

Draft Panel Questions

1. There was a statistically significant difference between the cooled and control groups for minor cardiac arrhythmias (9% for cooled versus 1% for controls) and “other” adverse events, primarily head/scalp edema/injury (46% for cooled versus 22% for controls). 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) and one patient in this investigation and two patients in the sponsor’s continued access trial had the onset of seizures after rewarming. Please discuss the safety of the device in view of these findings.
2. Logistic regression analysis adjusting for baseline aEEG background, seizure status, Apgar score, birth weight, gender and age of randomization indicated a treatment effect of statistical significance ($p=0.042$). Additionally, the sponsor performed an analysis in which they excluded patients with a severe aEEG background and seizures from the analysis. Based on the study results, please discuss whether use of the device should be limited to a particular subset of the HIE population (e.g., gestational age, weight, size, aEEG, etc.)
3. It was noted during the trial that due to several reasons, one being the patient population being treated, it was difficult to maintain the target temperature range specified in the study protocol ($34.5^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ for the cooled group and $37^{\circ}\text{C} \pm 0.5^{\circ}\text{C}$ for the control group) for the complete treatment duration of 72 hours. Please discuss any potential safety and/or effectiveness concerns raised by these findings and whether the instructions for use should be modified to include more detailed guidance for maintaining proper temperature.
4. The sponsor has provided draft labeling for the device which includes the indications for use, contraindications, warnings, precautions, and instructions for using the device. Please discuss whether the device should be further limited in its use (e.g., time of cooling start, duration of cooling, degree of cooling, etc.) and whether any additional information should be included in the labeling
5. 21 CFR 860.7(d) (1) states that there is a reasonable assurance that a device is safe when it can be determined that the probable benefits to health from use of the device for its intended uses, when accompanied by adequate instructions for use and warnings against unsafe use, outweigh any probable risks. Please discuss whether the data in the PMA provide a reasonable assurance of safety.
6. 21 CFR 860.7(e)(1) states that there is a reasonable assurance that a device is effective when it can be determined, based upon valid scientific evidence, that in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warning against unsafe use, will provide clinically significant results. Please discuss whether the data in the PMA provide a reasonable assurance of effectiveness.

7. A reasonable assurance of safety and effectiveness as defined in questions 5 and 6 must be demonstrated for device approval. If you believe the data in the PMA demonstrate a reasonable assurance of safety and effectiveness, but think there are specific focused questions regarding this device that still remain and can be addressed in a post-approval study, please identify those questions.