

**I. Efficacy Comparison with PROACT II.** While the results for efficacy compared to the PROACT II control arm and the arbitrary goal of 30% are impressive, given the lack of a contemporaneous control arm, it is important to address concerns that the results reflect or are limited only to the cohort in which the MERCI study was performed. The following additional analyses would be most informative in this regard.

1. Show the comparison of the baseline characteristics of the PROACT II study (Table 2, JAMA 1999 282, p 2003) and the MERCI study.
  - If available from the study authors, show the baseline characteristics for the PROACT II arm for middle cerebral artery occlusions only. If available from the study authors, show the inter-quartile ranges in addition to the median and range.

**An e-mail was sent to the Corresponding Author (A. Furlan) to request access to the PROACT II data. He indicated that Abbott Laboratories has exclusive rights to the PROACT II data base and it is unlikely that the data would be released to Concentric in time to meet the panel deadline.**

**Table 1 below shows the baseline characteristics for the entire MERCI study, the MERCI MCA patients, and the PROACT II placebo control. Please note that PROACT II enrolled/treated patients presenting with MCA M1 or M2 occlusions and MERCI enrolled/treated patients with ICA, MCA, Basilar and Vertebral occlusions.**

<b>Table 1, Baseline Characteristics, MERCI vs. PROACT II</b>			
<b>Characteristic</b>	<b>MERCI Overall n = 114</b>	<b>MERCI MCA n = 72</b>	<b>PROACT II Control n = 59</b>
Mean Age (SD)	66 (16)	68 (15)	64 (14)
Caucasian, No. (%)	91 (80)	50 (77)	52 (88)
Women, No. (%)	52 (46)	33 (51)	23 (39)
Weight, mean (SD) kg	79 (17)	77 (16)	81 (19)
NIHSS Score, median (range)	19 (9 – 40)	19 (9 – 40)	17 (4 – 28)
Blood Pressure, mean (SD), mm Hg			
Systolic	146 (25)	147 (27)	144 (19)
Diastolic	78 (77)	78 (18)	78 (17)
Time from stroke onset to randomization, median (interquartile range), h	N/a	N/a	5.1 (4.2 – 5.5)
Time from stroke onset to groin puncture, median (range)	4.0 (0.3 – 9.5)	4.0 (1.0 – 7.5)	N/a
Time from stroke onset to final angiogram, median (range)	6.1 (2.0 – 16.4)	6.1 (2.0 – 9.6)	N/a

2. Show the comparison of the baseline characteristics between subjects on the MERCI study who had successful revascularization and those that did not.
  - Baseline characteristics should include, in addition to gender, age, baseline NIHSS Score, and time to treatment shown in the MERCI Clinical Report, the other factors in Table 2 of the PROACT Report (JAMA 1999 282, p 2003) as well as CT hypodensity, shown in

Wechsler et al (Stroke 2003, **34**: 1224-1229) to be prognostic for outcome. Sow the inter-quartile ranges in addition to the median and range.

**Table 2 below shows the baseline characteristics for the successfully and unsuccessfully revascularized MERCI patients and the PROACT II placebo control. Please note, PROACT II only treated MCA occlusions.**

**Per the enrollment criteria, a patient presenting with an area of hypodensity of greater than one third the MCA Territory were excluded from the trial. No patients enrolled in the study were in violation of this exclusion. No additional specific CT data on hypodensity was collected on the MERCI case report forms and will not be available in time for the panel. Concentric Medical was not aware, nor did the Food & Drug Administration require, that this information be proactively collected when the study began in May 2001. The referenced paper was published in May 2003.**

<b>Characteristic</b>	<b>MERCI Successful Revascularization n = 61</b>	<b>MERCI Unsuccessful Revascularization n = 53</b>	<b>PROACT II Control n = 59</b>
Mean Age (SD)	68 (16)	65 (15)	64 (14)
Caucasian, No. (%)	49 (80)	42 (79)	52 (88)
Women, No. (%)	24 (39)	28 (53)	23 (39)
Weight, mean (SD) kg	79 (14)	80 (21)	81 (19)
NIHSS Score, median (range)	18 (10 – 39)	20 (9 – 40)	17 (4 – 28)
Blood Pressure, mean (SD), mm Hg			
Systolic	145 (25)	146 (26)	144 (19)
Diastolic	75 (16)	80 (21)	78 (17)
Time from stroke onset to randomization, median (interquartile range), h	N/a	N/a	5.1 (4.2 – 5.5)
Time from stroke onset to groin puncture, median (range)	4.3 (0.3 – 9.5)	3.5 (1.0 – 7.5)	N/a
Time from stroke onset to final angiogram, median (range)	6.1 (2.0 – 14.0)	6.0 (2.4 – 16.4)	N/a

3. Perform an analysis that allows for the assessment of baseline characteristics in distinguishing between the 61 subjects with successful and the 53 subjects with unsuccessful revascularization (e.g. logistic regression as suggested by FDA statistical reviewer)
  - Baseline characteristics should include, in addition to gender, age, baseline NIHSS Score, and time to treatment shown in the MERCI Clinical Report, the other factors in Table 2 of the PROACT Report (JAMA 1999 282, p 2003) as well as CT hypodensity, shown in Wechsler et al (Stroke 2003, **34**: 1224-1229) to be prognostic for outcome.

**Tables 3 and 4 detail the predictors of revascularization by baseline characteristic. Specific CT hypodensity data was not a key variable referenced in the MERCI Clinical Protocol. All patients treated had hypodensity less than 1/3 of the MCA territory (per the enrollment criteria). Both the univariate (Table 3) and multivariate (Table 4) have been provided for the available variables.**



[Redacted text block]

## **II. Safety Assessment**

1. Expand the secondary outcomes of 30 and 90 day analyses (mortality, NIHSS, Rankin) with more sophisticated multivariate analyses as suggested in item **I. 3** above, but add success or failure of revascularization as a covariate.

### **Secondary Outcomes – 30 Day**

**Tables 5 and 6 detail the predictors of achieving a Modified Rankin Score of 0 – 2 at 30 days post treatment. Table 5 details the results by variable from the univariate logistic regression and Table 6 details the results by variable from the multivariate stepwise (backwards/forwards) logistic regression.**

**Tables 7 and 8 detail the predictors of achieving at least a 10 point improvement in baseline NIH Stroke Scale Score at 30 days post treatment. Table 7 details the results by variable from the inivariate logistic regression and Table 8 details the results by variable from the multivariate stepwise (backwards/forwards) logistic regression.**

### **Secondary Outcomes – 90 Day**

**Tables 9 and 10 detail the predictors of achieving a Modified Rankin Score of 0 – 2 at 90 days post treatment. Table 9 details the results by variable from the inivariate logistic regression and Table 10 details the results by variable from the multivariate stepwise (backwards/forwards) logistic regression.**

**Tables 11 and 12 detail the predictors of achieving at least a 10 point improvement in baseline NIH Stroke Scale Score at 90 days post treatment. Table 11 details the results by variable from the inivariate logistic regression and Table 12 details the results by variable from the multivariate stepwise (backwards/forwards) logistic regression.**

### **Mortality**

**Tables 13 and 14 detail the predictors of mortality. Table 13 details the results by variable from the inivariate logistic regression and Table 14 details the results by variable from the multivariate stepwise (backwards/forwards) logistic regression.**

[Redacted]

---

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

---

[REDACTED]



<p>[REDACTED]</p>	
[REDACTED]	[REDACTED]

<p>[REDACTED]</p>	
[REDACTED]	[REDACTED]

[REDACTED]



### III. Eligibility Criteria for MERCI and PROACT II studies

1. Compare the baseline characteristics between subjects screened for the MERCI study (n = 1,412 -121 ) vs. those that were included in the study ( n = 121).
  - Describe the characteristics of subjects for which complete acute data was not available at the time of the submitted analyses (Clinical Review, “Patient demographics”)

**Baseline characteristics were collected for those patients enrolled and treated in the MERCI study. The patients who were not enrolled (1,291) were screened only to determine whether or not they met the inclusion/exclusion criteria. Since they did not meet these criteria, no further data was collected.**

**At this time, Concentric Medical has baseline characteristics for 129 patients treated. Table 3 below shows the baseline characteristics for the available patient data set.**

<b>Table 3, Baseline Characteristics, n = 129</b>	
<b>Characteristic</b>	<b>MERCI n = 129</b>
Mean Age (SD)	[REDACTED]
Women, No. (%)	[REDACTED]
NIHSS Score, median (range)	[REDACTED]
Time from stroke onset to groin puncture, median (range)	[REDACTED]
Time from stroke onset to final angiogram, median (range)	[REDACTED]

2. Assess the impact of the efficacy and safety outcomes on differences between the eligibility and exclusion criteria for the MERCI and PROACT II studies.

<b>Table 4, MERCI Inclusion vs. PROACT II</b>		
<b>MERCI Inclusion Criteria</b>	<b>PROACT II Inclusion Criteria</b>	<b>Rational for Inclusion</b>
≥ 18 years	18-85	[REDACTED]
Ischemic stroke in the internal carotid, middle cerebral artery (M1 or M2 segment), basilar, or vertebral arteries.	New focal neurological signs in the MCA distribution	[REDACTED]

**Table 4, MERCI Inclusion vs. PROACT II**

<i>MERCI Inclusion Criteria</i>	<i>PROACT II Inclusion Criteria</i>	<i>Rational for Inclusion</i>
<3 hrs of symptom onset, but not eligible for thrombolytic therapy	<i>Initiation of treatment within 6 hours of the onset of the symptoms</i>	[REDACTED]
>3 hrs of symptom onset but thrombectomy could be completed within 8 hrs from symptom onset	<i>Initiation of treatment within 6 hours of the onset of the symptoms</i>	[REDACTED]
NIHSS $\geq$ 8	NIHSS 4-30	[REDACTED]
Consent	<i>Consent</i>	[REDACTED]
TIMI grade 0 or 1 flow		[REDACTED]
Balloon guide catheter inserted <u>and</u> deployed to target vessel		[REDACTED]

<b>Table 5, MERCI Exclusion vs. PROACT II</b>		
<b><i>MERCI Exclusion Criteria</i></b>	<b><i>PROACT II Exclusion Criteria</i></b>	
Pregnant		
Glucose < 50		
Arterial tortuosity <i>excessive which precludes the device from reaching the target area</i>		
<i>Hemorrhagic diathesis, coagulation factor deficiency, or oral anticoagulation therapy with INR &gt; 3.0</i>	Hemorrhagic diathesis, international normalized ration > 1.7	
<i>Patient received heparin within 48 hours with a PTT 2 times the lab normal</i>	PTT > 1.5 normal	
Platelet count < 30,000	baseline platelet count < 100X 10 <sup>9</sup> /L (100X10 <sup>3</sup> /μl)	
Severe allergy to contrast dye	Contrast sensitivity	
<i>Severe, sustained hypertension (systolic &gt; 185 or diastolic &gt; 110 mm Hg). If blood pressure can be reduced &amp; maintained at the acceptable level using medication, patient can be enrolled.</i>	Uncontrolled hypertension	
<i>Significant mass effect with midline shift</i>	<i>CT Requirement: Significant mass effect with midline shift</i>	
<i>Large (&gt; 1/3 of the middle cerebral artery) regions of hypodensity. Sulcal effacement and/or loss of grey-white differentiation alone are not contraindications.</i>	<i>CT Requirement: Acute hypodense parenchymal lesion or effacement of cerebral sulci in more than one third of the MCA territory.</i>	

**Table 5, MERCI Exclusion vs. PROACT II**

<i>MERCI Exclusion Criteria</i>	<i>PROACT II Exclusion Criteria</i>	
>50% stenosis proximate to target occlusion		
< 3mos to live		
On another ID study <i>within 30 days prior to proposed entry into the MERCI study</i>		
<i>No upper NIHSSS limit.</i>	<i>NIHSS greater than 30</i>	
	<i>Recent stroke within 6 weeks</i>	
	<i>Seizures at onset of symptoms</i>	

**Table 5, MERCI Exclusion vs. PROACT II**

<i>MERCI Exclusion Criteria</i>	<i>PROACT II Exclusion Criteria</i>	
	SAH	[REDACTED]
	Previous ICH, Neoplasm	[REDACTED]
	Septic embolism	[REDACTED]
	Surgery, biopsy of a parenchymal origin, trauma with internal injuries or LP < 30 days	[REDACTED]
	Suspected lacunar stroke	[REDACTED]
	Head trauma < 90 days or hemorrhage <30 days	[REDACTED]

**Table 5, MERCI Exclusion vs. PROACT II**

<i>MERCI Exclusion Criteria</i>	<i>PROACT II Exclusion Criteria</i>	
	Coma	[REDACTED]
	Rapid improvement	[REDACTED]
	<i>Intracranial tumors, except small meningioma</i>	[REDACTED]
	<i>CT Requirement: Hemorrhage of any degree or location</i>	[REDACTED]

Note: Some inclusion/exclusion criteria as outlined in the MERCI protocol and the PROACT II study (JAMA 1999 282, p 2003) were not included in the above table as submitted to Concentric Medical. These have been added and are italicized.