Summary of Safety and Effectiveness Data

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I General Information

Device Generic Names: Water circulating cooling cap
Conductive cooling system
Thermal regulating system

Device Trade Name: Olympic Cool-Cap®

Applicant's Name and Address: Olympic Medical Corp.
5900 First Ave. South
Seattle, WA 98108

Premarket Approval (PMA) Number: P040025

Date of Panel Recommendation: _____

Date of Notice of Approval to the Applicant: _____

II Indications for Use

The Olympic Cool-Cap® is indicated for use in infants ≥ 36 weeks gestation at risk for moderate to severe hypoxic-ischemic encephalopathy to provide selective head cooling with mild systemic hypothermia to prevent or reduce the severity of hypoxic-ischemic encephalopathy.

III Device Description

A Basic scientific concepts

Due to the evolving pathogenesis of HIE, a window of opportunity exists to provide neuroprotection prior to the secondary phase of brain injury. This therapeutic window varies with individual physiology and circumstances. In general, however, hypothermia is believed to provide neuroprotection by suppressing a number of steps in the biochemical pathway leading to apoptotic cell death.

The type of hypothermic treatment administered with Cool-Cap is known as Selective Head Cooling. This technique entails cooling the head while providing radiant warmth to the remainder of the body. This allows the brain to be cooler than the rest of the body. As a result, neuroprotection is available to the brain while the relatively warmer (compared to the brain) core temperature results in fewer side effects than would occur if the entire body was maintained at a temperature low enough to ensure a therapeutic temperature in the brain.

B How the device functions

Cool-Cap is designed to provide selective head cooling with mild systemic hypothermia in newborns by maintaining water flow through the fitted cap and maintaining the cap water at an operator-specified temperature. To assist the operator in determining the appropriate cap-set temperatures, the device monitors and displays physiological temperatures (including the rectal temperature); the operator uses the rectal temperature reading as a guide to adjust the cap water temperature. The goal is to adjust the cap water appropriately in order to maintain the infant's rectal temperature at 34.5°C ± 0.5°C (34.0 – 35.0°C).

Cool-Cap consists of a mobile unit that supplies cooled water to a cap placed on the infant's head. Water is cooled with a thermostatically controlled cooler and circulated through the cap by an electrical pump and plastic tubing. The temperature of the cap is monitored and controlled to a user specified temperature within ± 0.1°C. The water circulation portion of the device is a closed system; it fills automatically from a 1000mL bag of sterile water. When cooling is complete, the system is drained into the same bag that may then be disposed of easily.

IV Contraindications, Warnings, and Precautions

A Contraindications

Contraindications for Cool-Cap include:

- Imperforate anus
- Evidence of head trauma or skull fracture causing major intracranial hemorrhage
- < 1,800 g birth weight
- Proven sepsis
- Hemorrhagic diathesis

B Warnings and Precautions

Warnings and Precautions for Cool-Cap include:

- This device should only be used by properly trained personnel and under the direct supervision of a licensed medical practitioner.
- Cooling should be in accord with the protocol used in the clinical trial:
  - Rectal temperature should be maintained within the range of 34°C – 35°C;
  - Cooling should be maintained for 72 hours; and
  - Active rewarming should not exceed 0.5°C per hour.
- Mild sinus bradycardia and hyperglycemia may occur during hypothermic treatment.
- Infants less than 2.5 kg may not require as much cooling.
- Place only the scalp (fontanel) temperature sensor under the cap. Other items may interfere with cooling or create areas of pressure.
- Remove diapers from infants undergoing treatment to allow maximum body exposure to the radiant warmer, and to allow for checks for meconium and/or a dislodged rectal temperature sensor.
- Infants with a birthweight of less than 2.5 kg and infants with cardiac compromise requiring inotrope support may require a higher cap temperature (e.g., 15°C) during the initial cool down and should be closely monitored. Make temperature adjustments early to avoid overshooting.
- Do not blow or circulate air over the patient. Convection caused by circulating air results in loss of heat from the patient – even if the air is warm.
- Hypothermia is known to increase oxygen consumption. Therefore, some infants may show a small increase in their oxygen requirement during the induction of hypothermia and require appropriate adjustments.
- Hypothermia can inhibit the metabolism and clearance of many anticonvulsants (including phenobarbitone, phenytoin, lidocaine, and the benzodiazepines) potentially prolonging their half-lives; therefore, whenever possible, measure the patient's blood levels and administer repeated doses with caution.

- Correct blood gases and pH values for core temperature.
- At very low temperatures (30-32°C) hypothermia may increase pulmonary hypertension. Over-cooling of infants, particularly very sick infants, should be avoided. Carefully manage ventilation and other therapies while cooling very sick infants.
- Do not initiate oral feeding during the cooling and rewarming processes of treatment.
- Remove the cooling cap set every 12 hours and carefully inspect the patient's scalp for irritative injury that may relate to the cap's use. Patients with hypotension or disseminated intravascular coagulation (DIC) are likely to be at greater risk of scalp injury. It is recommended that you advise parents that some degree of scalp edema is common but it resolves rapidly after removal of the cap or, in some cases, spontaneously despite continued cooling. Use of a larger cap size during cooling may help reduce scalp edema. In cases of local erythema, it is reasonable to briefly maintain the infant at the target rectal temperature with the cap off in order to give the scalp a chance to recover before reseating the caps and continuing with head cooling. If the erythema does not resolve, reseat the caps but recheck the scalp after 6 hours, then return to the every 12-hour check.
- Sclerema neonatorum – a generalized swelling and hardening of the skin, which is characterized by stony consistency that is cold and non-pitting – is an uncommon disorder associated with hypothermia. In the rare instance that it may occur, it may be characterized by an abrupt onset that may progress to generalized involvement within four days; however, there are not any reported long-term sequelae from this condition and it usually resolves within two weeks.
- Seizure activity may occasionally occur during rewarming. There is no evidence that rewarming is the cause of the seizures; rather, rewarming unmasks underlying seizure activity that was suppressed during cooling. The seizure activity is self-limiting and does not appear to have any implications for neurological recovery.

V Alternative Practices and Procedures

There are no approved alternative treatments for Hypoxic-Ischemic Encephalopathy. Support and treatment of symptoms are the current standard-of-care for HIE and include maintaining metabolic and respiratory parameters within the normal range as well as treating seizures with anticonvulsants.

VI Marketing History

The Olympic Cool-Cap® has no marketing history since it has not been sold in the U.S. or elsewhere.

VII Potential Adverse Effects of the Device on Health

Refer to Section IX-D-1 for details regarding the adverse events that occurred in the trial.

VIII Summary of Preclinical Studies

A Laboratory Studies

1 Biocompatibility Tests

The water cap is constructed of medical-grade polyurethane; only biocompatible materials are used in the cap. In addition to documentation provided by the polyurethane manufacturer, biocompatibility tests were performed by NAMSA in 1998 for the cap liner. Based on its contact with the infant's scalp, the cap is categorized as a surface device (skin) with prolonged contact (72 hours). Therefore, in accordance with ISO 10993-1 and FDA Blue Book Memorandum #G95-1 standards, the following tests were performed on the cap material: Cytotoxicity, Sensitization, and Irritation. Test results showed no evidence of cytotoxicity, sensitization or irritation. Tests for extractables were also performed; all results met the USP limits.

2 Electrical Safety Tests

Electromagnetic Immunity (EMI) and Compatibility (EMC) tests for the commercial version of Cool-Cap were performed. Cool-Cap was determined to meet the requirements of IEC 60601-1-2 (2nd Edition, 2001) "Medical Electrical Equipment: Part 1 General Requirements for Safety".

B Animal Studies

After IDE approval for the clinical study, the Cool-Cap was tested in the piglet by a group of researchers in Bristol, England. These data demonstrated that it was possible to use the device to cool the brain more than the body,[1] and to maintain this gradient for a 24-hour period, while keeping the core temperature mildly hypothermic.[2] Furthermore, brain measurements were made in the striatum, demonstrating that

selective head cooling can effectively cool deep brain structures, such as the basal ganglia, as well as the cortex. These studies confirmed clinical observations that it was possible to establish a temperature gradient between the deep brain structures and the body, when using a cooling cap, by warming the body with an overhead heater,[1] and that selective head cooling did not result in either skin injury or superficial brain hemorrhage.[2] These studies further demonstrated that this selective head cooling procedure safely improved outcome following a 45-minute global hypoxic-ischemic insult in the piglet model.[3]

IX Summary of Clinical Studies

A Study Design

The trial was an international multi-center, prospective, randomized study. The outcome measure of severe neurodevelopmental disability was fully masked.

In summary, within six hours of birth, and after inclusion/exclusion criteria were met and informed consent was obtained, infants were randomized to either a non-cooled control group with rectal temperature maintained at 37 ± 0.5°C or to a treatment group for head cooling with mild systemic hypothermia.

For those infants randomized to head cooling, a water-circulating cooling cap was fitted around the infant's scalp to cool the head and an overhead radiant warmer was set at 100%. The core rectal temperature of the infant was controlled by adjusting the cap water temperature to maintain the rectal temperature at the target range of 34.5 ± 0.5°C. The infant's rectal, nasopharyngeal, scalp (fontanel) and skin (abdominal) temperatures were continuously monitored along with metabolic, cardiovascular, pulmonary and coagulation status. Cooling was maintained for 72 hours, followed by slow rewarming (with the goal of raising the rectal temperature by 0.5°C/hour). This procedure is described in further detail in the trial's Study Manual.

There were two primary research objectives:

1) To determine whether treatment of moderate or severe hypoxic-ischemic encephalopathy in term infants with head cooling and mild systemic hypothermia could produce meaningful improvements in neurodevelopmental outcome and survival rates at 18 months of age.

2) To confirm the safety of prolonged head cooling with mild systemic hypothermia in term newborn infants with moderate or severe hypoxic-ischemic encephalopathy.

B Patient Assessment

Prior to treatment, and as a requirement of the inclusion criteria, aEEG recordings were taken and analyzed by qualified personnel. During the 72-hour treatment, cardiovascular, hematologic, metabolic, blood chemistry and temperature data were recorded.

Six-month follow-up visits were conducted to help cohort retention in the study. Data collected at this visit included head circumference, weight and length measurements; there were no outcome measures collected at this six-month visit.

At 18 months, subjects completed the study with the following: neurodevelopmental examination, measurements of head circumference, weight and length, psychometric testing with Bayley-II, audiology assessment, and ophthalmology examination. All exams were performed by qualified personnel who were masked to the treatment. A socio-economic status questionnaire was also administered.

C Demographic Data

There were a total of 25 sites that combined to enroll 235 patients in the clinical trial. One subject was canceled from the study due to inadequate consent resulting in a total patient count of 234. Of these 234 patients, 75% (176/234) were enrolled at U.S. sites and 25% (58/234) were enrolled internationally. The international enrollees were distributed as follows: 11% (26/234) from England, 9% (21/234) from Canada, and 5% (11/234) from New Zealand. See Table 1 for a breakdown of the patient enrollment distribution by site.

As seen in Table 2, baseline patient characteristics were generally well balanced. Due to a decision to stratify the treatment randomization by participating site only and the generally small number of patients enrolled per site, occasional imbalance can occur as in the case of Apgar score at five minutes after birth and aEEG background (both towards more severely injured infants in the cooled group).

Table 1 – Enrollment distribution by clinical site

Site	Cooled	Control	Total
U.S. SITES			
Children's Hospital of Denver (CO)	11	12	23
Children's Hospital of NY (Columbia Presby.)	9	9	18
Children's Hospital of Minneapolis (MN)	8	8	16
Schneider Children's Hospital (NY)	7	7	14
Duke University Medical Center (NC)	7	7	14
Vanderbilt University Medical Center (TN)	7	6	13
University of Michigan (Mott Children's)	6	6	12
Arkansas Children's Hospital	6	5	11
Children's Hospital of Pittsburgh / Magee	6	4	10
Golisano Children's Hospital (Rochester,NY)	4	6	10
Univ. of California – San Diego (Hillcrest)	4	4	8
Children's Hospital at Oakland (CA)	3	5	8
Thomas Jefferson University (Philadelphia)	3	3	6
Children's Hospital of Oklahoma	2	2	4
Northwestern (Chicago) – Children's Memorial Hospital / Prentice Women's	1	2	3
Univ. of California – San Francisco	1	1	2
Johns Hopkins Hospital (Baltimore, MD)	2	0	2
Wake Forest Univ. School of Medicine (NC)	1	0	1
Univ. of Illinois at Chicago	0	1	1
U.S. Subtotals	*88*	*88*	*176*
INTERNATIONAL SITES			
Southmead and St. Michael's* Hospitals (Bristol, England)	11	10	21
Univ. College Hospital (London, England)	1	3	4
Hammersmith Hospital (London, England)	0	1	1
Edmonton – University of Alberta / Royal Alexandra Hospital (Canada)	11	9	20
Children's Hospital of Eastern Ontario / Ottawa Hospital (Canada)	0	1	1
University of Auckland (New Zealand)	5	6	11
International Subtotals	*28*	*30*	*58*
GRAND TOTAL	**116**	**118**	**234**

* does not include subject canceled from this site

Table 2 – Baseline characteristics of all enrolled infants

	Cooled (n=116)		Control (n=118)		Total (n=234)	
Gestational Age (weeks)						
Mean (Std. Dev.)	38.9	(1.6)	39.1	(1.4)	39.0	(1.5)
Birth Weight (g)						
Mean (Std. Dev.)	3399	(663)	3504	(625)	3452	(645)
Birth Length (cm)						
Mean (Std. Dev.)	50.8	(3.5)	51.5	(3.0)	51.2	(3.2)
Head Circumference (cm)						
Mean (Std. Dev.)	34.6	(1.8)	35.0	(1.9)	34.8	(1.8)
Gender						
Female	52	45%	60	51%	112	48%
Male	64	55%	58	49%	122	52%
Apgar at 5 minutes*						
0 - 3	88	77%	77	68%	165	72%
4 - 6	25	22%	31	27%	56	24%
7 - 10	2	2%	6	5%	8	3%
Assisted Ventilation Pre-randomization						
No	0	0%	0	0%	0	0%
Yes	116	100%	118	100%	234	100%
Pre-randomization aEEG: Background						
Normal/Mildly Abnormal	7	6%	9	8%	16	7%
Moderately Abnormal	63	54%	76	64%	139	59%
Severely Abnormal	42	36%	32	27%	74	32%
Unclassifiable**	4	3%	1	1%	5	2%
Pre-randomization aEEG: Presence of Seizure						
No	48	41%	43	36%	91	39%
Yes	68	59%	75	64%	143	61%
Age at Randomization (hours)						
Median (range)	4.8	(2.6-6.0)	4.7	(2.1-6.1)	4.8	(2.1-6.1)
> 2 – 4	29	25%	24	20%	53	23%
> 4 – 6	86	74%	92	78%	178	76%
> 6	1	1%	2	2%	3	1%

* data available for 229 patients
** all unclassifiable aEEGs were eligible for the trial due to the presence of seizures

D Data Analysis and Result

1 Safety

Since all except one of the anticipated Adverse Events (AEs) (evidence of skin breakdown due to pressure of cooling cap; see Table 3) could be consequences of hypoxia-ischemia, detailed statistical testing was essential to determine whether cooling could be a contributing factor.

Per protocol, due to the multiplicity of adverse events being compared, two-sided p values < 0.01 are considered statistically significant. P values < 0.05 but ≥ 0.01 are considered borderline significant.

As shown in Table 3, there was no statistically significant difference in the rates of any of the Serious Adverse Events. There was also no statistically significant difference in the rates of 16 of the 18 types of anticipated AEs. Two anticipated AEs did, however, occur more frequently in the cooled group: minor cardiac arrhythmias and “other” AEs (most of which were scalp edema).

Although minor cardiac arrhythmias occurred more frequently in the cooled infants, this was not unexpected since mild sinus bradycardia is known to be associated with hypothermia. It is important to note that none of the cooled infants experienced a major cardiac arrhythmia. Thus, the 9-fold increase of minor cardiac arrhythmias (9%, or 10/112, in the cooled group vs. 1%, or 1/118, in the control group) is anticipated for hypothermic treatment and does not demonstrate a significant clinical safety concern.

Scalp edema also occurred in 21% (23/112) of the cooled infants. All except three (87%, or 20/23) of the edema cases were of mild to moderate severity; the remaining three were severe. However, all 23 cases of scalp edema resolved prior to or after completion of cooling treatment with either no action or massage, changing position, or cap adjustment. Scalp edema is presumably a direct result of thermal effects on capillary permeability and pressure from the cooling cap. However, it is common in all vaginally delivered infants and, most importantly, such edema does not cause long-term concern.

For the AE of elevated liver enzymes, the incidence in cooled infants (38%, or 42/112) was lower than that in control infants (53%, or 62/118) with a borderline statistical significance (p=0.02). This was possibly a chance occurrence due to the multiplicity of adverse events analyzed.

Table 3 – Analysis of device safety based on occurrence of adverse events (n=230; entire 234 population excluding four patients randomized to cooling but not cooled)

AE Code	Adverse Event	Cooled (n=112)		Control (n=118)		Fisher's exact P value
Major Adverse Events						
01	Major cardiac arrhythmia	0	0%	0	0%	----
02	Major venous thrombosis	0	0%	2	2%	0.50
03	Severe hypotension despite full support	3	3%	3	3%	1.00
04	Unanticipated serious adverse event	1	1%	0	0%	0.49
Other Anticipated Adverse Events						
05	Cardiac arrhythmia (not reaching code 01)	10	9%	1	1%	0.004*
06	Hypotension (not reaching code 03)	62	55%	61	52%	0.60
07	Coagulopathy	21	19%	17	14%	0.38
08	Prolonged coagulation times	56	50%	50	42%	0.29
09	Abnormal renal function	73	65%	83	70%	0.48
10	Hyponatremia	49	44%	46	39%	0.50
11	Hypokalemia	71	63%	73	62%	0.89
12	Bone marrow depression	36	32%	26	22%	0.10
13	Elevated liver enzyme levels	42	38%	62	53%	0.02**
14	Metabolic acidosis	22	20%	27	23%	0.63
15	Respiratory distress	94	84%	92	78%	0.31
16	Systemic infection	1	1%	2	2%	1.00
17	Hemoconcentration	3	3%	1	1%	0.36
18	Hypoglycemia	14	13%	20	17%	0.36
19	Hypocalcemia	49	44%	51	43%	1.00
20	Skin breakdown due to cooling cap pressure	0	0%	0	0%	----
21	Difficulties in temperature control	36	32%	27	23%	0.14
22	Other	51	46%	26	22%	0.0003*

* Statistically significant finding ($p < 0.01$)
** Borderline statistically significant finding ($0.01 \leq p < 0.05$).

With regards to mortality, as shown in Table 4, there was no evidence that the death rates differed between the two study groups (p=0.48). Mortality rates were 33% (36/108) in the cooled group and 38% (42/110) in the control group.

Table 4 – Mortality rates for enrolled population (n=234)

	Cooled (n=116)		**Control** (n=118)		**Total** (n=234)	
	N	%	N	%	N	%
Survival Status						
Alive	72	62%	68	58%	140	60%
Dead	36	31%	42	36%	78	33%
Unknown	8	7%	8	7%	16	7%

The majority of the deaths (53/78 or 68%) occurred within seven days after randomization. Deaths during this time period included 26 in the control group (26/78, or 33%) and 27 in the cooled group (27/78, or 35%).

Deaths of three cooled infants were reported as remotely related to study treatment with no explanation given; cause of death was listed as HIE. After a full review of the case history and post-mortem findings by the Medical Officer and Drug & Device Development Co., Inc. (DDD, a contract research organization), no connection was found to the study treatment. Therefore, the three deaths remain as classical HIE cases with no relationship to the study treatment.

Thus, considering rates of adverse events as well as mortality, it may be concluded that selective head cooling with mild systemic hypothermia may be safely administered with Cool-Cap for the patient population and indication for use discussed in this PMA.

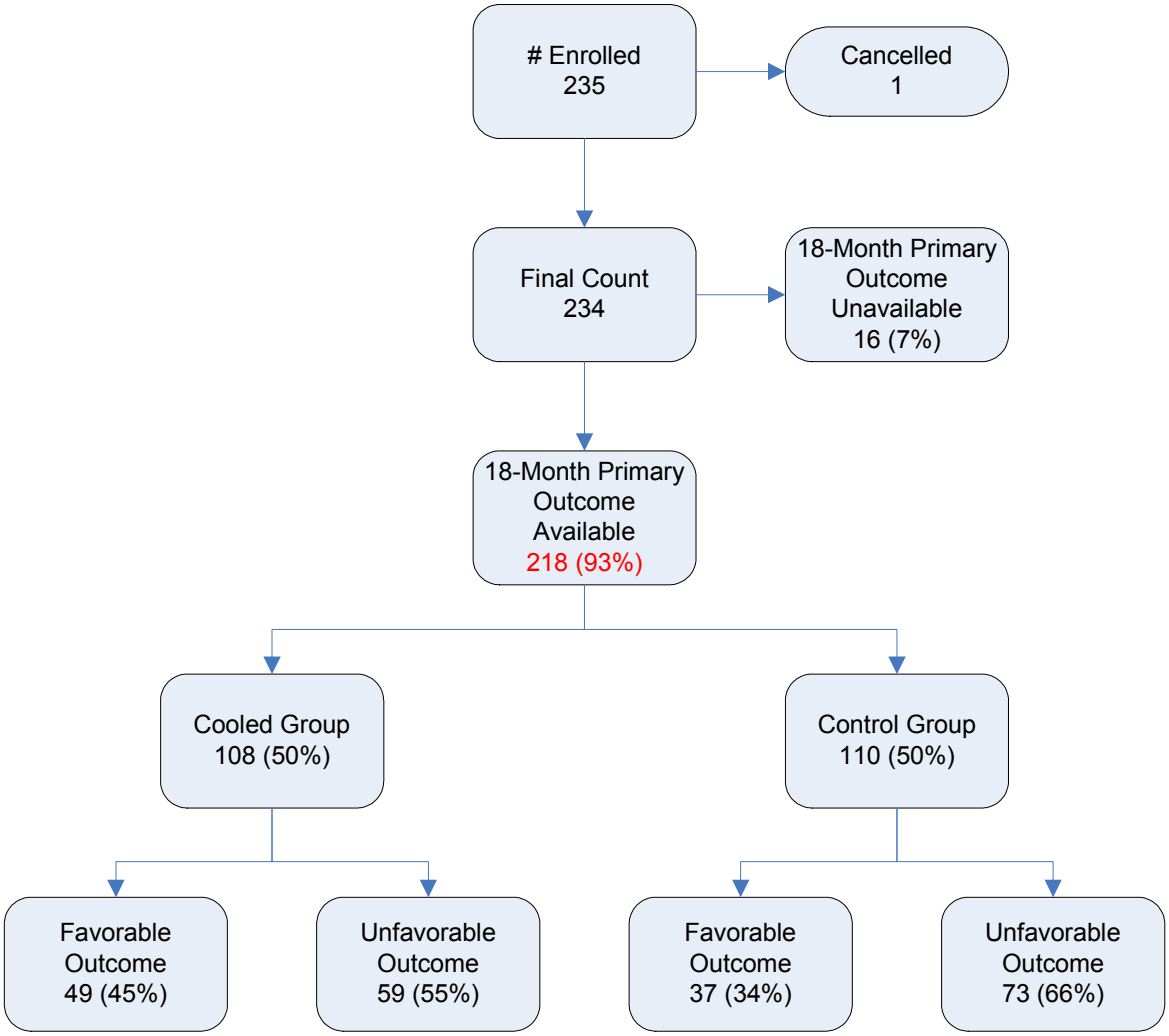
2 Effectiveness

As shown in Figure 1 on page 15, 18-month primary outcome results were available in 93% (218/234) of the subjects; primary outcome results were unavailable for 7% (16/234) of the subjects. Of the 218 subjects, 50% (110/218) were in the control group and 50% (108/218) in the cooled group. Within the control group, 34% (37/110) had a favorable outcome while 45% (49/108) had a favorable outcome in the cooled group. Fisher's exact test showed no statistical significance (p=0.10).

However, the randomization resulted in a greater proportion of infants with severe aEEG baseline in the cooled group (37%, or 40/108) as compared to the control group (28%, or 31/110). Logistic regression analysis adjusting for baseline aEEG background, seizure status, Apgar score, birth weight, gender and age at randomization indicated a treatment effect of statistical significance (p=0.042).

Therefore, it was concluded that, in term neonates with moderate to severe HIE, selective head cooling with mild systemic hypothermia, when administered with the Olympic Cool-Cap® in the manner described, is associated with a reduction in death and severe neurodevelopmental disability.

Figure 1 – Primary outcome (death and severe neurodevelopmental disability in survivors at 18 months of age) for subjects for whom18-month primary outcome is known (n=218)



Fisher's Exact Test for Primary Outcome: p=0.10
BUT
37% (40/108) of Cooled Group had Severe aEEG Baseline
28% (31/110) of Control Group had Severe aEEG Baseline
SO
Adjusting for baseline aEEG background, seizure status, Apgar score, birth weight, gender & age at randomization
Logistic Regression Analysis: p=0.042
(Statistically Significant Treatment Effect)

E Device Failures and Replacements

There were a total of 11 reported failures that were attributed to equipment issues as opposed to operator error or environmental conditions. Five of these were corrected in the field. Six were resolved by replacing the equipment.

The system was built with self-diagnostic capability. In the event of a system problem, the system was disabled and an error code was displayed. The failures are listed by error in the table code below.

The most common error (E-96) indicated that the system was not able to properly fill with water when starting up. Usually this involved a pinch valve that controls water flow into the system from the 1000 ml bag of sterile water. After the system was drained, water remained standing in plastic tubing above this valve. If the system was not used for a number of months, the water evaporated causing the tubing to become sticky. This kept the tubing closed when the valve opened and the system would not fill with water. This resulted in a system error E-96. This condition could be resolved in the field by applying pressure to the bag of water or removing a side panel and repositioning the tubing. In three cases it was necessary to replace the system, as the site personnel were unable to clear the blockage. The valve design was changed in the commercial version of Cool-Cap.

The rest of the errors were random electrical or mechanical component failures.

Only one infant of the 235 enrolled was not treated due to a failure of the equipment. Cooling was delayed until after 6 hours for one other infant due to an equipment issue that was resolved by using their backup system.

The following summarizes the failures:

Failures repaired in the field
- 2 – E-96 (Pinch Valve)
- 2 – E-91 (Non-volatile RAM reset)
- 1 – E-92 (Fan Failure)

Units Replaced
- 3 – E-96 (Pinch Valve)
- 1 – E-96 (Stuck Float Valve)
- 1 – Multi (Failed Power supply)
- 1 – E-97 (Failed Thermistor Circuit)

X Conclusions Drawn from the Studies

A Risk/Benefit Analysis

Neonatal hypoxic-ischemic encephalopathy is a difficult disease for which there is no treatment. A significant percentage of those infants afflicted have a very poor outcome with death or severe neuromotor disability. The syndrome is absolutely devastating to families with enormous emotional and economic cost. To date no effective therapy has been developed; only supportive care including anticonvulsant therapy can be offered.

Finding an effective therapy has been the subject of a large research effort internationally for over two decades. The results of this trial are the first to show efficacy. The reduction in unfavorable outcome (death or severe neurodevelopmental disability) in the absence of any evidence of safety concerns must be seen as a major clinical benefit of fundamental importance to the families involved.

While the benefits of neuroprotective treatment for HIE are substantial, the risks are minimal. Although mild sinus bradycardia and scalp edema occur in higher frequencies in treated patients, these are not life-threatening conditions. Mortality rates were not higher in the treated group than in the control group. Furthermore, all deaths were reviewed by the trial's Medical Officer and determined to be unrelated to Cool-Cap or to the trial protocol.

Olympic Medical neither proposes nor plans any additional studies or surveillance related to this clinical trial. Some of the enrolling sites have shown an interest in following the subjects to school age in order to assess cognitive differences between cooled and control patients. The Sponsor is working with this group to encourage their efforts but is unable to contribute any additional financial support to this scientific endeavor. Sites interested in additional school age follow-up are in the process of pursuing grant funding through other channels. In addition, the Vermont Oxford Network is investigating the possibility of creating a registry for HIE infants treated with hypothermia.

B Safety and Effectiveness

The randomized, controlled trial sponsored by Olympic Medical in support of the Olympic Cool-Cap® clearly demonstrates that selective head cooling with mild systemic hypothermia, when used in infants ≥ 36 weeks gestation at risk for moderate to severe hypoxic-ischemic encephalopathy (HIE), can safely prevent or reduce the severity of HIE.

In the population for whom 18-month primary outcome was known (n=218), after adjusting for randomization differences in the two groups, treatment effect was statistically significant (p=0.042) with favorable outcomes in 34% (37/110) of the control group and 45% (49/108) of the cooled group.

With regards to safety, there was no statistically significant difference in the rates of any of the Serious Adverse Events. There was also no statistically significant difference in the rates of 16 of the 18 types of anticipated AEs. Two anticipated AEs did, however, occur more frequently in the cooled group: minor cardiac arrhythmias and “other” AEs (most of which were scalp edema).

Although minor cardiac arrhythmias occurred more frequently in the cooled infants, this was not unexpected since mild sinus bradycardia is known to be associated with hypothermia. It is important to note that none of the cooled infants experienced a major cardiac arrhythmia. Thus, the 9-fold increase of minor cardiac arrhythmias (9%, or 10/112, in the cooled group vs. 1%, or 1/118, in the control group) is anticipated for hypothermic treatment and does not demonstrate a significant clinical safety concern.

Scalp edema also occurred in 21% (23/112) of the cooled infants. All except three (87%, or 20/23) of the edema cases were of mild to moderate severity; the remaining three were severe. However, all 23 cases of scalp edema resolved prior to or after completion of cooling treatment with either no action or massage, changing position, or cap adjustment. Scalp edema is presumably a direct result of thermal effects on capillary permeability and pressure from the cooling cap. However, it is common in all vaginally delivered infants and, most importantly, such edema does not cause long-term concern.

Thus, it may be concluded that selective head cooling with mild systemic hypothermia, as administered with Cool-Cap, can safely prevent or reduce the severity of moderate to severe hypoxic-ischemic encephalopathy when used in infants ≥ 36 weeks gestation.

XI Panel Recommendations

XII CDRH Decision

XIII Approval Specifications

XIV References

1. Thoresen,M., Simmonds,M., Satas,S., Tooley,J. & Silver,I.A. Effective selective head cooling during posthypoxic hypothermia in newborn piglets. *Pediatr. Res.* **49**, 594-599 (2001).

2. Tooley,J., Satas,S., Eagle,R., Silver,I.A. & Thoresen,M. Significant selective head cooling can be maintained long-term after global hypoxia ischemia in newborn piglets. *Pediatrics* **109**, 643-649 (2002).

3. Tooley,J.R., Satas,S., Porter,H., Silver,I.A. & Thoresen,M. Head cooling with mild systemic hypothermia in anesthetized piglets is neuroprotective. *Ann Neurol.* **53**, 65-72 (2003).