Appendix 4 – Emails in Response to FDA Questions

P100014 additional data contained in email responses from sponsor to FDA queries and referred to in FDA executive summary

Sent: Mon 11Oct2010 6:10 PM

Larry,

In our discussion (and in your email below), you asked for additional analyses of 1) learning curve, and 2) AEs by site. Those analyses are in the attached.

Also, I've added the p-values Pablo mentioned to our formal response document.

If you have any questions, please give me a call.

Danny

Attachment "Additional analyses for Larry"

Additional Analysis for Larry
October 11, 2010

Learning Curve

Cases performed by each primary operator were grouped by "tens" into the following categories:

- First 10 cases
- Second 10 cases
- Third 10 cases
- Etc.

Table 1 shows experience with PED in PUFS. Examples help to explain the table:

- Dr. Becske's first 10 procedures are shown in column 1. 1 case was removed from the effectiveness cohort, as previously described. His second 10 cases are in the second column. His third 10 cases are in the 3rd column.

- Dr. Cekirge's first 8 cases in PUFS contribute to the first column. (He has subsequently treated >80 patients outside of PUFS in Turkey, where PED is approved.)

- Dr. Fiorella was primary operator in 20 PUFS cases. His first 10 cases contribute to the first column. (One case was removed as it did not qualify.) His second 10 cases contribute to the second column, etc.

- Dr. Szikora had experience with PED in >20 cases prior to starting PUFS. Therefore his first PUFS cases were put into the third column.

Table 1. Operator experience in PUFS (effectiveness cohort).

Operator	1st 10	2nd 10	3rd 10	4th 10	Total
Becske	9	10	10	0	29
Cekirge	8	0	0	0	8
Fiorella	9	10	1	0	20
Geyik	1	0	0	0	1

Grobelny	1	0	0	0	1
Kallmes	6	0	0	0	6
Levy	5	0	0	0	5
Lopes	2	0	0	0	2
Moran	4	0	0	0	4
Saatci	6	0	0	0	6
Siddiqui	2	0	0	0	2
Szikora	0	0	10	5	15
Woo	4	0	0	0	4
Yavuz	3	0	0	0	3
Total	60	20	21	5	106

You can see that the analysis of "learning effect" in PUFS will be limited because:

1. The number of cases performed is relatively small
2. The number of investigators with >10 cases is even smaller

Table 2 shows the relationship between case experience and effectiveness success and safety failure. There is no obvious "uptick" in success rate or "downtick" in major stroke/death rate.

Table 2. Relationship of operator experience to effectiveness and safety outcomes in PUFS.

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

*Cochran-Armitage trend test

Adverse Events by Site

You also requested an analysis of adverse events (AEs) by site. **Table 3** shows the number of patients with serious adverse events (SAEs) by site and **Table 4** shows the number of patients with AEs by site. There was no difference in the proportion of subjects with SAEs across sites (chi-squared exact p-value 0.1049). The proportion of subjects with AEs across sites shows statistically significant variation (p-value 0.0165).

Table 3. Patients with SAEs by site.

siteID	Num with SAE / Num at Site
1	0/3
2	2/5
4	8/29
5	6/20
8	5/7
9	0/4
10	2/14
12	4/18
13	0/1

15	0/6
Total	27/107

Table 4. Patients with AEs by site.

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

Our conclusions are:

1. The proportion of subjects with SAEs did not vary across sites.

2. The proportion of subjects with adverse events varied across sites, with lower proportions in Budapest and Turkey. The low p-value appears to be driven by events in Turkey; an analysis excluding the Turkey site showed a p-value of 0.3087. The lower proportion of events in Budapest and Turkey could be for the following reasons:

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

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

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

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Sent: Thu 12/2/2010 2:07 PM

Larry,

I thought it would be best to put my response into a Word document. Please review and let me know if you have any questions.

Danny

Attachment "Information for Larry 2010 1202

To: Larry Rodichok
From: Daniel Cher
Date: December 2, 2010
Re: Questions from FDA

Larry, I thought a Word document would be a better way for us to exchange information.

You wrote:

> *Please check Table 30 in the page 1943 in the response to deficiencies - Amendment 2*
>
> *There are 98 subjects with an occlusion rating at 180 days (N of 99) and 88 at 1 year (N of 89) - there seems to be one subject missing*
> *The numbers do add up for the percent stenosis assessment*
>
> *I believe that title of this table should be changed to "aneurysms" rather than "subjects" - or perhaps "subject aneurysms" would make sense.*

The numbers can be confusing, since we included 2 subjects [redacted] and [redacted] with contralateral qualifying aneurysms who were treated with PED. (In answer to your question, for the two subjects whose contralateral aneurysms were also treated with PED, in both subjects both aneurysms were effectiveness successes.) In addition, when I sent you this information, some of the cases had not yet been read by the core lab. All cases are now read but for one, which I received yesterday.

Table 30 below is updated. The table contains the two contralateral aneurysms mentioned above. This analysis is mostly at the subject level, but since it includes two contralateral aneurysms, one could also say it's at the aneurysm level. Since nearly all subjects had only one aneurysm treated, the difference is semantic. You are correct that the information in Amendment 2 was more up-to-date than in our 90-day update. The information below is even more up-to-date and can be considered nearly complete.

Table 30 ~~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~~91
Occlusion Ranking	Complete occlusion	81 (81.8%)	78~~5~~ (85.7~~4.3~~%)
	Residual neck	8 (8.1%)	~~4~~5 (~~4.5~~5.5%)
	Residual aneurysm	6 (6.1%)	~~4~~5 (~~4.5~~5.5%)
	Other	4* (4.0%)	3~~2~~** (3.3~~2.2~~%)
Percent stenosis	0 – ≤25%	84 (84.8%)	8~~0~~5 (94.4~~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§(2.2~~3~~%) 1*** not read
~~Not yet read~~Total		~~0 (0%)~~99 (100%)	~~4 (4.6%)~~91~~01~~ (100%)

*1 case of carotid-cavernous fistula and 3 cases of carotid occlusion
**2 cases of carotid occlusion [redacted]), 1 transvenous coil embolization
#3 cases of carotid occlusion
§2 cases of carotid occlusion, "stenosis" not relevant
***1 case of transvenous embolization ([redacted] just received preliminary images). I don't see stenosis, but coils block visualization of the parent artery

Subject follow-up is shown below in **Tables A** and **B**. Of 108 subjects treated, 104 (106 aneurysms) were in the effectiveness cohort. Reasons for excluding 4 subjects from the effectiveness cohort were provided in the PMA on page 97, Table 12-19. Of the 104 subjects, 97 (93.3%) had angiogram at 180 days and 89 (85.6%) had angiogram at 1 year.

Table E. Subjects in effectiveness cohort (n=104 subjects) with angiograms at 180 days or 1 year.

Group	Statistic
Angiogram at 180 days	
Y	97 (93.3%)
N	7 (6.7%)
Angiogram at 1 year	
Y	89 (85.6%)
N	15 (14.4%)

Table F. Subjects in effectiveness cohort by angiogram status at 180 days and 1 year.

		Angiogram at 1 year		
		Yes	**No**	**Total**
Angiogram at 180 days	**Yes**	88	9	97
	No	1	6	7
	Total	89	15	104

Error! Reference source not found. shows a breakdown of angiograms at both time points:

- **88** subjects had angiograms at both time points
- **6** subjects did not have angiogram at either time point due to:
  - Postoperative death (3 subjects)
  - Poor follow-up (1 subject, [redacted], described in detail in PMA on p. 103). Given her suspected non-compliance with dual antiplatelet therapy, the investigator was not surprised when CT angiogram at 10 months showed carotid occlusion.
  - Loss to follow-up (1 subject, [redacted])
  - Study withdrawal (1 subject [redacted]). Both [redacted] and [redacted] L felt well at last study contact.
- **1** subject refused angiogram at 180 days but had angiogram at 1 year ([redacted]. 1-year angiogram showed complete occlusion of the target aneurysm.
- **9** subjects had angiogram at 180 days but not at 1 year due to:
  - 2 ([redacted]) had carotid occlusion at 180 days. 1-year angiogram is not indicated in this case.
  - 2 ([redacted]) had insurance problems preventing obtaining a 1-year angiogram. Both had complete occlusion at 180 days.
  - 4 ([redacted]) refused 1-year angiogram. All 4 had complete occlusion at 180 days. Of these:
    - 2 [redacted]) simply refused.
    - 1 ([redacted]) was diagnosed with lung cancer and was dealing with these issues at the time of the 1-year study visit.
    - 1 [redacted] wanted to avoid excessive radiation.
  - 1 ([redacted] withdrew after the 180-day follow-up. She had complete occlusion at the 180-day angiogram.

As you can see, follow-up is fairly complex.

An obvious question is how to calculate the 1-year success rate. In your previous requests, you had asked for an analysis of angiographic occlusion at 180 days and 1 year amongst subjects who had angiograms at both time points or either time point. This was reported in **Amendment 2** in **Tables 29** and **30**, respectively. I think this might be a reasonable way of approach effectiveness success rates at both time points as well. Note that the primary effectiveness endpoint includes <u>both</u> complete occlusion of the aneurysm <u>and</u> lack of stenosis. This analysis is shown below in Error! Reference source not found. and Error! Reference source not found..

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

	180 days (n=99)	**1 year (n=91)**
Effectiveness rate	78/99 (78.8%)	75/91 (82.4%)

Table H. Effectiveness rate for subjects who had angiogram at both time points.

	180 days (n=90)	1 year (n=90)
Effectiveness rate	71/90 (78.9%)	74/90 (82.2%)

One potential drawback of this approach is that subjects who did not have angiogram may have been more likely to be effectiveness failures. What follows is a commonly used Bayesian approach to imputing success rates when data are missing. Bayesian imputation is mentioned in an FDA guidance document (see section 5.3[1]) and is easy to understand. I suggest this approach as it is reasonable and has been accepted by FDA in the past for many other devices. I acknowledge that methods to calculate a 1-year rate were not outlined in the protocol, and the best approach might simply be to report rates of effectiveness success at 1 year amongst those who underwent angiogram (i.e., your original suggestion, data shown in Error! Reference source not found.).

Bayesian imputation would be as follows. Of the 104 subjects in the effectiveness cohort, 89 subjects (91 aneurysms) underwent angiogram at 1 year. Of these 91 aneurysms, 75 (82.4%) met the primary effectiveness endpoint. 15 subjects did not undergo angiogram at 1 year. Some of these were obvious failures at 180 days and would not have been successes at 1 year. However, some of the 15 had very high chances of being successes had they undergone 1-year angiogram. We can impute 1-year outcomes amongst these 15 subjects using the information shown in Error! Reference source not found. and discussed below.

Table I. Presumed 1-year status of subjects who did not undergo 1-year angiogram.

Subject	180-day status	Theoretical angiographic findings had 1-year angiogram been done	Predicted success at 1 year? (n)
[redacted]	Carotid occlusion	Carotid occlusion	No (3)
	Carotid occlusion	Carotid occlusion	
	Carotid occlusion due to med non-compliance	Carotid occlusion	
	Eff succ*	Eff succ	Yes (97% x 7 = 6.79)
	Eff succ	Eff succ	
	Eff succ	Eff succ	
	Eff succ	Eff succ	
	Eff succ	Eff succ	
	Eff succ	Eff succ	
	Eff succ	Eff succ	
	Postoperative death	Not relevant, since dead	No (3)
	Postoperative death	Not relevant, since dead	
	Postoperative death	Not relevant, since dead	
	Withdrew	Pred	Yes (76.5% x 2 = 1.53)
	Withdrew	Pred	

*Eff succ = effectiveness success; Pred = predictive distribution

[1] http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071072.htm#5, see section 5.4

- 3 subjects had carotid occlusion at 180 days and would almost certainly have had the same at 1 year had angiogram been done. Although recanalization of occluded carotids has been reported, it is very rare, and these reports were in the setting of atherosclerotic disease, not a metallic implant. In discussions with investigators, most have told me that they believe that spontaneous recanalization of an occluded carotid with PED in place is highly unlikely. I believe this is why physicians did not push these 3 subjects to have an angiogram at 1 year – it would expose them to risk for no clear benefit. We can therefore be quite confident that at 1 year, none of these subjects would have been a success according to the protocol's definition had they undergone angiogram. (However, given no blood flow in the carotid, their aneurysms are certainly occluded.)

- 7 subjects had effectiveness success at 180 days but did not undergo angiogram at 1 year. What would their 1-year angiograms have looked like? Almost certainly they would have been continued successes. Why? Let's consider the 71 subjects who had complete occlusion at 180 days and also had an angiogram at 1 year. Of these 71, 69 (97%) had complete occlusion at 1 year, meaning that once an aneurysm is occluded with PED, it has a very high chance of staying occluded. The two who were not successes at 1 year were rare exceptions.[2] For these 7 subjects, we can therefore assume a very high chance (97% based on available data) that all would have been completely occluded at 1 year had they undergone angiogram. I want to emphasize the robustness of this assumption; in our global experience with PED, we have not seen aneurysm recanalization after PED placement.

- 3 subjects had postoperative death. They were not successes at 180 days and would not be successes at 1 year. You have to be alive to be a success.

- Finally, 2 subjects withdrew prior to the 180-day angiogram. Assuming that withdrawal was unrelated to likelihood of occlusion (there is no reason to think this would be the case, both were doing very well at the time of withdrawal), we can assume that their likelihood of success was the same as the other 102 subjects in the cohort who had angiogram, i.e., 78 successes in 102 subjects or 76.5%. For these two subjects, the "expected" success rate at 180 days is therefore 2 x 76.5% = 1.5. If the subjects' aneurysms were occluded at 180 days, there is a very strong chance (see paragraph above) that they would also be occluded at 1 year.

According to a Bayesian approach to imputation, the expected number of successes at 1 year can be calculated as:

$$\text{Expected} = \text{observed successes} + \text{predicted successes}$$

$$= 75 + (6.79 + 1.53) = 83.32$$

which is a success rate of 83.32/104 = 80.1%. I have not presented a confidence interval for this rate, but there is a standard Bayesian approach for this calculation.

---

[2] 2 aneurysms showed complete occlusion at 180 days and "non-success" at 1 year. Subject PACKA had complete occlusion at 180 days and carotid occlusion at 1 year. We hypothesized in the PMA that the lung cancer she was harboring (which was diagnosed during the year after PED placement) made her hypercoagulable, potentially leading to carotid occlusion. The other subject (AUSLE) had a small residual seen at 1 year follow-up. This residual was not seen at 180 days but is evident in retrospect.

Tables C and D above show 1-year success rates of ~82%. The Bayesian imputation approach gives a result of 80.1%, which is very similar. Consistent with the experience reported in Argentina by Dr. Lylyk, we saw some aneurysms go from small residuals at 180 days to complete occlusion at 1 year. Thus, I'm not surprised that the 1-year success rate, however it is calculated, is somewhat higher than the 180-day success rate (73.6%).

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Sent: Sun 1/2/2011 5:53 PM

Larry,

For ease of reading, I put my analysis into a Word document. I will be in the DC area on Tues-Wed evening. I could meet with you in person on Wednesday if you wanted to review anything.

The executive summary is just about ready. Hope to send it Wed or Thursday.

I'll get to your other questions later this week.

Danny

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Attachment:

Heparin Dosing

Larry, here are responses to your questions regarding heparin dosing. You wrote:

> ***We are going to need additional information regarding the use/dosing of heparin along with ACT results in PUFS. At the very least we will want to see the data for those subjects listed in Appendix 19, Table 17-25 whose heparin bolus was not in range as well as for all subjects who experienced an ischemic or hemorrhagic stroke. Data from sections 10 through 14 of form 004A_INDEX PROCEDURE will be needed. However since we will need to compare the results of those groups to those who had the recommended heparin dosing or to those who did not experience a stroke. Of course we***

will be interested in whether the protocol deviations regarding heparin dosing resulted in ACTs out of the recommended range and/or any adverse consequences. I will leave the details of how to present the data to you.

Table 10 shows the distribution of heparin administered to subjects. Values are missing in two subjects: in 1 case heparin was given but the amount was not recorded in the CRF; in the other case, heparin was not given [redacted] in which the physicians could not pass the micro-guidewire into the distal parent artery, so a microcatheter was not placed).

Table 10. Heparin bolus prior to microcatheter placement.

Heparin Bolus #1 (IU)	N
Missing	2
1000	1
2000	1
2500	1
3000	25
3150	1
3500	2
4000	11
4200	1
4500	5
4600	1
5000	26
5400	1
5500	1
5600	2
6000	4
6500	1
6800	2
7000	5
7500	7
8000	3
8500	1
9000	1
10000	2
11000	1
Total	108

Table 11 summarizes pre- and post-heparin ACT values. Post-heparin values were on average 1.94 times the pre-heparin value. This is consistent with the protocol asking that post-heparin ACT be at least 2 times the pre-heparin value.

Table 11. Baseline and post-heparin ACT values.

	N	Mean (SD)	Median	Range
Pre-heparin ACT	103	138.6 (34.3)	129.00	84 – 252
Post-heparin ACT	104	261.4 (51.4)	260.00	151-400
Ratio	102	1.94 (0.45)	1.98	1.06-3.01

Figure 1 shows the ratio of post- to pre-heparin ACT values as a function of "baseline" ACT. In the lower right-hand corner of the graph, you can see that some subjects had high (>200, out of normal range) pre-heparin ACTs, suggesting contamination of the sample with heparin. It's not surprising that the post-heparin value was barely increased over the pre-heparin value; the pre-heparin sample was probably contaminated.

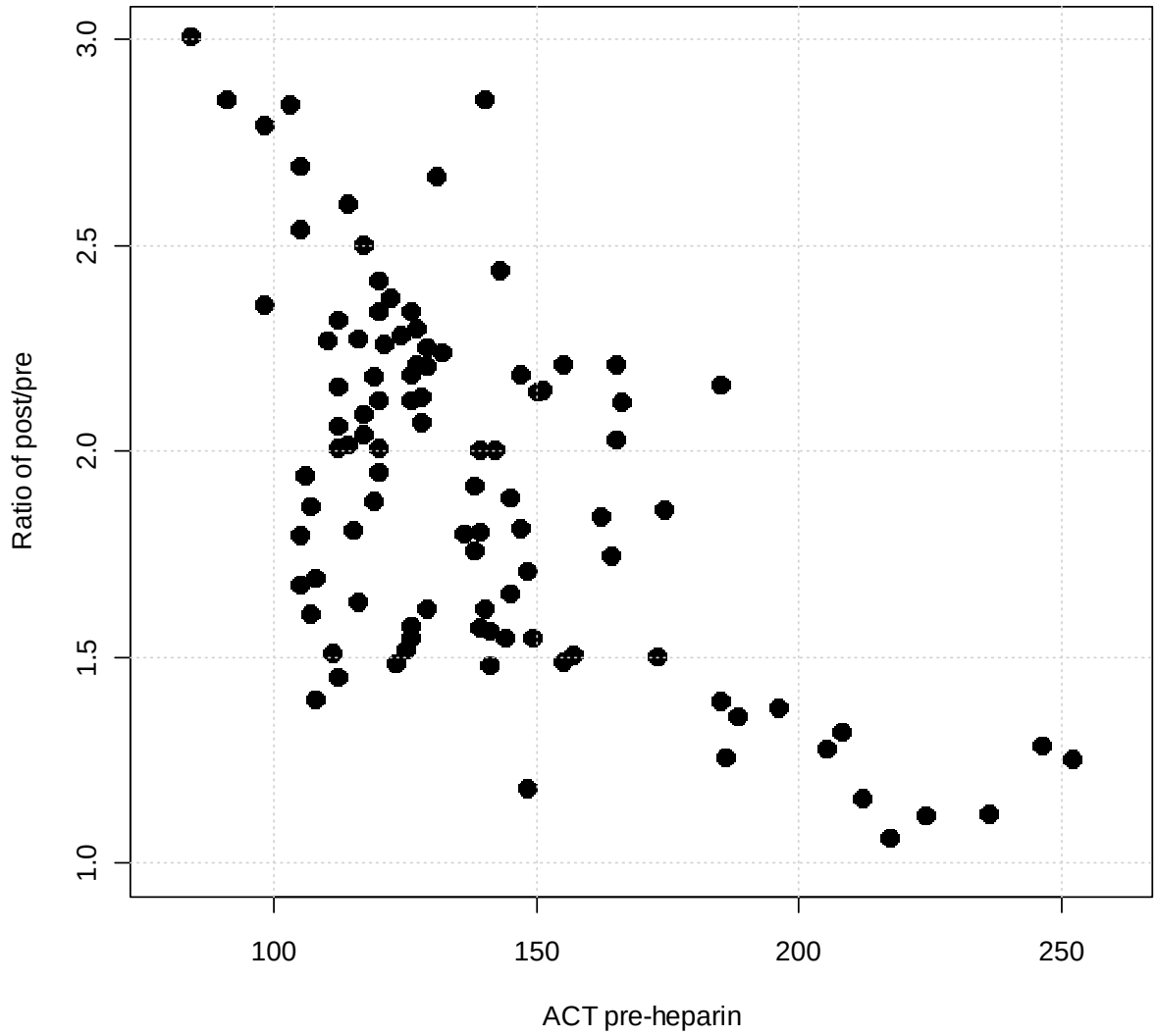

Figure 1. Ratio of post/pre-heparin ACT as a function of pre-heparin ACT.

Whether heparin dosing was in the pre-specified range (50-100 U/kg) was determined by study monitors and deviations were created when dosing was out of range. I recalculated heparin dosing from raw data (i.e., initial heparin dose ÷ body weight). **Table 12** shows dosing in the 107 subjects.[3] In 24% of cases, heparin dosing was <50 U/kg and in 12% of cases, heparin dosing was >100 U/kg.

Table 12. Heparin dose range.

Heparin dose	N (%)
<50 U/kg	26 (24.3)
50-100 U/kg	65 (60.7)
>100 U/kg	13 (12.1)

[3] Subject [redacted] excluded because microcatheter could not be placed into distal parent artery.

Missing	3 (2.8)
Total	107 (100)

It is of interest to know whether heparin dosing within the specified weight-adjusted range affected the "bump" in ACT from pre- to post-heparin. **Figure 2** plots the ratio of post- to pre-heparin ACT as a function of pre-heparin ACT, with dots colored by whether the dose range was <50 U/kg (red), 50-100 U/kg (green) or >100 U/kg (blue). In the range of pre-heparin values less than about 180 (i.e., normal, probably not contaminated), I don't see much of a relationship between the "bump" in ACT after heparin and whether the dosing was in the suggested range. This suggests that the initial bolus of heparin being in the recommended 50-100 U/kg range or not made little, if any, difference as to how "anticoagulated" the subject became. It should be recalled that each site may use different measurement tools for ACT, and these tools are not known to be highly accurate or reproducible. Moreover, the physician had the opportunity to deliver additional heparin if he thought that the subject was not sufficiently anticoagulated.

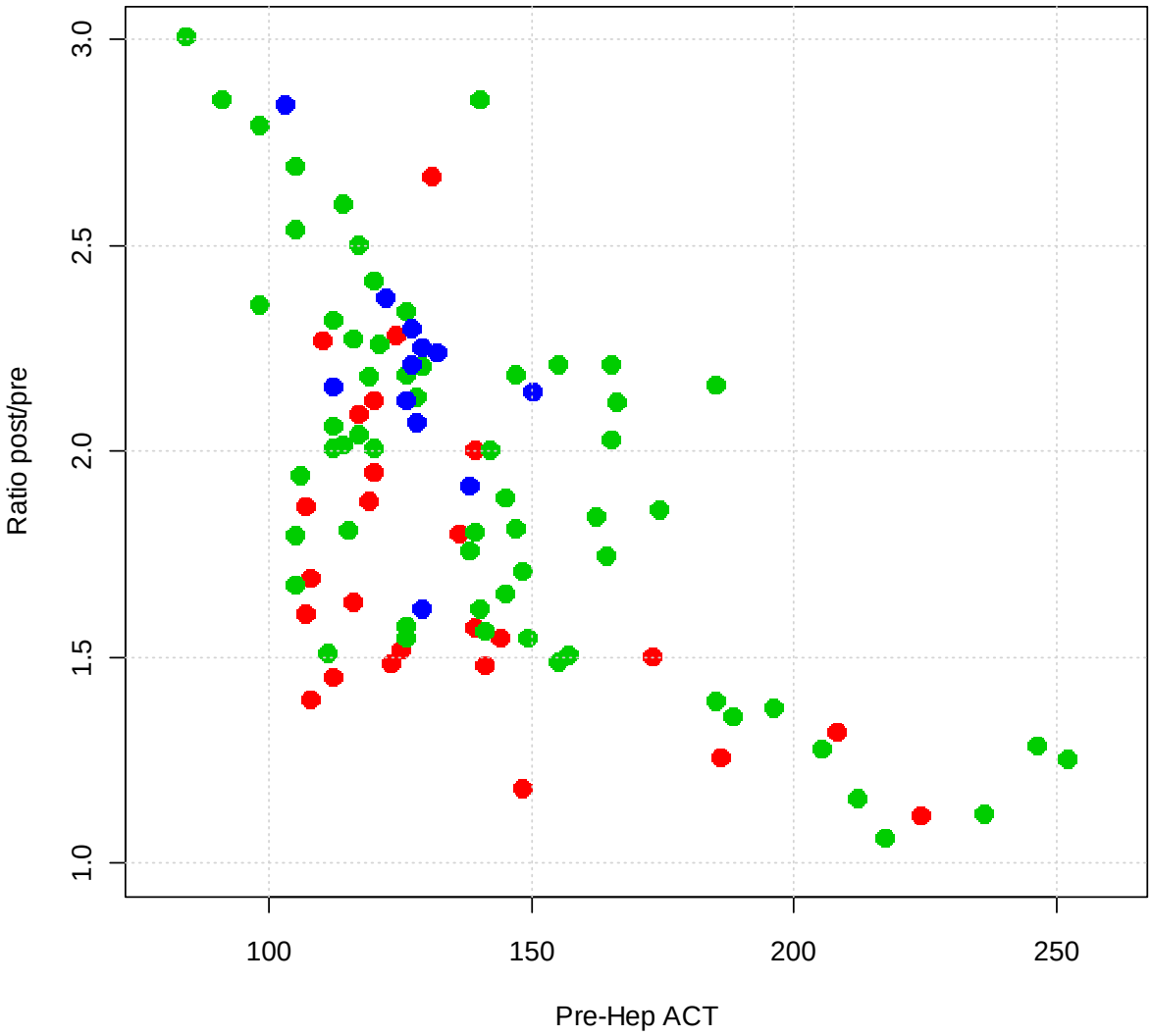

Figure 2. Ratio of post- to pre-heparin ACT as a function of pre-heparin ACT and dose range. Red dots indicate a dosing of <50 U/kg; green dots indicate a dosing of 50-100 U/kg; blue dots indicate a range of >100 U/kg.

Question 13 on the procedure form recorded whether additional heparin was given. Additional heparin was at the physician's discretion. **Table 13** lists each patient and whether further doses of heparin were given. I'm not sure what, if any, analysis you would want.

Table 13. Further heparin dosing after initial dose.

ptID	Initial dose	Further dose 1	Further dose 2	Further dose 3
[redacted]	6000	2000	.	.
	5000	2000	1000	.
	6000	.	.	.
	.	.	.	.
	4000	.	.	.

7000	.	.	.
5000	.	.	.
5000	1000	500	500
3000	.	.	.
3000	1000	.	.
3000	.	.	.
3000	1000	.	.
3000	.	.	.
3000	.	.	.
2500	.	.	.
3000	3000	500	.
3000	1000	500	.
3000	3000	500	.
3000	3000	500	.
3000	3000	1000	.
3000	1000	.	.
3000	.	.	.
3000	.	.	.
2000	1000	.	.
1000	2000	.	.
3000	1000	1000	.
3000	1000	.	.
4000	1000	.	.
3000	.	.	.
3000	.	.	.
4000	.	.	.
3000	.	.	.
3000	.	.	.
3000	.	.	.
3000	1000	.	.
3000	.	.	.
3000	500	.	.
7000	.	.	.
3150	1200	.	.
7000	.	.	.
5600	1200	.	.
5000	1000	2000	4000
4000	2500	.	.
3500	.	.	.
4500	1000	1000	.
4000	.	.	.
6800	1500	.	.
4500	1500	1000	.
5600	.	.	.
4600	.	.	.
5400	.	.	.
4000	.	.	.
3500	1500	1500	1000
4200	1000	1000	.
6800	.	.	.
4500	1000	1000	750
4500	2000	.	.
4000	.	.	.
4000	500	.	.
4500	.	.	.

5000	.	.	.
4000	2000	.	.
5000	2000	.	.
5000	.	.	.
6000	1500	500	.
8000	.	.	.
10000	1000	1000	.
9000	900	.	.
5000	500	.	.
3000	.	.	.
5000	.	.	.
4000	2000	.	.
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5000	.	.	.
4000	1000	.	.
7500	1000	.	.
5000	1000	1000	.
5000	.	.	.
5000	1000	.	.
7500	1000	.	.
7500	.	.	.
7500	.	.	.
7500	1000	.	.
7500	1000	.	.
8000	.	.	.
7000	1000	.	.
8500	750	.	.
10000	1000	.	.
6500	1000	1500	.
7000	1000	.	.
8000	1000	.	.
7500	1000	.	.
11000	1000	.	.
5000	1000	1000	.
5000	2000	.	.
5000	2000	.	.
5000	1500	.	.
.	.	.	.
5500	.	.	.
6000	.	.	.
5000	3000	.	.

The protocol recommended a range of 50-100 U/kg of heparin. I am not aware of any evidence to suggest that this is the "best" dose, but we tried to standardize dosing based on current practice. As you noted, the most interesting analysis is whether heparin dosing in the pre-specified range was related to a lower occurrence of AEs. **Table 14** shows adverse events whose

start date is between days 0 (day of PED placement) and day 14. (To me, drawing any conclusion about a relationship between intraprocedural heparin dosing and an adverse event occurring after day 14 is implausible.) Combined with the information shown in **Table 12** we can calculate a "Day 0-14 day risk of AE" as a function of heparin dosing. I don't see much in the way of trends and there is a substantial multiplicity issue that prevents any definitive comparisons. We should also note that 1) this comparison is not randomized, and 2) if the post-heparin ACT was not sufficiently elevated, the physician had the opportunity to give additional heparin.

Table 14. Adverse events occurring within first 14 days after PED treatment

Heparin dose	Adverse Event	N (%)
<50 U/kg (n=26)	Anemia	1 (6.3%)
	Arrhythmia: atrial fibrillation	1 (6.3%)
	Back pain	1 (6.3%)
	Carotid cavernous fistula	1 (6.3%)
	Corneal abrasion	1 (6.3%)
	Fever	1 (6.3%)
	Headache	4 (25%)
	Hypotension	1 (6.3%)
	Intracranial hemorrhage	1 (6.3%)
	Ischemic stroke	1 (6.3%)
	Nausea	2 (12.5%)
	Possible intracranial hemorrhage	1 (6.3%)
	Ptosis	2 (12.5%)
	Sore throat	1 (6.3%)
50-100 U/kg (n=65)	Achiness	1 (1.5%)
	Arrhythmia: bradycardia	1 (1.5%)
	Arterial line site swelling	1 (1.5%)
	Blurry vision	1 (1.5%)
	Cilioretinal artery embolism	1 (1.5%)
	Deep/superficial venous thrombosis	1 (1.5%)
	Diplopia	4 (6.2%)
	Diplopia (CN6), ptosis (CN3)	1 (1.5%)
	Dizziness	1 (1.5%)
	Eye floater	1 (1.5%)
	Facial pain	1 (1.5%)
	Femoral puncture site infection	1 (1.5%)
	Floaters in vision	1 (1.5%)
	Headache	17 (26.2%)
	Intracranial hemorrhage	3 (4.6%)
	Nausea	8 (12.3%)
	Nausea / vomiting	1 (1.5%)
	Non-neuro bleeding: Groin bleeding	1 (1.5%)
	Non-neuro bleeding: Groin hematoma	2 (3.1%)
	Non-neuro bleeding: Hematuria	1 (1.5%)
	Non-neuro bleeding: Scalp hematoma	1 (1.5%)
	Non-neuro bleeding: Vitreal hemorrhage	1 (1.5%)
	Non-neuro bleeding: compartment syndrome	1 (1.5%)
	Non-neuro bleeding: groin bleeding	1 (1.5%)
	Non-neuro bleeding: groin hematoma	1 (1.5%)
	Non-neuro bleeding: ruptured splenic artery aneurysm	1 (1.5%)
	Numbness in fingertips	1 (1.5%)

	Pulmonary embolism	1 (1.5%)
	UE vein thrombosis	1 (1.5%)
	Urinary tract infection / pneumonia	1 (1.5%)
	Vomiting	1 (1.5%)
>100 U/kg (n=13)	Anemia	1 (7.7%)
	Diplopia	2 (15.4%)
	Headache	2 (15.4%)
	Intracranial hemorrhage	1 (7.7%)
	Non-neuro bleeding: Groin hematoma	1 (7.7%)
	Non-neuro bleeding: retroperitoneal hematoma	1 (7.7%)

You also asked about heparin dosing in the subjects who had stroke. **Table 15** shows the dose of heparin used, as well as the "bump" in ACT value, among the 6 subjects who met the primary safety endpoint (major stroke or neurologic death). My comments are:

- [redacted] had thrombosis inside PED 8 hours after the procedure; it is possible that a low heparin dose resulted in a smaller-than-recommended "bump" (ratio 1.18), which may have precipitated thrombosis.

- [redacted] had spontaneous thrombosis of the treated artery at some point approximately 2 months after PED placement. I'm not sure how we could relate this to intraprocedural heparin dosing. You will recall that she was noted to be non-compliant with aspirin/clopidogrel; this is much more plausibly related to spontaneous thrombosis than heparin use during the procedure.

- [redacted] had severe cardiomyopathy with sudden cardiac death on postoperative day #3. This event was eventually interpreted by the core lab to represent neurologic death (despite any evidence to support this). His "bump" in ACT was 1.88. Whether this had anything to do with his event is entirely unclear.

- [redacted] had distal intracranial hemorrhage on POD #13. Her dosing was consistent with recommended and the bump in ACT was as expected (about 2-fold). In the PMA we noted that she was started on new serotonin reuptake inhibitors, which are known to affect platelet function.

- [redacted] had ischemic stroke due to stenosis inside PED. She had heparin dosing consistent with the protocol and a "textbook" bump in ACT. How this could be related to stenosis at the 3rd month is unclear to me.

- [redacted] had a dose of 11,000 U of heparin, i.e., 157 U/kg. Her procedure was prolonged due to complexity of the aneurysm. 13 PEDs were placed in the target aneurysm. She had intracranial hemorrhage the day of the procedure, probably resulting from administration of IV tirofiban, an antiplatelet agent. Thus, any potential relationship between a "high" dose of heparin and intracranial hemorrhage is confounded by use of tirofiban. Chronologically, the relationship with tirofiban is much stronger.

Table 15. Heparin dosing among 6 subjects who met the study's primary safety endpoint.

Patient ID	Event	Days from	Heparin dose	Heparin dose range	Pre-Heparin	Ratio of Post/Pre

		proc to AE			ACT	ACT
[redacted]	Ischemic stroke	0	3000	<50 U/kg	148	1.18
	Ischemic stroke	66	3000	<50 U/kg	112	1.45
	Possible intracranial hemorrhage	4	5000	<50 U/kg	119	1.88
	Intracranial hemorrhage	13	4000	50-100 U/kg	112	2.32
	Ischemic stroke	62	7500	50-100 U/kg	121	2.26
	Intracranial hemorrhage	0	11000	>100 U/kg	122	2.38

Finally, I want to note that we asked physicians whether there was any unwanted thrombus on the microcatheter at the end of the procedure; the answer was no in all cases. Heparin use is very common in patients undergoing neurovascular procedures, including stent placement. I believe that physicians are quite skilled with heparin use and can plan dosing carefully.

-----Original Message-----
From: Rodichok, Lawrence [mailto:Lawrence.Rodichok@fda.hhs.gov]
Sent: Thursday, December 30, 2010 8:58 AM
To: Cher, Daniel
Subject: RE: Heparin dosing and ACT results in PUFS

I am specifically interested in where the variations in heparin dosing during the procedure resulted in significant deviation from the desired ACT range and whether subjects who did have peri-procedureal thrombotic events were the ones with ACTs way out of range - I doubt it but we should know the answer.

Don't read any more of my emails until Monday - I am just getting them out so I don't forget. Take time with the family.

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-----Original Message-----
From: Cher, Daniel [mailto:DCher@ev3.net]
Sent: Thursday, December 30, 2010 10:00 AM
To: Rodichok, Lawrence
Subject: RE: Heparin dosing and ACT results in PUFS

Larry, I'll try to get this to you early next week.

Adverse events associated with heparin use would be those occurring during PED placement and during the immediate perioperative period, while the effect of heparin is wearing off. In all cases but one [redacted], who had Factor V Leiden), heparin was stopped at the end of the placement procedure. From my memory (I will check when I get back), only one patient had an adverse event in the immediate perioperative period related to thrombosis; this was patient [redacted] who had acute thrombosis of the carotid inside PED. Whether this was related to heparin is not known.

I'm not sure how to interpret a table that tries to correlate heparin dosing with events that occur outside of the perioperative period. Causality would be difficult to interpret in this case. Also, you are probably aware that responses to heparin, as well as the tests used to measure response to heparin (e.g., ACTs measured intraoperatively), are widely variable. "ACT increase by 2" is a rough guide that physicians use.

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From: Rodichok, Lawrence [Lawrence.Rodichok@fda.hhs.gov]
Sent: Wednesday, December 29, 2010 8:38 AM
To: Cher, Daniel
Cc: Hutter, Joseph C.; Bonangelino, Pablo; Misra, Sanjay
Subject: Heparin dosing and ACT results in PUFS

Hi Dan

We are going to need additional information regarding the use/dosing of heparin along with ACT results in PUFS. At the very least we will want to see the data for those subjects listed in Appendix 19, Table 17-25 whose heparin bolus was not in range as well as for all subjects who experienced an ischemic or hemorrhagic stroke. Data from sections 10 through 14 of form 004A_INDEX PROCEDURE will be needed. However since we will need to compare the results of those groups to those who had the recommended heparin dosing or to those who did not experience a stroke. Of course we will be interested in whether the protocol deviations regarding heparin dosing resulted in ACTs out of the recommended range and/or any adverse consequences. I will leave the details of how to present the data to you.

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