SUPPLEMENTAL MATERIAL

This supplement contains two sets of analyses from phase 2 of The Intravascular Cooling in the Treatment of Stroke 2/3 (ICTuS 2/3) trial. The report is based on data locked by informatics as of May 15, 2015. For each analysis we present the ITT followed by the PP sample. These analyses were requested by reviewers at STROKE journal.

Summary of Adverse Events

This section presents the Safety report summary, including adverse events and deaths.

Frequency and percentages of AE's, SAE's and Deaths are reported by treatment group and overall.

Comparisons were performed using Fisher's exact test.

Table I. Adverse Events in the ITT Sample

	NORMOTHERMIA	HYPOTHERMIA	Overall
Number of subjects randomized	57	63	120
Number of AE events	307	456	763
Number of randomized subjects who experienced at least one AE*	53	63	116
Percent of randomized subjects who experienced at least one AE	92.98%	100%	96.67%

*Fisher's Exact Test p-value: 0.0481

Table II. Serious Adverse Events in the ITT sample

	NORMOTHERMIA	HYPOTHERMIA	Overall
Number of subjects randomized	57	63	120
Number of SAE events	31	35	66
Number of randomized subjects who experienced at least one SAE*	20	26	46
Percent of randomized subjects who experienced at least one SAE	35.09%	41.27%	38.33%

*Odds Ratio: 1.297 (0.582,2.917) Fisher's Exact Test p-value: 0.5737

Table III. Deaths in the ITT sample.

	NORMOTHERMIA	%	HYPOTHERMIA	%	Total	%
No	52	91.2	53	84.1	105	87.5
Yes	5	8.8	10	15.9	15	12.5
Total	57	100.0	63	100.0	120	100.0

Odds Ratio: 1.952 (0.561,7.792) Fisher's Exact Test p-value: 0.2795

Table IV. Adverse Events in PP Sample

	NORMOTHERMIA	HYPOTHERMIA	Overall
Number of subjects randomized	49	51	100
Number of AE events	250	398	648
Number of randomized subjects who experienced at least one AE*	45	51	96
Percent of randomized subjects who experienced at least one AE	91.84%	100%	96%

*Fisher's Exact Test p-value: 0.054

Table V. Serious Adverse Events in the PP Sample

	NORMOTHERMIA	HYPOTHERMIA	Overall
Number of subjects randomized	49	51	100
Number of SAE events	25	29	54
Number of randomized subjects who experienced at least one SAE*	16	21	37
Percent of randomized subjects who experienced at least one SAE	32.65%	41.18%	37%

*Odds Ratio: 1.438 (0.591,3.552) Fisher's Exact Test p-value: 0.413

Table VI. Deaths in the PP Sample

	NORMOTHERMIA	%	HYPOTHERMIA	%	Total	%
No	44	89.8	42	82.4	86	86
Yes	5	10.2	9	17.6	14	14
Total	49	100.0	51	100.0	100	100

Odds Ratio: 1.874 (0.514,7.729) Fisher's Exact Test p-value: 0.3896

Multi-variable Regression

This section presents the Day 90 mRS report for phase 2 of the study The Intravascular Cooling in the Treatment of Stroke 2/3 (ICTuS 2/3). The report is based on data locked as of May 15, 2015. Note, participants who died prior to the day 90 visit had their 90 day mRS set to 6.

• Primary Analysis: Univariate dichotomized day 90 mRS (defined as 0-1 vs 2-6)

A Fisher's Exact test was used to compare the rates (defined as a 0-1 vs 2-6) in day 90 mRS between the two groups, due to sites with sparse data the analysis was not stratified by study site.

• Sensitivity Analysis: Multivariable dichotomized day 90 mRS (defined as 0-1 vs 2-6)

A multivariable logistic model was performed to study the association between outcome and treatment, adjusting for the following pre-specified known confounders: baseline NIHSS score, history of diabetes, admission glucose, age and time to treatment.

Table VIIa. Univariate 90-day full scale modified Rankin scores for the ITT sample

	NORMOTHERMIA	%	HYPOTHERMIA	%	Total	%
0	4	7.3	9	14.3	13	11.0
1	17	30.9	12	19.0	29	24.6
2	4	7.3	7	11.1	11	9.3
3	7	12.7	10	15.9	17	14.4
4	14	25.5	12	19.0	26	22.0
5	4	7.3	3	4.8	7	5.9
6	5	9.1	10	15.9	15	12.7
Total	55	100.0	63	100.0	118	100.0

Table VIIb. Univariate 90-day dichotomized modified Rankin scores for the ITT sample

	NORMOTHERMIA	%	HYPOTHERMIA	%	Total	%
mRS 2-6	34	61.8	42	66.7	76	64.4
mRS 0-1	21	38.2	21	33.3	42	35.6
Total	55	100.0	63	100.0	118	100.0

Odds Ratio: 0.811 (0.355,1.846) Fisher's Exact Test p-value: 0.7003

Table VIII. Multi-Variable Regression of the 90-day modified Rankin scores in the ITT sample

This analysis was pre-specified in the trial statistical analysis plan. The included variables were chosen because they are known to influence 90-day outcomes (using the modified Rankin score). Note that only baseline stroke severity, as measured by the NIHSS, significantly influenced outcome.

	Odds Ratio	Lower 95% CI	Upper 95% CI	P-value
ARMHYPOTHERMIA	0.6221	0.2564	1.5097	0.2941
NIHSSBL	0.7865	0.7077	0.8742	<0.0001
AGE	0.9916	0.9509	1.0341	0.6943
DMYes	0.7062	0.2278	2.1891	0.5468
GLUCOSE	0.998	0.9902	1.0059	0.6212
ONSTOTPA.MIN	0.9938	0.9814	1.0064	0.3365

Table IXa. Univariate 90-day full scale modified Rankin scores for the PP sample

	NORMOTHERMIA	%	HYPOTHERMIA	%	Total	%
0	3	6.4	5	9.8	8	8.2
1	15	31.9	7	13.7	22	22.4
2	3	6.4	6	11.8	9	9.2
3	6	12.8	9	17.6	15	15.3
4	11	23.4	12	23.5	23	23.5
5	4	8.5	3	5.9	7	7.1
6	5	10.6	9	17.6	14	14.3
Total	47	100.0	51	100.0	98	100.0

Table IXb. Univariate 90-day dichotomized modified Rankin scores for the PP sample

	NORMOTHERMIA	%	HYPOTHERMIA	%	Total	%
mRS 2-6	29	61.7	39	76.5	68	69.4
mRS 0-1	18	38.3	12	23.5	30	30.6
Total	47	100.0	51	100.0	98	100.0

Odds Ratio: 0.499 (0.187,1.293) Fisher's Exact Test p-value: 0.1294

Decreased odds of a good outcome in the Hypothermia group.

Table X. Multi-Variable Regression of the 90-day modified Rankin scores in the PP sample

This analysis was pre-specified in the trial statistical analysis plan. The included variables were chosen because they are known to influence 90-day outcomes (using the modified Rankin score). Note that only baseline stroke severity, as measured by the NIHSS, significantly influenced outcome.

	Odds Ratio	Lower 95% CI	Upper 95% CI	P-value
ARMHYPOTHERMIA	0.2885	0.0983	0.8471	0.0237
NIHSSBL	0.7924	0.7023	0.8941	0.0002
AGE	0.9890	0.9398	1.0407	0.6690
DMYes	1.6408	0.4628	5.8181	0.4432
GLUCOSE	0.9984	0.9892	1.0076	0.7282
ONSTOTPA.MIN	0.9900	0.9759	1.0042	0.1638