Executive Summary

Introduction

This is the Executive Summary for the Olympic Cool-Cap® Premarket Approval Application (P040025). The device has been reviewed by the Restorative Devices Branch of the Division of General, Restorative and Neurological Devices at the Center for Devices and Radiological Health of the Food and Drug Administration. Your time and effort in review of this application is greatly appreciated.

The Executive Summary contains FDA's summary review memo of the preclinical, clinical and statistical information. The memo contains the following sections:

Information	Page Number
Manufacturer information	2
Device Description	3
Indications for Use	10
Preclinical	11
Clinical	17
Statistical	29
Deficiencies and Responses	31

Manufacturer Information

Applicant name and address:
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Seattle, Washington 98108

Manufacturing sites/addresses
Olympic Medical
5900 First Ave. So.
Seattle, Washington 98108

Device Description

A complete description, with diagrams and photographs, of the Olympic Cool-Cap® can be found in the device description section of the CD ROM supplied by the sponsor. For completeness of the Executive Summary, a brief description of the device is presented here.

General Device Description

The Olympic 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).

The Olympic 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 water circulation portion 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 easily discarded.

The Olympic Cool-Cap® allows the operator to adjust the cap temperature within ± 0.1°C. The operator is responsible for monitoring the infant's rectal temperature and adjusting the cap temperature to keep the rectal temperature within the target range. The system displays patient temperatures with the rectal temperature reading prominently displayed. Cool-Cap is designed to work with a radiant warmer to maintain the infant's core temperature, as indicated by the rectal temperature, within the target range of 34.5°C ± 0.5°C (34.0 – 35.0°C).

Main components

- Cooling Unit: Portion of the Olympic Cool-Cap® responsible for controlling the cap water's temperature and for pumping water through the Water Cap

- Control Unit: Portion of the Olympic Cool-Cap® responsible for displaying temperatures and providing user control buttons. The Control Unit also sends appropriate commands to, and obtains data from, both the Cooling Unit and the Temperature Sensor Module to provide overall control of the system.

- Temperature Sensor Module: Component with input from five Temperature Sensors [redacted] and output to Control Unit.

- Water Cap: Polyurethane water-filled cap placed in direct contact with infant's scalp for effective heat conduction. (Note that the former term for this component was "Cap Liner".)

- Water Cap Retainer: Blue fabric cap made of Spandex responsible for holding the Water Cap firmly to the infant's scalp.

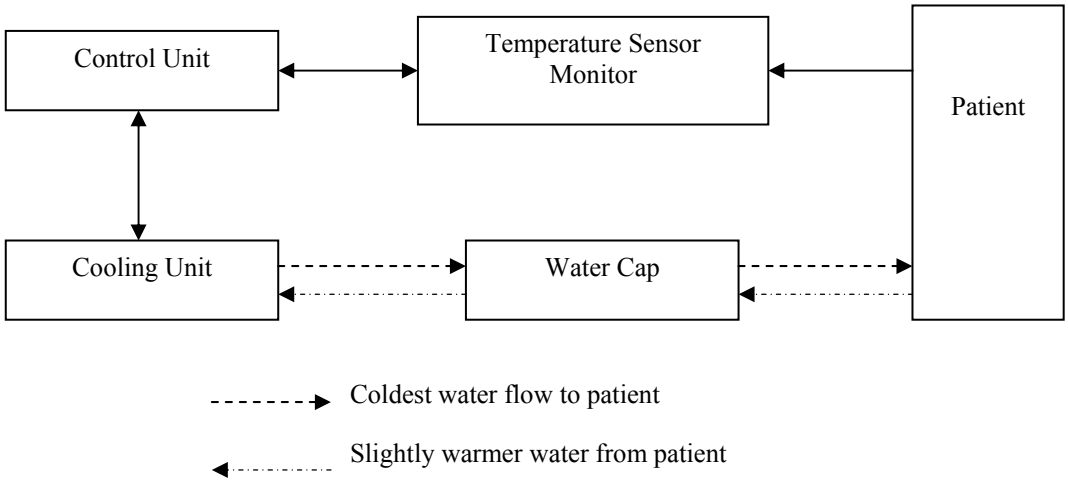
- Insulating Cap: Polyester fleece with metallicized polyester outer surface placed over the Water Cap Retainer and meant to provide insulation from radiant warmth.

The functional components of the Olympic Cool-Cap® relate to each other in the following manner:

1. The Control Unit sits on top of the mobile Cooling Unit. The operator enters the target cap water temperature into the Control Unit; the Cooling Unit then makes the system adjustments required to maintain the target cap water temperature.

2. The Cooling Unit pumps water through the Water Cap. The Water Cap is in contact with the patient's scalp.

3. Temperature sensors for recording the patient's physiological temperatures are connected to the Temperature Sensor Module. The Temperature Sensor Module is then electronically connected to the Control Unit to allow for display of the patient temperatures.



Control Unit:

Olympic Cool-Cap® and Components:

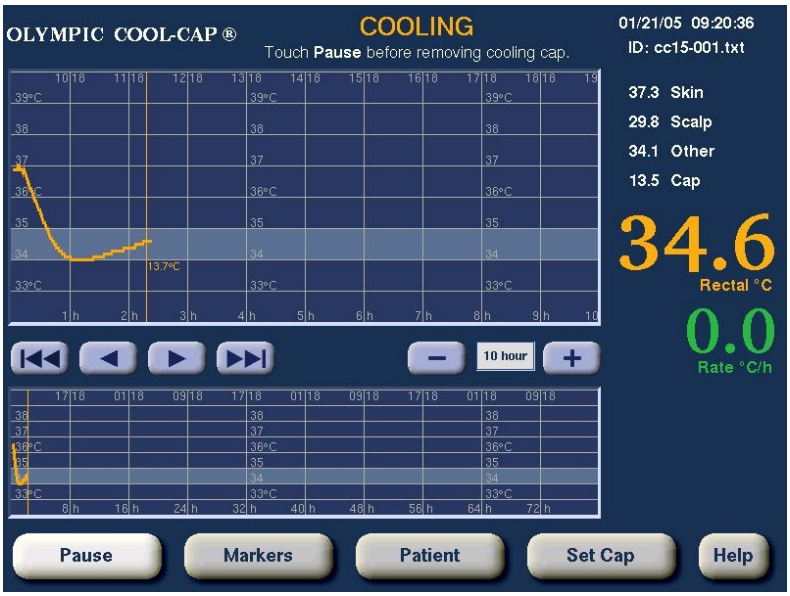
User Interface

The user primarily monitors the infant's rectal temperature using the built-in temperature measurement/display circuitry to determine the level of cooling being achieved. The user may also monitor skin (abdominal) and scalp (fontanel) temperatures. The user adjusts the cap target temperature to produce appropriate cooling in the infant (i.e. obtaining a target rectal temperature of 34.5°C ± 0.5°C). The unit sounds an alarm when the rectal temperature is above or below the target range. There is a time lag between adjustments to the cap temperature and rectal temperature response. As a result, it is recommended that the user allow 45 minutes to pass before making subsequent adjustments to the cap temperature in order to allow time for the infant's body to equilibrate to the temperature change.

The user interface displays rectal temperature is displayed prominently on the right side of the screen. A graphical representation of the rectal temperature is also provided. There is a highlighted region of the graph represents the target rectal temperature range (34.0 – 35.0°C). Additional patient temperatures are displayed numerically in the top right corner: skin, scalp and an optional reading. The rate of change for the rectal temperature

is displayed because of its value during the induction and rewarming phases. Treatment duration is also displayed throughout the treatment procedure.

The use interacts with the screen by touch (i.e., it is a touch-screen).



Wizard Screens

Since infants at risk for HIE present at a low frequency (1 to 4 in 1,000 live births), the Olympic Cool-Cap® system may be used infrequently. The purpose of the Setup Wizard is to assist the user in performing the steps needed prior to commencing treatment. Setup steps include connecting the water bag, main hose and cap connector tubes, attaching the Temperature Sensor Module and the various patient temperature sensors, applying the water cap, water cap retainer and insulating cap, and positioning the heat shield above the infant's head. Note that the wizard also recommends a cap size and starting cap water temperature based on the infant's weight as entered by the user. A Rewarm wizard is provided to assist with rewarming (removing the cap components and heat shield and prompting the user to increase the radiant warmer servo-control setting). Also, the Shutdown Wizard leads the user through system shutdown (removing the temperature sensors, disconnecting and draining the hose and tubing, and cleaning the system).

Cooling System

Thermoelectric solid-state devices are attached to an aluminum heat-transfer block that has been [redacted]. When power is applied to the thermoelectric devices, the heat-transfer block is cooled. Water circulating through this block is also cooled.

The temperature of the water entering and leaving the heat-transfer block is monitored. Power to the thermoelectric modules is controlled to obtain a target temperature that is

the average of the cap inflow and outflow temperatures. This average temperature has been shown to accurately represent the temperature at the cap.

Radiant Warmer

The system is used in conjunction with a standard, commercially available radiant warmer. The radiant warmer is directed at the infant's torso and adjusted to maintain 100% output. The infant's head is shielded from the radiant warmer. After completing 72 hours of hypothermic treatment, the patient is rewarmed slowly so as to prevent cardiovascular difficulties. The target rate of increase for the patient's rectal temperature during this rewarming period is 0.5°C per hour.

Temperature Sensors

Cool-Cap uses [redacted] medical temperature sensors. The thermistors used to obtain temperature measurements from the scalp/fontanel and abdomen/skin are [redacted]. The [redacted] probe is designed for skin surfaces [redacted]. The rectal probe is a smaller (9 Fr, rather than 12 Fr) version of the [redacted] general-purpose esophageal/rectal probe; the smaller diameter better accommodates the neonatal patient. The sensors are capable of an accuracy of ±0.1°C from 25° to 45°C.

All original [redacted]packaging is retained; additional identification stickers are placed on each of the packages in order to identify which sensor is used for a given patient location. The sensors (rectal, skin, scalp, radiant warmth) and [redacted]adhesive pads (also from [redacted]) are all packaged together and identified as the Cool-Cap "Temperature Sensor Set". The customer will be able to purchase additional temperature sensor sets after purchase of the Cool-Cap device.

The rectal, scalp, skin and radiant warmth sensors are provided in the "Temperature Sensor Set" provided with Cool-Cap. Additional sets of these disposable sensors will be available for purchase.

The radiant warmth sensor is not sold by[redacted]. It is a commercially available temperature sensor and is being used to provide relative readings rather than precise measurements. So, with regards to accuracy, it is not critical for the radiant warmth sensor because it is meant only to give a qualitative reading of the amount of radiant warmth reaching the infant (0%, 20%, 40%, 60%, 80%, 100% of maximum warmth). Note that, unlike the other temperature sensors, the radiant warmth sensor is not in contact with the infant.

As a result of receiving questions from the FDA, the sponsor reviewed their labeling further and determined that the Operator's Manual will clearly state that any "other" sensor used is not provided by Olympic Medical and must be a [redacted] disposable medical temperature sensor or equivalent. The Sponsor will further state that Cool-Cap's temperature readings are only accurate when used with temperature sensors capable of an accuracy of ±0.1°C from 25° to 45°C (as is provided with the [redacted]probes made available by Olympic Medical for the Cool-Cap device). Note that these changes have been incorporated into the Operator's Manual.

Differences between trial device configuration and proposed commercial device configuration

Nearly seven years have elapsed since the devices used in the clinical trial were originally designed. Some of the system components, such as the microprocessor, have become obsolete in that time. As a result, Olympic Medical redesigned the electronic control section of the Cool Olympic Cool-Cap® system and has proposed that the redesigned system be commercially distributed if the PMA is approved. This has required rewriting the software control system as well. The proposed commercial configuration uses the identical cooling hardware, water circulation, cap design, and cooling system control algorithms. Experience from the clinical trial is also reflected in the labeling, and the sponsor has revised the instructions to provide more information on how to operate the device to achieve the desired cooling protocol.

The key difference in the two configurations of the Olympic Cool-Cap® is the software control system. The new system has been redesigned with improvements in the user interface. For example, a full color graphic display is included. This provides flexibility in the data presented to the user as well as more informative displays, such as temperature trend graphs. More importantly, automated, context appropriate prompts have been built in to guide the user through the cooling protocol based on input from the various measurements from the system. For example, in the clinical trial system, during the cool-down period the user had to estimate the rate of change of the rectal temperature by observing the rectal temperature display. If the temperature were falling too fast or too slowly they would make adjustments of the cap temperature. In the proposed commercial device, the system calculates and displays the rate of change for the user. The device also provides prompts for adjustment of the radiant warmer and other critical parts of the protocol. Note that the proposed commercial system does not make these adjustments itself. Instead, the user continues to control the cap water temperature and the radiant warmer setting.

The sponsor believes that these modifications will result in an improved device and should allow the user to more reliably implement the cooling protocol while maintaining the performance-critical, cooling-related components from the clinical trial system.

Differences between the Olympic Cool-Cap® used in the clinical trial and that designed for commercial distribution.

Item	**Clinical Trial System**	**Proposed Commercial System**
Microprocessor	NEC V25 Microcontroller	Pentium style microprocessor
Operating System	Custom embedded	Linux
Displays	7 segment LED	10.4” color LCD
Controls	Push buttons	Touch-screen
Cooling System	2 Peltier devices	2 Peltier devices
Water Circulation	[redacted]	[redacted]

Coolant	Sterile water	Sterile water
Cap	Custom design, 2 sizes	Same w/ an additional larger size
Sensors	5 physiologic; 3 system	5 physiologic (nasopharyngeal now optional, radiant warmer sensor added; 6 System (3 additional exchange block thermistors added for redundancy
User prompts	None – hard copy user manual	Built-in study manual based on patient specific data
Data displayed	Physiologic and system	Physiologic Rate of change of rectal temp Trend graphs (rectal & rate) User prompts System temperatures through service mode
Alarms	Rectal temp over/under range System performance	Rectal temp over/under range System performance (alarms now include user and/or protocol prompts)

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 (HIE) to provide selective head cooling with mild systemic hypothermia to prevent or reduce HIE.

Preclinical Testing

Device Verification Testing

The following table summarizes the verification testing performed on the Olympic Cool-Cap:

Test performed	Standard to which tested	Test Facility
Biocompatibility tests for water cap • Sensitization • Cytotoxicity • Skin irritation	AAMI/ANSI/ISO 10993-1:1997 • 10993-10 • 10993-5 • 10993-10	[redacted]
Validation tests for Cool-Cap	N/A	Olympic Medical
Type tests regarding basic safety (as per 60601-1) • Electrical shock hazards • Mechanical hazards • Excessive temperature • Hazardous output • Abnormal operation & fault conditions • Constructional requirements	IEC 60601-1 (1998) CSA tests actually performed to: • IEC CAN/CSA C22.2 No. 60601-1-M90 • EN 60601-1-1 (IEC60601-1, Amendment I and II) • UL 60601-1:2003	[redacted]
Type tests regarding electromagnetic compatibility	IEC 60601-1-2 (2nd edition, 2001)	[redacted]
Type tests verifying Cool-Cap meets design specifications	N/A	Olympic Medical
Package (shipping) vibration tests	ASTM D4169 – Schedule A, ALII	[redacted]

Device Validation Testing

Due to design differences between the device that is the subject of this PMA and the actual device used in the clinical investigation validation testing was required to demonstrate that the differences between the two devices will not affect the safety and effectiveness of the device. Thus, the sponsor has provided results of a series of validation tests which include the following:

- Assessment Test: control module → partial software – setup, rewarming and shutdown wizards
- Preliminary Validation Test: prototype device at Olympic Medical → preliminary software

- Validation Test

Assessment Test

The purpose is for NICU-based clinicians to assess the graphical user interface, software controls, and software-based wizards developed for the commercial device. This test was performed in August 2004 with five NICU personnel on the control module. The test participants reviewed the graphical user interface, software controls and soft-ware based wizards (setup, rewarming and shutdown). All test participants completed an 8-page test questionnaire.

A total of five test participants were questioned at two locations: [redacted], both being test sites in the clinical investigation. The test participants may be described as follows: TP #1: [redacted], *Nurse coordinator*, 0 infants cooled in trials TP #2: [redacted], *Neonatologist*, 3 infants cooled in Pivotal Trial TP #3: [redacted], *Neonatologist*, 13 infants cooled in Pivotal Trial and 1 infant cooled in Continued Access Trial TP #4: [redacted], *Research nurse*, 13 infants cooled in Pivotal Trial and 1 infant cooled in Continued Access Trial TP #5: [redacted], *Nurse coordinator*, 1 infant cooled in Pivotal Trial.

Subjects responded to questions regarding the following: First screen impressions, Setup Wizard, Main Screen, Rewarming, and Shutdown Wizard. Test participants were also asked to compare the user interface for the commercial configuration of Cool-Cap to that of the clinical trial configuration. All test participants concluded that the proposed commercial device is easier to use than the clinical trial device.

Preliminary Validation Test

A usability / pre-validation test on the user interface of the new commercial configuration of the Olympic Cool-Cap® was performed in September 2004. A total of seven subjects participated: 1 neonatologist, 1 neonatal nurse, 2 nurse coordinators, 1 clinical trial coordinator, 1 PICU nurse and 1 respiratory therapist/research. Six subjects were involved in the clinical investigation and had experience with the investigational device design.

The subjects performed the following tasks:

1. Set-up and start cooling scenario (enter patient data, enter patient information, connect temperature sensors, set the cap temperature, connect water supply & tubing and fill & remove air bubbles, and place the complete cap set.);
2. Observe cooling treatment;
3. Edit patient information
4. Pause/resume cooling;
5. Adjust cap temperature;
6. Respond to low-priority alarm condition;
7. Respond to medium-priority alarm condition;
8. Respond to multiple alarm condition;
9. Rewarm treatment; and
10. Shutdown.

Two of the subjects completed operator's manual validation and five completed label validation. In general, the pre-validation test confirmed that the prototype software is user-friendly, the wizards/functions are easily learnable, and the product meets the users' needs.

Validation Test

A usability / validation test was performed on a production unit of the proposed commercial configuration of the Olympic Cool-Cap®. A total of three NICU nurses from the [redacted] Center were tested from 3/22/05 to 3/24/05 at the offices of Olympic Medical.

This test had the following purposes:

- To confirm that the final software is user-friendly and the wizards/functions are easily learnable
- To confirm that the product meets the users' needs
- To confirm that users can use the device to:
  o Circulate temperature-controlled water through a patient-applied cap
  o Adjust the cap water temperature
  o Display cap and physiological temperatures
- To confirm that users can administer hypothermia treatment with effectiveness, efficiency, and satisfaction in a specified context of use

The preliminary usability validation test performed in September 2004 required users with prior direct experience using, or coordinating use of, the clinical trial configuration of Cool-Cap. By contrast, the types of users required for this final validation are individuals with some type of clinical experience but, preferably, without any prior experience with Cool-Cap. At least one of the testers is required to have had clinical experience in the NICU.

Methods used for this validation test included:

- *User testing* of realistic, representative tasks (i.e., *context analysis*)
- *Questionnaire* response to obtain direct feedback
- *Observation* of user testing with documentation of user actions, observer comments, assists provided by observers, and descriptions of user errors

The test environment was a conference room at Olympic Medical. In addition to the Cool-Cap device, a radiant warmer was present as well as some sort of bed (such as a Bili-Bassinet). The baby was simulated with a baby doll and, during a portion of the validation test, background NICU sounds were provided via a tape-recording in order to compare Cool-Cap's auditory alarms.

Tasks:

*E represents the evaluator (primary observer), U represents the user, and O represents secondary observers.

Tasks were performed in the following order:

1. Welcome/overview script, attach microphone to user, and turn on video recording (E*)
2. Completion of pre-test questionnaire (U*)
3. Read the task scenario (E), perform the task (U), record observations (E/O*), remind user to "think aloud" while performing tasks (E):
   a. Task 1: setup and start cooling
   b. Task 2: observe cooling
   c. Task 3: edit/add patient information
   d. Task 4: pause/resume cooling
   e. Task 5: respond to low-priority alarm condition
   f. Task 6: adjust cap temperature
   g. Task 7: respond to medium-priority alarm condition
   h. Task 8: respond to multi-alarm condition
   i. Task 9: respond to alarm with background NICU sounds
   j. Task 10: rewarm
   k. Task 11: shutdown
   l. Task 12: validation of Operator's Manual
   m. Task 13: validation of Product Labeling (PALs)
4. Complete post-test questionnaire (U) and verbal questions (E)
5. Questions/comments and thank you (E/U)

Results

According to the sponsor, overall, the usability / validation test confirmed that the final software is user-friendly, the wizards/functions are easily learnable, and the product meets the users' needs to provide selective head cooling with mild systemic hypothermia to prevent or reduce the severity of hypoxicischemic encephalopathy in infants ≥ 36 weeks gestation at risk for moderate to severe hypoxic-ischemic encephalopathy.

Animal Studies

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 (Thorenson et al., 2001), and to maintain this gradient for a 24-hour period, while keeping the core temperature mildly hypothermic (Tooley et al., 2002). 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 (Thorenson et al.,

2001), and that selective head cooling did not result in either skin injury or superficial brain hemorrhage (Tooley et al., 2002). 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 (Tooley et al., 2003).

References for this section

Thorenson, M, Simmonds, M, Satas, S, Tooley, J, and Silver, IA, Effective selective head cooling during posthypoxic hypothermia in newborn piglets. *Pediatric Research* 49, 594-99 (2001)

Tooley, J, Satas, S, Eagle, R, and Silver IA, Significant selective head cooling can be maintained long-term after global hypoxia ischemia in newborn piglets. *Pediatrics* 109, 643-49 (2002)

Tooley, J, Satas, S, Porter H, and Silver IA, Head cooling with mild systemic hypothermia in anesthetized piglets is neuroprotective, Ann Neurology 53, 65-72 (2003)

Clinical

Study Objectives

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

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

Primary Outcome
The primary outcome is the combined rate of mortality prior to 18 months of age and severe neurodevelopmental disability in survivors. The presence of any one of the following constitutes severe neurodevelopmental disability: (a) Gross Motor Function (GMF) impairment level 3-5, (b) Bayley mental scale (MDI) <70, (c) bilateral cortical visual impairment.

Secondary Outcomes

During Hospitalization:

- Length of hospitalization during NICU course in those surviving to discharge and for whom support was not withdrawn
- Multi-organ dysfunction (3 or more organ systems) in the neonatal period.

After Discharge/at Follow-Up:

- Rate of multiple handicap in survivors (Multiple handicap will be defined as the presence of any two of the following in an infant; neuromotor disability (Level 3- 5 on GMF classification), mental delay, epilepsy, cortical visual impairment, sensorineural hearing loss.
- Bayley PDI score
- Sensorineural hearing loss: ≤ 40 dB.
- Epilepsy (defined above)
- Microcephaly: head circumference < (mean – 2SD).

Study Design
An international multi-center, prospective, randomized study of term infants following perinatal asphyxia comparing those allocated to selective head cooling (plus mild systemic hypothermia) for 72 hours and non-cooled control infants. This study was unmasked because the clinical staff must know the rectal temperature of the control and cooled infants to adjust the cooling and heating appropriately. The non-cooled (control) infants will not wear a cap because this may adversely affect the head temperature. The primary outcome measure of severe neurodevelopmental disability was fully masked.

Inclusion Criteria

The infant was assessed sequentially by criteria A, B and C listed below:

A. Infants >36 weeks gestation admitted to the NICU with **ONE** of the following:

- Apgar score of < 5 at 10 minutes after birth
- Continued need for resuscitation, including endotracheal or mask ventilation, at 10 minutes after birth
- Acidosis defined as either umbilical cord pH or any arterial pH within 60 minutes of birth < 7.00
- Base Deficit ≥ 16 mmol/L in umbilical cord blood sample or any blood sample within 60 minutes of birth (arterial or venous blood)

If the infant met criteria A then they were assessed for neurological abnormality (by certified study personnel):

B. Moderate to severe encephalopathy consisting of altered state of consciousness *and* at least one or more of lethargy, stupor or coma, hypotonia, abnormal reflexes including oculomotor or pupillary abnormalities, an absent or weak suck or clinical seizures, as recorded by study personnel.

If the infant met criteria A & B then they were assessed by aEEG (read by certified study personnel):

C. At least 20 minutes duration of amplitude integrated EEG recording that shows abnormal background aEEG activity or seizures (see Appendix A). The aEEG may be performed from one hour of age. If subsequently an abnormal aEEG is recorded before 5.5 hours of age, the infant would then become eligible for enrollment. The aEEG should not be performed within 30 min of IV anticonvulsant therapy as this may cause suppression of EEG activity. In particular, high dose prophylactic anticonvulsant therapy (e.g., >20mg/kg phenobarbitone) should not be given prior to performing the aEEG.

   Interpretation of amplitude integrate EEG (aEEG):
   The aEEG was interpreted using the quantitative voltage criteria reported by Dr. Denis Azzopardi, as follows:

   1a. Normal: Lower margin of band of aEEG activity above 7.5 μV; sleep - wake cycle present.

   1b. Mildly abnormal: Lower margin of band of aEEG activity above 5μV; sleep-wake cycles absent.

   2. Moderately abnormal: Upper margin of band of aEEG activity above 10 μV and lower margin below 5 μV.

3. Severely abnormal: Upper margin of band of aEEG activity below 10 μV and lower margin below 5 μV.

Seizures on the aEEG are characterized by a sudden increase in voltage accompanied by narrowing of the band of aEEG activity and followed by a brief period of suppression.

Exclusion Criteria

- Infants expected to be >5.5 hours of age at the time of randomization.
- Prophylactic administration of high dose anticonvulsants (eg. >20mg/kg phenobarbitone). After trial entry phenobarbitone or other anticonvulsant therapy may be given as clinically indicated to treat seizures (see *co-treatment* below).
- Major congenital abnormalities, such as diaphragmatic hernia requiring ventilation, or congenital abnormalities suggestive of chromosomal anomaly or other syndromes that include brain dysgenesis.
- Imperforate anus (since this would prevent rectal temperature recordings).
- Evidence of head trauma or skull fracture causing major intracranial hemorrhage.
- Infants <1,800 g birth weight.
- Head circumference < (mean-2SD) for gestation if birth weight and length are >(mean-2SD).
- Infants "in extremis" (those infants for whom no other additional intensive management will be offered in the judgment of the attending neonatologist). Record in detail reason for exclusion.
- Unavailability of essential equipment (eg. cooler, aEEG).
- Planned concurrent participation in other experimental treatments.

Treatment

Eligible infants were randomized to the cooling cap or the noncooling, control group. All infants were treated under a servo-controlled overhead heater. Incubators were not used for any infant accepted for the study. In both groups, transfer to a standard cot only occurred after the infant was fully stabilized after re-warming, with a rectal temperature of 37.0°C ± 0.2°C for the treatment group, or after 76 hours for the control group.

Control Treatment

All infants who were randomized to the control, non-cooled group continued to receive the present standard of clinical care. Infants thus received symptomatic therapy aimed at maintenance of homeostasis. In particular, the management of the temperatures of the infants continued to aim to maintain normothermia. All infants were dried at birth, and kept warm during resuscitation. The infants were cared for under an overhead radiant heater, servo controlled to the infants' abdominal skin temperature to maintain the rectal temperature at 37.0°C ± 0.2°C. The rectal, nasopharyngeal, fontanel, and abdominal skin temperatures were recorded hourly for the first 12 hours from entry to the study and then every 4 hours until 76 hours after randomization. Their treatment differed only in that a cooling cap was not placed on the head.

Hypothermia Treatment

Initiation of cooling:
For infants randomized to head cooling the cap of the Olympic Medical Cool-Cap System was fitted around the infants' head for 72 hours. Care was taken to ensure that the cooling cap fit snugly and remained in contact with the scalp in all areas, otherwise cooling did not take place. The forehead and ears were not covered. The fontanel temperature was monitored continuously using a temperature probe secured under a reflecting insulated cover. During cooling a fontanel temperature below 30°C was an indicator of the effective application of the cooling cap to the scalp of the infant. The warmer bed was kept flat to allow optimal contact between the cooling cap and the infant's head.

The initial temperature of the circulating water was 10°C. Adjustments of the circulating water temperature were to be made for infants at the extremes of birth weight. Growth retarded infants may have required cap temperatures of 12°C, and large infants may have required 8°C. The cap temperature was adjusted to maintain the rectal temperature at 34.5°C ± 0.5°C. To avoid overheating the skin, the abdominal skin temperature was monitored constantly by a temperature probe secured under a reflecting insulating cover. Typically, the initial target abdominal skin temperature was 37°C ± 1°C, although lower temperatures may have been ultimately required in large for gestational age infants. Turning off the overhead heater for a period of approximately 20 to 30 minutes was to be used to accelerate attainment of the target rectal temperature during the initiation of cooling. The overhead heater was to be turned back on once the rectal temperature has fallen to 35.5°C. If CPAP was clinically indicated then it was to have been given by endotracheal or nasopharyngeal tube.

Rewarming Procedures:
When cooling was concluded 72 hours after randomization, or if the infant was withdrawn from the study, the cap was removed and the overhead heater set-point dropped to 34.5°C. The rectal temperature was allowed to rise by no more than 0.5°Cper hour, to 37°C ± 0.2°C. The heater set-point was adjusted as needed, half hourly, using 0.25°C increments, to rewarm the infants. The infants' temperature was carefully monitored for at least 4 hours to prevent rebound hyperthermia.

Study Results

Demographic Data
There were a total of 25 sites that combined to enroll 235 patients in the clinical trial. One subject was withdrawn from the study and data analysis 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 below for a breakdown of the patient enrollment distribution by site.

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

See Table 2 below for baseline patient characteristics. 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 2 – Baseline characteristics of all enrolled infants

		Cooled		Control		Total	
		(n=116)		(n=118)		(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							

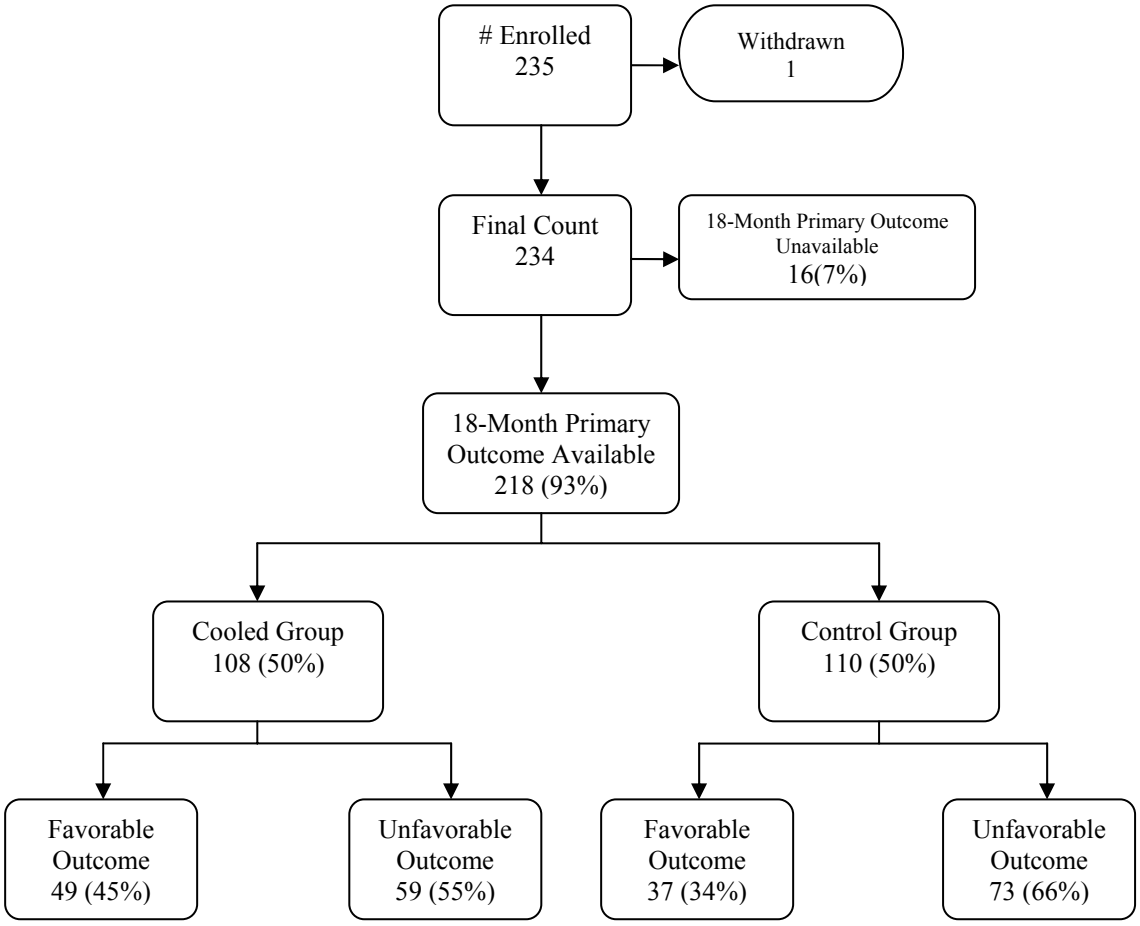
		Cooled		Control		Total	
	No	48	41%	43	36%	91	39%
	Yes	68	59%	75	64%	143	61%
Age at Randomization (hours)							
	Median (range)	4.8	(2.6-6.0)	4.7	(2.1-6.1)	4.8	(2.1-6.1)
	> 2 – 4	29	25%	24	20%	53	23%
	> 4 – 6	86	74%	92	78%	178	76%
	> 6	1	1%	2	2%	3	1%

*data available for 229 patients

**all unclassifiable aEEGs were eligible for the trial due to the presence of seizures

Primary Efficacy Results

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)



As shown in Figure 1 above, 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. One patient was withdrawn due to inadequate consent. Of the 218 subjects, 50% (108/218) were in the cooled group and 50% (110/218) in the control group. Within the cooled group, 45% (49/108) had a favorable outcome while 34% (37/110) of the control group had a favorable outcome. Fisher's exact test showed no statistical significance (p=0.10). 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).

Subpopulation Analysis

In the original PMA submission, the sponsor performed a subpopulation analysis which they stated was postulated *a priori* but was not included in their IDE investigational plan. The subpopulation analysis excluded those infants with severely abnormal aEEG background and seizure. The sponsor hypothesized that neuroprotection was not likely in the group of excluded patients because the initial injury was too severe or because the therapeutic window has already closed. In this subpopulation of 172 patients, there was a 52% favorable outcome in the cooled infants compared to a 34% favorable outcome in the control group. The Fisher's exact test for primary outcome in this group showed a p=0.021 and after logistic regression analysis adjusting for aEEG background, seizure status and age at randomization, p=0.009. The FDA did not consider this subpopulation analysis to be appropriate based on the lack of literature to support this subgroup as a homogeneous population and the difficulty in identifying, early in their course, a group of patient's with HIE who universally would not be able to respond to head cooling because the therapeutic window would have closed. Please refer to question number 2 of the Deficiency section.

Safety

There was a 9-fold increase of minor cardiac arrhythmias (9%, or 10/112, in the cooled group vs. 1%, or 1/118, in the control group). The sponsor has stated that this was not unexpected since mild bradycardia is known to be associated with hypothermia. None of the cooled infants experienced a major cardiac arrhythmia.

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 using either massage, changing position, cap adjustment or no treatment. The sponsor states that scalp edema is presumably a direct result of thermal effects on capillary permeability and pressure from the cooling cap.

Statistical analyses of the safety data were performed. 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 were no statistically significant differences 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). However, as noted in the statistical section of this executive summary, the study was designed to detect a statistically significant difference in the primary effectiveness endpoint, which is the proportion of unfavorable outcomes (either death or alive with severe neurodevelopmental disability at 18 months). Therefore, the sample size was likely insufficient to detect a statistically significant difference with regard to some rare adverse events.

For elevated liver enzymes (AE 13), the incidence in control infants (53%, or 62/118) was higher than that in the cooled infants (38%, or 42/112) 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 ($0.01 \leq p < 0.05$).

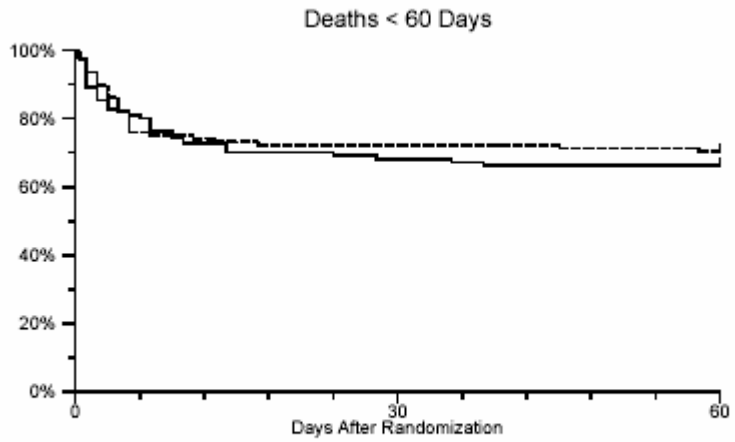
With regards to mortality, as shown in, there was no statistical evidence that the death rates differed between the two study groups (p=0.48). Mortality rates were 33% (36/108) in the cooled group and 38% (42/110) in the control group. The majority of the deaths (53/78 or 68%) occurred within seven days after randomization. Deaths during this time period were subdivided into 27/36 (75%) in the cooled group and 26/42 (62%) in the control group. Additionally, although not statistically significant, there were more deaths in cooled infants than controls for 4 and 5 days after birth (11 cooled versus 2 controls)

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 a contract Medical Officer hired by the sponsor, they concluded that there was no connection to the study treatment.

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

		Cooled		**Control**		**Total**	
		(n=116)		(n=118)		(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 sponsor provided Kaplan-Meier survival curves (see figure below). The sponsor also performed a Cox regression (N=218) which showed that there was no significant difference in survival curves between the two groups. The point estimate of the hazard ratio of Cooled versus Control groups is 0.81 with p=0.38. It may be of some clinical interest to note that whereas there is no suggestion of a difference in early neonatal mortality, 9 cooled infants and 16 control infants died after 7 days. These cases of late mortality were associated with early indicators of severe disability.



Treatment	N	Deaths
Cooled ---	108	32
Control —	110	37

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 proposed 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)

Statistical

A summary of the clinical trial design, data and results are provided in the clinical section of this memo.

Follow-up

Eighteen-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% (108/218) were in the cooled group and 50% (110/218) in the control group. A total of 116 (49.6%) of the 234 infants were randomized (stratified by center) to cooled with the remaining 118 to the control group. Eight infants from each group were lost to follow-up (LTF) at 18-month of age.

Effectiveness

Within the cooled group, 45% (49/108) had a favorable outcome and 34% (37/110) of the control group had a favorable outcome. Fisher's exact test showed no statistical significance (p=0.10). The sponsor performed a logistic regression in which the covariates include the following covariates: aEEG background, seizure status and age at randomization, birth weight, gender and Apgar score at 5 minutes from birth). The sponsor's results indicate a statistically significant treatment effect (p=0.042) with a cooling versus control odds ratio of 0.53 (95% confidence interval: 0.29-0.98) for unfavorable outcome. However, instead of imputing the unknown values for 5 aEEG background unclassifiable cases (4 cooled and 1 control) and 5 patients with missing Apgar scores, the involved patients were set up as a separate category by using an "unknown" indicator variable. Sensitivity analyses were conducted to assess the impact of 16 lost-to-follow-up cases on the primary outcome.

	Regression Parameter for Cooled Vs. Control			Odds Ratio		
Sensitivity Assumptions	Estimate	Standard Error	p-value	Point Estimate	95% Confidence Limits	
All LTFs as Failures	-0.58	0.30	0.053	0.56	0.31	1.01
All LTFs as Successes	-0.58	0.29	0.048	0.56	0.32	0.995
Cooled LTFs as Successes Control LTFs as Failures	-0.91	0.30	0.003	0.40	0.22	0.73
Cooled LTFs as Failures Control LTFs as Successes	-0.25	0.29	0.39	0.78	0.44	1.38

Safety

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. The study was designed to detect a statistically significant difference in the primary effectiveness endpoint, which is the proportion of unfavorable outcomes (either death or alive with severe neurodevelopmental disability at 18 months). Therefore, the sample size was likely insufficient to detect a statistically significant difference with regard to some rare adverse events.

As shown in Table 3 in the clinical section of this review memo, there were no statistically significant differences 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).

With regards to mortality, as shown in of the clinical section of this review memo, there was no statistical 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. The majority of the deaths (53/78 or 68%) occurred within seven days after randomization. Deaths during this time period were subdivided into 27/36 (75%) in the cooled group and 26/42 (62%) in the control group.

The sponsor provided Kaplan-Meier survival curves (see figure in the clinical section of this review memo) and a Cox regression (N=218) which showed that there was no significant difference in survival curves between the two groups. The point estimate of the hazard ratio of Cooled versus Control groups is 0.81 with p=0.38.

Deficiencies

Deficiencies were noted in FDA's review of the sponsor's application. The deficiencies are provided here with the sponsor's answers reviewed per deficiency.

1. **FDA has concerns with your provided subgroup analysis as discussed in number 2 below. However, we believe that in addition to amplitude integrated electroencephalogram (aEEG) background, seizure status and age at randomization, the following covariates are important and should be simultaneously considered in your primary outcome logistic regression analysis: birth weight, gender and categorized Apgar score. Therefore, please perform a primary outcome logistic regression analysis including the following baseline covariates: birth weight, gender, categorized Apgar score, aEEG background, seizure status and age at randomization and discuss your results. Please note that Apgar scores may be included in the model as a continuous variable and interaction terms of treatment by each covariate should be further investigated if the main effect is significant (e.g., treatment*aEEG, treatment*seizure). Please also note that multiple imputations are recommended (SAS PROC MI) to handle the missing data problem (i.e., 16 patients had missing outcome due to loss-to-follow-up, 5 patients had missing Apgar scores and unclassifiable aEEG background may better be treated as missing). The resulting multiple imputed datasets can then be analyzed by the logistic regression and valid statistical inferences can be obtained by combining estimates from the multiple datasets (SAS PROC MIANALYZE).**

Olympic Medical's statistician performed the requested logistic regression analysis including the covariates of aEEG background, seizure status, age at randomization, birth weight, gender and Apgar score at 5 minutes. The results indicate a statistically significant treatment effect (p=0.042) with a cooling versus control odds ratio of 0.53 (95% confidence interval: 0.29-0.98) for favorable outcome. The sponsor declined to perform the multiple imputation analysis, but instead performed a sensitivity analysis for the 16 lost to follow-up cases. Only in the worst case scenario (all cooled lost to follow-up were failures and all control lost to follow-up were successes) would cooling not continue to be statistically significant.

The FDA statistician performed the logistic regression analysis including all randomized patients (N=234). After multiple imputations the results showed that the cooling treatment effect was statistically significant based on the combined results from 12 imputations (p=0.04, Odds ratio of failure Cooled/Control 95% CI: [0.286-0.957]). Among the 12 imputations as performed, the p-value for treatment effect ranged from 0.01 (Impute #2) to 0.08 (Impute #7) and correspondingly, the point estimate and its 95% CI of the odds ratio of failure (dead or alive with neurodevelopmental disability) were 0.46 [0.26, 0.84] and 0.59 [0.33, 1.06], respectively.

The sponsor also undertook an alternative approach to the subpopulation analysis using the Sarnat score as another clinically established index of pre-randomization disease severity. A similar neurologic evaluation was used as a primary element in patient

selection for the NICHD whole body cooling trial. Infants in this study with Sarnat 3 exhibited a high incidence of unfavorable outcomes (91% for control and 70% for cooled infants). There was a small randomization bias to more severe encephalopathy in the cooled group which was consistent with the more severe aEEG scores and Apgar scores. Table 15 below demonstrates the outcomes of patients by Sarnat score. The treatment effect did not diminish in the infants with the most severe (Sarnat 3) encephalopathy. Primary logistic regression analysis performed with the addition of Sarnat score showed a statistically significant treatment effect (p=0.04).

Table 15 – Incidence of favorable and unfavorable outcomes as a function of modified Sarnat score at trial entry

	Cooled			Control		
Sarnat Score	**Unfavorable**	**Favorable**	**Total**	**Unfavorable**	**Favorable**	**Total**
Stage 1	2 (40%)	3 (60%)	5	0 (0%)	3 (100%)	3
Stage 2	28 (45%)	34 (55%)	62	39 (57%)	30 (43%)	69
Stage 3	28 (70%)	12 (30%)	40	32 (91%)	3 (9%)	35
Unknown	1 (100%)	0 (0%)	1	2 (67%)	1 (33%)	3
Totals	59 (55%)	49 (45%)	108	73 (66%)	37 (34%)	110

In the analysis of patients by Sarnat score, there continued to be a therapeutic effect of cooling, even in the most severe cases. In addition, there seemed to be no effect (or possible worse effect) in patients with Sarnat 1 (mild encephalopathy) although the numbers of patients were extremely small (n=8). Sarnat 1 patients generally recover without sequelae so the 100% favorable outcome in the Sarnat 1 study patients would be consistent with previous clinical observations (Sarnat and Sarnat 1976; Robertson and Finer et al. 1989).

The two separate population analyses (Sarnat score and the original PMA defined subpopulation of patients with severe aEEG background and seizure) confirm the difficulty in trying to prospectively accurately predict outcome and ability to respond to intervention in patients with HIE soon after birth. This is complicated by the lack of clinical tools to quantify the severity of the injury and the time course of that injury. There may be a population of patients where secondary energy failure is already in process and they may not respond to hypothermia treatment, but it has been difficult to identify that population. The ability to identify those patients where it is too late to implement hypothermia may be more critical than identifying those patients with the most severe disease.

2. **Prior to analyzing the data you determined that there might be three prognostic groups, based on aEEG and seizure status, and that the group with a severely abnormal aEEG and seizures would be the worst prognostic group. Thus, you removed these patients from the data analysis. We do not believe**

the subpopulation analysis that you have provided has been clinically or statistically justified for the following reasons:

- **In support of your subpopulation analysis, you have provided published literature reporting on neonatal animal experiments that suggest that the combination of a severely abnormal aEEG and seizures is seen late in the progression of encephalopathy. The literature you provided seems to lend credence to the assumption that seizures may indicate a progression of secondary energy failure. However, most of the literature reported on histopathologic damage post-insult. It is not clear that histopathological damage in a human infant correlates with a poor clinical outcome. Immature individuals are capable of different degrees of compensatory adaptation and function might be primarily regulated or taken over by subcortical undamaged structures (Bona et al., 2000). Additionally, the seizures reported in the animals studied seemed to begin between 6 and 8 hours post-insult and epileptiform activity appears to have been continuous for several hours once started. It is not clear whether these seizures correlate with the seizures in the infants in this study where treatment was started anywhere from 3 to 6 hours post-birth and the timing of the clinical insult is unknown for most patients.**

The sponsor provided information on the ability of MRI to determine the extent and the location of neuronal injury, and the correlation of outcome with this imaging information. They provided a discussion that the concept of compensatory adaptation is not consistent with the results of formal clinical follow-up studies, stating that many infants recovering from neonatal HIE who seemed normal by neurological exam at two years of age have subtle disabilities when they are assessed at school age. The sponsor provided references suggesting that motor outcome is mainly related to the severity of basal ganglia and internal capsule involvement, and isolated cortical and white matter injury is typically associated with less severe motor abnormality. They discussed the animal models of seizures where there is a wide range of patterns of seizure development after hypoxic-ischemic insults which are related to the type, severity/duration, and pattern of the insult. The sponsor states, "mathematical rigidity with respect to the timing of seizures is not possible for comparison with human studies."

The comments in the deficiency letter were meant to address the difficulty in extrapolating the injury at the cellular level in animal models to clinical outcomes. It is true that as imaging technologies have become more precise, the ability to predict long-term outcome has improved, but these modalities are not practical to use early in the course of the hypoxic-ischemic injury. The literature supports the observation that school age evaluation of children recovering from neonatal HIE has demonstrated subtle disabilities that would not have been predicted based on previous neurological evaluations. While the sponsor still views seizures as an ominous sign, particularly in association with a severely abnormal aEEG background, they agree that the timing of seizures in an animal model cannot be used as an absolute measure in clinical trials because of the unclear onset, severity and pattern of the hypoxic-ischemic injury. The

literature does support the use of seizures as one factor among a number of factors used to predict outcome following HIE (Ekert and Perlman et al. 1997, Scher 1997, Selton and Andre 1997, Thompson and Puterman et al. 1997).

- **You did not provide any literature data regarding seizures as predictors of outcome on human infants. FDA's literature search produced several articles examining the predictive value of aEEG in infants experiencing asphyxia (Azzopardi, 2000; al Naqeeb et al., 1999; Shalak et al., 2003; Toet et al., 1999; Tier Horst et al., 2004 and Shankaran and Laptook, 2003). While the literature seems to support some prognostic value of aEEG classification, comparison among the literature studies is difficult due to differences in aEEG classifications among articles. Note that the aEEG classifications used by Toet (1999) and Hellstrom-Westas (1995) and their colleagues use a five group classification scheme. No literature studies specifically reported on any differences in outcome between infants with severely abnormal aEEGs with seizures and those without seizures. However, in a study by al Naqeeb and his colleagues (1999), there were 12 infants with a severely abnormal aEEG, 6 with seizures and 6 without seizures, and all had similarly bad outcomes.**

  Additionally, published literature studies on human infants with seizures have not been shown to be absolutely predictive of death or severe neurodevelopmental outcome and there does not appear to be a clear correlation between clinical outcome and presence of seizures. For example, in a study by Azzopardi and his colleagues (2000) there were 10 infants with seizures and a prognostic aEEG of bad outcome and 70% (7/10) of these infants had a good outcome. In another study, seizures on aEEG 3 hours after birth were associated with normal outcome in 44.4% (4/9) cases and absence of seizures on aEEG at 3 hrs was not predictive of normal neurodevelopmental outcome (MC Toet et al, 1999). Mercuri et al., 1999 report that EEG abnormalities such as epileptic discharges in the presence of normal background were not associated with abnormal outcome and Shankaran and Laptook (2003) report in their article that, "Electrical background activity is more predictive of outcome in infants than the presence or absence of seizure activity ..."

The sponsor states that seizures are one of the most prominent and consistent signs of moderate to severe neonatal encephalopathy and their presence in infants with HIE is known to be associated with adverse outcome. However, there is considerable controversy over whether they simply reflect the presence of injury or they cause further injury. For those infants who do have seizures, there is no clear information on the relationship between numbers or timing of events and outcome. Animal models demonstrate increasing seizures with evolving cortical infarction and decreasing numbers with the most profound injury. The findings of variable timing and a biphasic relationship with severity help explain why clinical seizures do not seem to correlate well with outcome. However, the sponsor's scientific advisors have not proposed that they do.

In the subpopulation analysis in the original PMA submission, seizure events were not used as a marker of severity, but rather as a clinically available index of the evolution of injury. This is the first time that the aEEG has been used in this way, but it was strongly supported by experimental findings in different models. The sponsor states that while the subgroup analysis isn't the strongest, it was defined prospectively and lends support to the other statistical analyses showing a treatment effect for selective head cooling. The question addressed in this subpopulation analysis was not how seizures affect outcome but, instead, was whether or not the seizures give an indication as to the infant's potential response to therapy. No other papers have addressed this hypothesis and, although the results of the analysis are dependent on the individual investigator's ability to effectively discern aEEG readings with seizures on a severely abnormal background, the subpopulation results lend credence to the hypothesis that disease progression in those particular infants exceeded the window of opportunity for effective hypothermia treatment.

Seizures may be an indication that secondary energy failure has commenced but, because the timing, severity and type of injury are not generally known clinically, it may be difficult to correlate seizures with the timing of injury. In the subpopulation analysis the presence of seizures was coupled with the severity of background aEEG to identify a group of patients where the therapeutic window had closed for them either due to the severity or the timing of the hypoxic-ischemic insult. The Sarnat score would be another measure of severity of injury and the sponsor's subpopulation analysis with Sarnat score suggested that head cooling might be most beneficial for those patients with the most severe disease. The hypothesis that there is a therapeutic window for head cooling is plausible based on both animal and human data. However, it is not clear that it is possible to accurately and prospectively identify that population that has passed this therapeutic window. In addition, seizures identified by aEEG may be subclinical and the relationship between subclinical seizures, clinical seizures and outcome has not been well identified.

- **The control group in your study does not support your assertion that patients with a severely abnormal aEEG and seizures have a worse prognosis than those with a severely abnormal aEEG without seizures. While one should consider that the patient numbers are small, in the control group, the percentage of patients with seizures and a severely abnormal aEEG meeting study success criteria was 32 % (7/22), which was higher than those without seizures and a severely abnormal aEEG, 11.1 % (1/9).**

The sponsor states that the sample size in the control group involved was very limited. The favorable primary outcomes of 32% and 11% were consistent with either the hypothesis favoring the seizure group or one favoring the non-seizure group. In other words, either hypothesis could have resulted in the observed data; therefore, no inferences can be drawn. From a clinical perspective, seizure events are not considered a marker of severity but an index of the evolution of injury. The observed trend of favorable outcome in these control patients is not surprising.

It was shown in the sponsor's subpopulation analysis with patients grouped by Sarnat that patients with the most severe injury associated with HIE, Sarnat 3, frequently do not have seizures (Sarnat and Sarnat 1976). It is then difficult to tease out the clinical difference between severity of injury and timing of injury.

- **A potential limitation of any evaluation performed shortly after birth is that data obtained at one time interval may not represent later times, because the process affecting the infant (i.e., hypoxia-ischemia) is not static.**

The sponsor's scientific advisors agree with the FDA statement. The trial's scientific advisors were concerned that if profound aEEG suppression was used alone, as measured relatively soon after birth, then in cases where the aEEG was performed early, this criterion would include both infants with profound, end-stage injury and those whose injury was still evolving. The combination of seizures with suppression was chosen to help distinguish cases that had already reached the secondary phase from those that might still be evolving, and thus most likely to be treatable. The pre-specified subgroup analysis supports the hypothesis that there may be a group of patients who have passed the therapeutic window for intervention with hypothermia. However, as the sponsor has stated, no other papers have addressed this hypothesis.

- **FDA's logistic regression analyses found that the inclusion of the interaction terms did not lead to a better fitted model as compared to the main effects only model. Therefore, there was no strong statistical evidence indicating that the cooling treatment effect was significantly different across the three subgroups and thus, the results from your subpopulation analyses could be exaggerated.**

The sponsor believes FDA's definition of a 'better fitted model' uses the conventional $p<0.05$ as the criterion, which would explain the differences. The sponsor agrees that, if the conventional $p<0.05$ criterion is used to judge statistical significance here, inclusion of the interaction term does not lead to a better fitted model.

If you have additional information that you believe supports your subpopulation analyses please provide the following information:

a. Please address the inter-rater reliability of the aEEG recordings in your investigation. If the recordings are still available you may want to consider having an independent, blinded rater to confirm the inter-rater reliability.

The sponsor states that the trial, as designed and carried out, was a real world test of the use of aEEG recordings by local clinicians to help improve the recruitment of infants who might, potentially, benefit from induced hypothermia. It would have been impractical to have such urgent recordings independently reviewed by an expert. The sponsor accepts

that the corollary is the potential for significant inter-investigator variation. The possibility of having the records rescored is impractical since copies exist for only a subset of the traces. The sponsor notes that the original findings of the raters were collected prospectively, pre-randomization, so that there was no potential bias between the treatment groups. However, if treatment effects are to be evaluated based on the aEEG readings, those readings should be analyzed and scored by an independent group of experts

b. The following should be considered with using aEEG monitoring as predictive of outcome:

- **Artifacts can occur during readings with a loose electrode;**
- **Gasping respirations can occur;**
- **High-frequency ventilation can interfere;**
- **Poor head positioning can affect results; and**
- **Readings may be dampened because of subglial hemorrhage or may be asymmetric due to intraparenchymal infarcts.**

Please discuss how you took the above considerations into account during the investigation to prevent inaccurate aEEG recordings.

The sponsor states that all of these factors are correct and can affect conventional EEG records just as much as the aEEG. Previous published studies on aEEG recordings have suggested significant predictive value despite these issues. The clinical investigators received training in the application of aEEG including an awareness of the importance of clean recordings.

There is debate in the literature on how to best evaluate aEEG to optimize the ability to predict outcome. The criteria for aEEG used by the applicant are published in two articles (al Naqeeb and Edwards et al. 1999, Shalak and Laptook at al. 2003). There are a number of articles clearly outlining 5 categories of aEEG waveforms that include not only the voltage but the discontinuity and burst suppression (Eken and Toet et al 1995, Hellstrom-Westas 1992, Hellstrom-Westas and Rosen et al 1995, Ter Horst and Sommer et al. 2004, Toet and Hellstrom-Westas et al. 1999). One source suggests that pattern recognition as described above requires experience and they do not advocate the use of absolute values alone in predicting outcome (Groenendaal and de Vries 2000).

c. The following factors with respect to aEEG recordings could also affect outcome and the data were not provided:

- **Timing of aEEG (post-birth) used for classification;**
- **Duration of low amplitude aEEG;**
- **Duration of aEEG seizures; and**
- **Seizures during treatment.**

Please either provide the above information for each infant and discuss whether any of these factors could have affected the final outcome of the infant or provide valid scientific evidence supporting that these factors should not affect final outcome.

The sponsor provided a table with aEEG background, aEEG seizures, aEEG timing, aEEG duration, clinical seizures during treatment, age of first clinical seizure, and whether anticonvulsant therapy was given. Sites did not report the duration of low amplitude aEEG or the duration of aEEG seizures. The sponsor's scientific advisors do not believe that this additional seizure related information is of value in evaluating outcome. Although the presence of seizures in newborns with HIE is known to be highly associated with adverse outcome, there is considerable ongoing controversy over whether they simply reflect the presence of injury or themselves cause further injury; there is no agreement even on whether treatment of the seizures affects outcome. There are no clinical data on the significance of timing of onset. From the literature, it remains highly unclear whether hypothermia significantly affects seizures.

As HIE is a constantly evolving process, the timing of the aEEG, the duration of the tracing, and the presence of seizures could influence subgroup assignment and ultimately correlate with outcome. The correlation between aEEG seizures, clinical seizures, and outcome remains controversial. In this study, there were 11 cases of aEEG tracing less than 20 minutes (2 with no time specified) of which 2 had no seizures and 9 had seizures. Of the total of 234 patients, 143 had evidence of aEEG seizures and 188 had clinical seizures. Of the 188 patients with clinical seizures, 92 were in the cooled group and 96 were in the control group, and 130 had the onset of seizures before 6 hours of age. Five patients had late onset seizures (after 76 hours of age) with 3 in the cooled group and 2 in the control group. Of the patients who had seizures on aEEG, no clinical seizures were noted in 12. Of those with no aEEG seizures, 55 had clinical seizures. This would confirm evidence in the literature that it is difficult to correlate subclinical and clinical seizures. In addition, it may highlight that this aEEG snapshot in time may be too brief to identify all the patients with seizures. It is reassuring to know that there was not a significant increase in late onset seizures in patients in the cooled group.

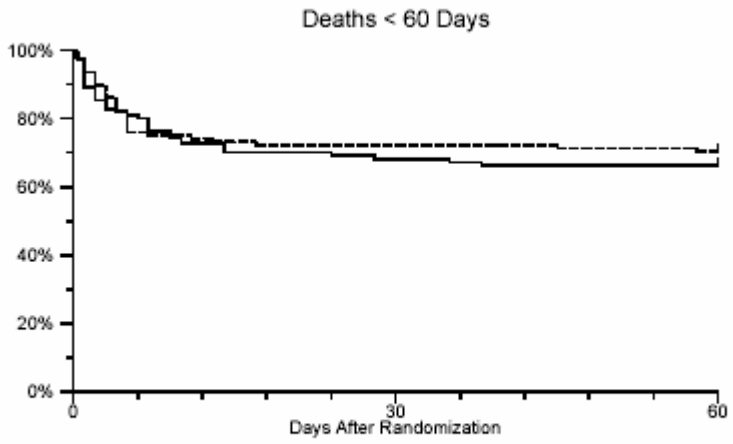
d. **To examine the strength of evidence for differential cooling effects across the postulated subgroups (best, intermediate and worst prognosis), you have fitted a logistic regression model to perform the interaction tests for treatment by subgroups (page D-5, Appendix D, Vol. 2). Although you have reported parameter estimates with p-values for the interaction terms (-1.36, p=0.27 for the cooling vs. best prognosis subgroup interaction, 1.22, p=0.11 for the cooling vs. worst prognosis subgroup interaction), you did not report the results for all main effects (e.g., treatment, subgroup). Please report the parameter estimates, standard deviations and p-values for the main effects. You should also show that the inclusion of the interaction terms results in a better fitted model as compared to the main effects model by evaluating the change of deviance. In addition, since gender, birth weight and Apgar scores were thought to**

be important prognostic factors, you should consider adding these three baseline covariates into the logistic regression model.

Per FDA request, interaction analyses were performed with gender, Apgar score, and birth weight added to the logistic regression. The groups were divided into normal/mildly abnormal aEEG background with seizure, moderately abnormal aEEG background (with or without seizure) and severely abnormal background without seizure, and severely abnormal background with seizure for three group analysis, and severely abnormal aEEG with seizure and all other patients with aEEG data for the two group analysis. With the inclusion of gender, Apgar score and birth weight, the treatment vs. worst prognosis patient group interaction p value was 0.05, indicating a contribution to the logistic model fit. The p-values of Wald Chi-square tests for the treatment by subgroup interaction of the three-subgroup analyses are 0.65 and 0.07 for the best vs. intermediate and the worst vs. intermediate, respectively. The sponsor did not evaluate *the change of deviance* to show that the addition of the interaction terms leads to a better fitted model as compared to the main effects model, i.e., the overall log-likelihood ratio test may be more appropriate to examine the statistical significance of the treatment by subgroup interaction effects.

3. **You have shown that the survival rate of patients at 18 months was comparable between the two groups according to the Fisher's exact test (p=0.48). However, the Fisher's exact test ignored the death related information prior to 18 months (e.g., 16 patients were lost to follow up at 18 months) that might have a large impact on the comparison between the cooled and control groups. Note that most deaths occurred within the first week of birth (75% (27/36) of the cooled infants and 62% (26/42) of the control infants as listed on page 76 of Volume 1). Some researchers report that for infants with HIE mortality is higher in the first month of life than after one month of age and thus, it may be inappropriate to pool data of mortality during the neonatal period with mortality and developmental outcome after that initial high risk period. Therefore, please perform a survival analysis to compare time to death between the two groups (e.g., log-rank test and Cox proportional hazards regression analysis adjusting for all important covariates).**

Since the logrank test ignores the timing of death just like the Fisher's exact test, the sponsor's statistician only performed the Cox regression as requested. There was no significant difference in survival duration between the two treatment groups. Kaplan-Meier survival curves for all subject deaths were provided. It is of some clinical interest to note that whereas there is no suggestion of a difference in early neonatal mortality, 9 cooled infants and 16 control infants died after 7 days. These cases of late mortality were associated with early indicators of severe disability.



Treatment	N	Deaths
Cooled ---	108	32
Control —	110	37

Although the sponsor performed Cox proportional hazard regression analysis indicating no significant difference in survival function between the two groups, the analysis did not include all randomized patients in the model (i.e., the 16 lost-to-follow-up patients were excluded) and did not verify the assumption of proportional hazard. The cross-over of the two Kaplan-Meier survival curves suggests that the proportional hazard assumption for the Cox model might not be met. Therefore, the Cox proportional hazard model may not be appropriate to compare the survival functions through the whole study period between the two treatment groups, but may be performed separately for early period (before Day 6) and late period (after Day 6) using stratified Cox regression analysis.

According to the sponsor's response regarding the withdraw of care, the cross-over of the survival curves might be due to the physician's delay in withdrawing care until the cooling period had been completed (Day 3). Such delayed withdrawal of care might explain the time shift of death leading to an increased number of deaths in the cooled group on Day 4 right after 3 days of cooling treatment (Cooled 11 vs. Control 2).

4. **For many patients the decision to withdraw care was based on the clinical exam and aEEG findings. However, there were more deaths in cooled infants than controls (26 cooled infants versus 21 controls) during the first 5 days of life and for days 4 and 5 there were 11 cooled deaths versus 2 control deaths. Therefore, please discuss whether the cooling treatment affected the clinical exam and/or aEEG findings and resulted in the clinical caregivers being more likely to withdraw care.**

The trial's protocol stated, "in patients where a decision is made by the attending pediatrician and parents to withdraw life support, the cooling cap will be removed 30 minutes before support is withdrawn." The reasoning for this was that if it happened that an infant appeared to be lethargic because of hypothermia, this would become apparent after rewarming was completed and thus the final decisions to withdraw care should be

made once the infant was returned to normothermia. The aEEG was used as enrollment criteria but was not used to determine whether or not to withdraw care. Withdrawal of care decisions were more often based on formal, independent EEG studies that were, in almost all cases, performed following completion of the hypothermic treatment. Table 22 shows the distribution of patient deaths as a function of time.

Table 22 – Distribution of patient deaths as a function of time (N=78)

Time Period	Cooled (n=108)	Control (n=110)
During 1st Week (Days 0–7)		
Days 0 – 3	15	19
Days 4 – 5	11	2
Days 6 – 7	1	5
Subtotal for Days 0 – 5	26	21
Subtotal for Days 4 – 7	12	7
Total for Days 0 – 7	27	26
During 1st 2 months (<60d)	32	37
During 1st 18 months (Total trial deaths)	36	42

There is no suggestion of increased early death with cooling treatment. Four of the patients in the cooled group were not actually cooled so that only 23 cooled infants died within the first 7 days of life. Although it is not statistically significant, there is an interesting trend in the timing of death. The time of death seems to have been shifted by several days. The sponsor's review of these cases suggests that this is likely a consequence of the unmasked trial of a novel physically administered therapy. In other words, in some cases the attending physicians delayed withdrawing care for a few cooled infants until the treatment period had been completed, presumably in order to offer their parents the best possible chance of recovery during the first trial of a novel treatment. These data demonstrate that care can still be withdrawn from infants with profound HIE even if withdrawal is delayed. This is reassuring because the investigators were concerned before the onset of the trial that head cooling might result in saving infants who otherwise would have died and subjecting them to a lifetime of disability. The early neonatal mortality is due to either severe multisystem compromise or to profound encephalopathy with eventual withdrawal of care. The sponsor's Medical Officer's review of the deaths after the early neonatal period suggests that most were a consequence of severe neurological disability. The sponsor's Medical Officer examined the effect of hypothermia on death after the first week of life or disability in survivors. This analysis strongly supports the overall safety of hypothermia and secondly suggests that the effect of hypothermia is mediated through a reduction of neurological injury, and not through a beneficial systemic effect.

It is reasonable to expect that the shift in deaths in the cooled group was due to the fact that the attending physicians and the parents were trying to complete therapeutic cooling

before making a decision to withdraw care. It is reassuring that this delay in deciding about withdrawing care does not result in an increased survival with disability. In the group of patients who died after 4 days of age, it would be expected that the cooled infants would have returned to normothermia, and that the formal neurologic evaluation would have been completed when the patients were normothermic. There is still a possibility that withdrawal of care 30 minutes after being off the cap would not be long enough time to reach normothermia and that the formal neurologic evaluation, in these cases, would have been done during hypothermia.

5. The cardiac arrhythmia incidence was significantly higher in the cooled group. In reviewing the primary data, a number of patients appeared to have prolonged QT intervals. Please provide the following regarding the QT interval:

a. Documentation of the QT interval for all infants and identify those infants with a prolonged interval.

b. Documentation of follow-up EKGs and the time to normalization of the QT interval for all infants experiencing a prolonged QT interval and a discussion as to whether this population would be vulnerable to prolonged QT in the future.

c. Discuss whether any changes in clinical care (e.g., limitation of additional drugs affecting QT) need to be instituted because of this clinical finding.

QT interval data are not available for all infants enrolled in the trial because formal EKGs were only recorded for infants exhibiting clinically significant sinus bradycardia or other arrhythmia. Furthermore, QT intervals were not recorded for all of the EKGs. The sponsor provided tables for all EKGs that were obtained in the trial. The tables included the date and time of the EKG, temperature during the EKG, whether the EKG was normal or contained an arrhythmia, EKG heart rate, EKG QT interval reported, EKG QT interval actual and the 98% confidence interval for QT interval based on heart rate. In summary, one or more EKGs were recorded for a total of 28 cooled and 5 control infants. One or more QT intervals were recorded for 24 cooled and 4 control infants. There were a total of 13 cooled and no control infants with a prolonged QT interval. Follow-up EKGs were performed for several of these infants and established normalization of the QT interval for seven cooled infants. One subject, [redacted], had a prolonged QT interval that normalized and then increased again after completion of the treatment. For the remaining 6 cooled infants with prolonged QT intervals without evidence of normalization, the sponsor contacted the clinical sites for additional information. Four of the patients did not have follow-up EKG information. Four of the patients, including one with no additional EKG information, had hypotension treated with dopamine, and one patient had hypocalcemia requiring therapy. The increase in QT interval during head cooling, which has previously been reported, is partly a consequence of the fall in heart rate, which is physiological, and partly due to slower intracardiac conduction. [redacted]

[redacted] Formal EKGs in the Cool-Cap® trial enabled the trial to demonstrate that no ventricular arrhythmias occurred in any of these infants, thus, there are no direct safety implications of cooling as carried out in the Cool-Cap® trial. The only potential implication of this well known QT interval effect is that the combination of therapeutic hypothermia with medications which also impact the QT interval could be of concern. Fortunately, none of these type of medications are routinely used in newborns with HIE in intensive care. Although the chance of an adverse interaction is low, the sponsor's Medical Officer believes that this should be a relative contraindication.

The exposure to medications which prolong the QT interval is limited in neonates but may become a problem as more drugs are approved and utilized in the Neonatal Intensive Care units. Caregivers and parents should be made aware of the potential for QT prolongation associated with head cooling and patients with documented prolongation of the QT interval should be followed until it is documented to be normal.

6. **There were a total of 32 of 112 (28.6%) cooled infants with scalp edema. Twenty-three (20.5%) had scalp edema as the only adverse event listed and an additional 9 (8 %) cooled infants had scalp edema and other adverse events. Due to the high number of infants experiencing scalp edema/injury, it is important to determine whether the edema is related to birth injury with delivery, pre-existing conditions, or the cap itself. Review of case report forms (CRFs) and medical notes of patient deaths (Volumes 3-12) revealed a significant amount of scalp edema/injury in cooled infants who died, while no control infants who died experienced scalp edema/injury. If scalp edema was related to birth circumstances, e.g., traumatic delivery, large size of infant, instrumental deliveries, we would expect to see a greater number of controls with scalp edema. Therefore, please provide the clinical details for all cooled and control infants who may have skin injuries or scalp edema and discuss why you do not feel that the scalp edema/injury contributed to adverse events and/or death.**

   Please note that the CRFs and medical notes indicate more infants experienced scalp edema/injury than reported in your adverse event (AE) summaries. The following is a list of some of these instances, cooled infants [redacted]:

   - [redacted]**- Had scalp edema according to record notes.**
   - [redacted]**- Autopsy report states moderate posterior, scalp and neck edema.**
   - **Four infants ([redacted]) died in the first 5 days of life. The other 2 died within first two weeks of life.**

- **[redacted]- AE listed scalp edema, but detailed notes on day that infant died (day 5) reports more details of "abraded skull with large caput and probable underlying cephalohematoma". This infant appeared to have rewarming problems.**

- **An additional case of "edema" ([redacted]) is listed as an AE, however not specifically stated as scalp edema; it was coded as severe and probably related to cooling therapy. This edema was present from day 1 until death on day 7.**

- **Two additional infants ([redacted]) died during the first 5 days of life and were not listed as having scalp edema AE, however their medical notes reported significant bruising or bleeding in scalp and head area.**

Please carefully review all of the CRFs and medical notes and make sure all instances of scalp edema/ injury have been reported as adverse events.

The sponsor states that clinical experience gained as part of the Cool-Cap® trial, and further review by the sponsor's scientific advisors, suggests that there is no apparent or likely link between this scalp edema and other adverse events. The edema was transient and reversed either during or shortly after the end of the study in all cases. In a few cases, a larger cap size was necessary to adjust for the effective increase in head circumference. Olympic Medical contacted the individual sites for additional information on the cases cited by the FDA. There were a total of 34 cases of scalp edema related AEs reported from the clinical trial (32 cooled and 2 control infants). The FDA cited an additional 9 cases in cooled infants who died. The sponsor subsequently identified an additional 26 cases of scalp edema/injury (13 cooled and 13 control infants) from a review of the clinical trial paperwork. The details of these cases were reported. Of these 26 unreported events, 10 cooled and 8 control infants were confirmed as scalp edema/injury adverse events. For those infants who reported scalp injury/edema, 24% (12/51) of the cooled infants died, whereas 50% (5/10) of the control infants died. Appendix G contains a case-by-case analysis of the scalp edema/injury in these patients. The sponsor postulated that the likely mechanism of scalp edema was reduced venous return from the scalp secondary to local pressure and hypothermic vasoconstriction. The sponsor also noted that generalized edema is common in infants with HIE, and scalp edema/injury are also common following delivery. They felt that there may have been a reporting bias, where scalp edema/injury was underreported in the control group.

Scalp injury and edema are common following delivery. Nurses were asked to document scalp injury/edema associated with head cooling but they may not have been as accurate in describing the scalp injury/edema in the control population, especially in the cases of global edema. All cases of scalp edema/injury resolved unless the patients died early in the course of treatment. There does not seem to be an increase in coagulopathy or sepsis associated solely with the scalp injury.

7. **One death of a cooled infant ([redacted]) was reported to be related to an inadvertent overdose of clonazepam (toxic high levels of clonazepam). This raises the question of whether abnormal liver clearance would be more likely to occur in cooled patients and pose higher risk for these infants. Therefore, please assess the likelihood that this liver-related death was related to the use of the device.**

The sponsor states that the case records of this infant were reviewed in detail and discussed with the attending neonatologist. The infant had evidence of very severe encephalopathy with intractable seizures. Treatment with phenobarbital was started followed by a clonazepam infusion according to published dosage guidelines. There was evidence of very severe and irreversible brain injury but no clinical or biochemical evidence of circulatory or hepatic failure. Following discussion with the parents it was agreed that intensive treatment should be withdrawn as the prognosis was hopeless. Anticonvulsant treatment was stopped prior to withdrawal of intensive support. A blood sample drawn prior to withdrawal of treatment showed a high concentration of clonazepam, above the therapeutic range. Following detailed review of the case, it was agreed that the cause of death was severe encephalopathy and that there was no evidence that cooling or the high level of circulating clonazepam or hepatic injury contributed to the outcome. On a theoretical basis, hepatic metabolism of some drugs may be reduced in the presence of mild hypothermia; however, hepatic enzymes in general were reduced in the cooled group compared with controls suggesting that hypothermia may protect the liver from ischemic related injury. It is well known that hypothermia can change the kinetics of drugs, so caution is appropriate due to the possibility of reduced hepatic clearance of drugs in cooled infants. This precaution was provided to participants in the continued access trial. This precaution was mistakenly omitted from the earlier version of the Cool-Cap® Operator's Manual but has now been added to the manual.

8. **Seizures were not included in the list of potential adverse events. However, one patient who died developed severe seizures on rewarming that exacerbated the hypoxic-ischemic injury and ultimately contributed to the death. Please discuss whether any other patients experienced seizures on rewarming.**

The patient who developed seizures on rewarming had a severely abnormal neurologic exam. After rewarming at the correct time and rate the patient developed CFM and clinical seizures. One of the seizures coincided with a severe bradycardia that required CPR and adrenaline. The baby survived to 19 months of age and was unable to swallow, needed suction, required oxygen, and had quadriplegic CP. On further review of information from the site, the infant had difficult to control seizures in the two days after birth which required treatment with Phenobarbital and a continuous infusion of benzodiazepine. On day three, the seizures appeared to be under control and the benzodiazepine infusion was weaned and stopped. Rewarming was uneventful but seizures recurred several hours after rewarming, requiring further anticonvulsant therapy. An acute hypoxic bradycardic event occurred shortly after rewarming which was most likely due to a blocked endotracheal tube. This apparent life-threatening event may have had a deleterious effect but does not appear to be linked to the increase in seizures or

rewarming. The decision to withdraw the anticonvulsant infusion immediately before rewarming is likely to have been a major contributor to the apparent increase in seizures following the completion of warming. There were no reports of patients who exhibited a significant increase in numbers of seizures during rewarming. All clinical sites were contacted to see if any investigators recalled any seizures on rewarming. The investigator from the [redacted] provided information on two patients in the continued access program who had the onset of or increase in seizures on rewarming. He felt that, most likely, the seizure tendency was unmasked when the hypothermia was completed. The good neurologic outcome in both infants with lack of ongoing seizure disorder suggests that the post-cooling seizures do not necessarily portend a bad outcome. Rewarming after cooling for HIE is potentially a more complex process than the induction of cooling because of destabilizing cardiovascular changes and the potential release of excitatory amino acid neurotransmitters that have been suppressed by hypothermia. A recent research letter reports transient, clinical rebound seizures in a patient treated in the pilot studies preceding the Cool-Cap® trial. The major implication for the Cool-Cap® from these two reports is that it would be reasonable to warn parents that rebound seizure activity may occur occasionally but when it happens it is brief and does not seem to impair neurologic recovery. Clinicians should be informed of this potential seizure suppression and be aware that seizures may be seen soon after rewarming. Patients treated with anticonvulsants prior to cooling should not be weaned off those medications until rewarming is completed.

9. One cooled infant ([redacted]) had excess problems with controlling temperature and repeatedly had removal of the cool cap to check scalp and finally therapy was stopped early. This infant died at age 2 days, 10 hours. Additionally, technical problems with cool cap occurred at the same time as serious injury/illness in several infants ([redacted]). Please discuss how you determined whether treatment and/or temperature control problems resulted in the death/adverse event experienced by these infants.

None of the technical difficulties referred to for these patients played a role in death or serious injury. The sponsor has stated, that temperature control difficulties are generally not a result of the Cool-Cap®, but, instead, result from the underlying disease condition. One exception to this is an operator's occasional struggle to properly adjust for the time lag between cap temperature adjustments and the resulting rectal temperature adjustments. Case [redacted] should be patient [redacted]. This patient was critically ill, and the patient died of respiratory failure and HIE. The sponsor believes that the sinusoidal nature of the patient's temperature should not be defined as excess problems with controlling temperature. The sponsor anticipates that the temperature chasing of this nature will be less common with the commercial version of Cool-Cap® since the operator will have a graphical display of the rectal temperature. The cap was actually only removed twice (duplicate entries were noted in the chart). Therapy was not stopped because of technical difficulties but because of the infant's underlying poor prognosis. Case number [redacted] had the first episode of apnea 1.5 hours into rewarming. The apneic event that required bag ventilation reportedly occurred more than 3 hours following the original 72 hours of cooling (still in the rewarming phase that took 4 hours). Several

more apneic events occurred following rewarming. The site investigator felt that the apnea events were independent of cooling or rewarming, and noted that two episodes of apnea occurred during cooling. The patient also had temperature instability during the remainder of the hospitalization, almost certainly related to HIE. Case [redacted] had a larger cap applied due to scalp edema and the cap was left off for 20 minutes because the rectal temperature was low. This case demonstrated that there is a significant time lag for the rectal temperature to respond to cap temperature changes. Changing the cap is not problematic for maintenance of rectal temperature. Paperwork for case [redacted] described an alarming redness and purple color of the skin but a further review of the paperwork revealed that the episode was described as mild and resolved within an hour. The trial's medical officer concluded that the temperature problems were not causing the harm but the temperature problems were secondary to the underlying clinical problems. Clinicians should be made aware that it may be more difficult to achieve and maintain target temperatures in patients with severe hypoxic-ischemic injury.

10. Maintaining the appropriate temperature gradient, during both cooling and rewarming, is a crucial component in hypothermia treatment. Additionally, there is increasing experimental evidence that hyperthermia during and after cerebral hypoxia-ischemia is associated with earlier and more severe neurologic deterioration. However, it appears that several infants, both cooled and controls, had recorded rectal temperatures outside of the protocol specified ranges during treatment. The protocol specified a target temperature range for the cooled group of 34.5°C ± 0.5°C (34.0 – 35.0°C), and for the control group of 37°C ± 0.5°C (36.5 – 37.5°C). Please provide a listing of all cooled and control patients experiencing temperatures outside of the protocol specified ranges (i.e., 34.5°C ± 0.5°C for cooled infants and 37°C ± 0.5°C for control infants). For <u>each</u> of these infants, please provide the following information:

a. A listing of the temperatures recorded at each time-point and an associated graph depicting the temperature at each recorded time-point.

b. A patient line listing that includes all recorded efficacy and adverse event data.

c. A discussion as to whether any adverse events may be due to the temperature being outside of the protocol specified ranges.

d. A justification as to why having a rectal temperature outside of the protocol specified range should not affect the infant's final outcome.

Additionally, you should justify why temperature control problems with the CoolCare System in this investigation should not affect the safe and effective use of the device for the requested indication.

Rectal temperatures were recorded in the case report form hourly for the first 12 hours, once every 4 hours for hours 16-72 and hourly for the 4 hour rewarming period. The target temperature was 34.0-35.0^{0}C for cooled infants and 36.5-37.5^{0}C for control infants. A major temperature deviation occurred if the rectal temperature dropped below 33^{0}C for cooled infants or if it exceeded 38^{0}C for any control or cooled infant. Temperature control difficulties were defined as occurring when an infant had rectal temperature readings less than 33.5^{0}C and difficulties maintaining the rectal temperature. Babies experiencing rectal temperatures outside the 34.0-35.0^{0}C range were not necessarily "temperature control problems" as defined by "protocol deviations" or "adverse events". There were 23 cooled infants and 29 control infants that experienced major temperature deviations. A further review of case [redacted] demonstrated that the recorded temperature was an error and the patient did not experience a major temperature deviation. It is difficult to maintain the target temperature for 72 hours, and only 6 cooled infants and 8 control infants actually stayed within the target range for all 76 hours. The sponsor documented, in tabular and graphic form, all of the temperature recordings for the cooled and control infants who had major temperature deviations. The sponsor included efficacy data for the 23 cooled and 29 control infants who experienced major temperature deviations. For both cooled and control infants who had hyperthermia, 82% exhibited an unfavorable outcome. Of the cooled infants with rectal temperature less than 33^{0}C, 57% had an unfavorable outcome. The sponsor included a table documenting all the adverse events for the 23 cooled and the 29 control infants. According to the trial's medical officer, it is impossible to assess whether adverse events may be due to temperature deviations on a case-by-case basis in view of the sheer number of factors affecting each infant and the severe, multisystem nature of HIE. It was noted that brief excursions outside the specific ranges were relatively common. AEs occurred at a high rate of incidence for all infants regardless of their randomization group and rectal temperature. Adverse events were reported for all except 7 of the 234 enrolled patients, and 6 of those 7 infants came from one clinical site ([redacted]), and their underreporting may have reflected [redacted] previous significant experience with HIE. The HIE condition makes the infants more susceptible to fluctuations in temperature, so temperature deviations can be a surrogate for how badly the infant is doing. Analysis of patients with brief falls in temperature less than 33^{0}C suggested that these temperature deviations were not deleterious. Only 11 cooled patients had temperatures greater than 38^{0}C and since the majority of these events occurred prior to randomization, they are not related to the device or the trial protocol. There is not a statistically significant difference in hyperthermic and non-hyperthermic cooled infants. There are times when the operator may "chase" the desired temperature when there is a time lag between when a water temperature change manifests as a change in the infant's rectal temperature. Olympic Medical anticipates that "chasing" the desired rectal temperature will be less of a concern with the commercial version of Cool-Cap® due to the graphical display of the rectal temperature.

While temperatures less than 33^{0}C are reflective of cooling deviations, it is not clear that a temperature above 38^{0}C is a reasonable temperature deviation for cooled patients. It is clear that it is difficult in these patients to maintain temperature within a narrow range in the first few days of life, especially in patients with severe HIE. It is important that all

clinicians be aware that it may be difficult to control temperatures in patients with severe HIE. A combination of this recognition and the proposed commercial version of the Cool-Cap® may decrease the tendency to "chase" the temperature in these infants. Adverse events are common in these critically ill infants. It is difficult on a case-by-case basis to identify any specific increase in adverse events associated with temperature deviations. There is an increase in unfavorable outcomes for both cooled and control infants with temperatures greater than 38^0C, but this does not appear to be related to the trial. It is impossible to determine if the outcome is related to the hyperthermia or the hyperthermia is a reflection of the severity of the underlying disease. No significant increase in adverse events was documented in patients in the cooled group with temperatures less than 33^0C.