change in cranial nerve status for each relevant cranial nerve.[*] **Appendix 14** provides detailed per-patient descriptions of changes in neurologic function as well as changes in the function of individual cranial nerves. The number of subjects whose cranial nerves improved was larger than the number that worsened.

Table 12-28. Summary of neurologic changes among patients with abnormal function at baseline.

Cranial Nerve	N*	Improved	Possibly Improved	Same	Worsened	Worse but	Unclear

[*] IAs of the ICA are expected to affect only cranial nerves 2 through 6 because of the proximity of these nerves to the artery. No patient in PUFS had documented cranial neuropathy of the other cranial nerves.

Table 12-35. Timing of serious adverse events.

Event started at or during interval before…	N (%)
Procedure	1 (2.5%)
Post-procedure /prior to discharge	12 (30%)
30 day follow-up	8 (20%)
90 day follow-up	5 (12.5%)
180 day follow-up	7 (17.5%)
1 year follow-up	7 (17.5%)
Total	40 (100%)

Table 12-36. Relatedness of SAE to PED, PED placement procedure, use of antithrombotic medications and preexisting conditions as determined by CEC.

Relatedness per CEC	PED	PED Placement Procedure	Antithrombotic Meds	Preexisting Condition
Unrelated	14 (35%)	24 (60%)	28 (70%)	11 (27.5%)
Unlikely	2 (5%)	3 (7.5%)	1 (2.5%)	6 (15%)
Possibly	9 (22.5%)	5 (12.5%)	1 (2.5%)	8 (20%)
Probably	9 (22.5%)	2 (5%)	8 (20%)	11 (27.5%)
Definitely	6 (15%)	6 (15%)	2 (5%)	4 (10%)
Total	40 (100%)	40 (100%)	40 (100%)	40 (100%)

2 recently reported additional SAEs occurred in one patient that were reported recently, were not included in the tables above, and have not yet been evaluated by the CEC. As described previously, patient [redacted] did not undergo PED treatment because the parent artery could not be catheterized distal to the target IA. SAEs occurring in this patient are not relevant to the PED experience since she was not treated with PED. Instead she underwent additional coil packing of her IA. Post-coiling, the patient experienced postoperative confusion and fever. CT scan showed no change in IA-related hydrocephalus and both confusion and fever resolved after lumbar puncture. The patient was rehospitalized on POD 129 for a hypertensive crisis.

12.5.11.2 Non-Serious Adverse Events

One-hundred fifteen AEs not meeting the definition for SAE occurred in PUFS. Non-serious adverse events are shown in **Table 12-37**. **Table 12-38**, **Table 12-39** and **Table 12-40** 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 13 were probably or definitely related to an underlying condition. Most events resolved completely.

Missed visits. 6 patients had missed visits. 2 missed visits were in a patient who did not receive PED and had moved out of the country. This patient is in contact with the study site by telephone.

Other deviations. In 1 case ([redacted], previously described), coils were placed into the target IA to enable the investigator to catheterize the distal parent artery in order to place PED. Although the patient had an excellent angiographic result with complete IA occlusion in the absence of stenosis (**Appendix 12**), the protocol required that this case be classified as a treatment failure as the goal of the study was to evaluate the effectiveness of PED treatment alone (i.e. without the concomitant use of coils). In 1 case ([redacted]), the parent artery could not be catheterized distal to the target IA. The protocol disallowed crossover to a salvage procedure "on the table." However, the investigator decided that it was in the patient's best interest to undergo additional coiling of the target IA with polymer-coated coils. The patient experienced postoperative mild fever and confusion, possibly from increased mass effect of coiling of the target IA. The patient's confusion improved after lumbar puncture.

In summary, the number of major deviations was low. Minor deviations from the protocol did not interfere with interpretation of study results and did not affect the scientific validity of the study.

12.6 Discussion

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

12.6.1 Primary Effectiveness Endpoint Discussion

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

180-day complete occlusion of the target IA without major stenosis was selected as the primary effectiveness endpoint because incomplete IA occlusion predicts an elevated risk of target IA rupture.[4] A pre-study review of the literature showed that conventional endovascular treatment of large and giant IAs is associated with very low rates of long-term complete IA occlusion. This is not surprising as many large and giant IAs arise from dysplastic vessels with circumferential involvement of the artery and therefore cannot effectively be treated with coils