

SUMMARY MINUTES

MEETING OF THE CIRCULATORY SYSTEM DEVICES ADVISORY PANEL

OPEN SESSION

March 17, 2005

**Gaithersburg Hilton
Gaithersburg, MD**

**Circulatory System Devices Advisory Panel Meeting
March 17, 2005**

Attendees

Chairperson

William H. Maisel, M.D., M.P.H.
Brigham & Women's Hospital
Boston, MA

Myron Weisfeldt, M.D.
Johns Hopkins Hospital
Baltimore, MD

Voting Members

Richard L. Page, M.D.
University of Washington School of Medicine
Seattle, WA

Industry Representative

Michael C. Morton
Medtronic, Inc.
Minneapolis, MN

John Somberg, M.D.
American Institute of Therapeutics
Lake Forest, IL

Consumer Representative

Linda Mottle, MSM-HSA, RN, CCRP
Gateway Community College
Phoenix, AZ

Consultants

Brent A. Blumenstein, Ph.D.
TriArc Consulting
Seattle, WA

Executive Secretary

Geretta Wood
Executive Secretary

Jeffrey A. Brinker, M.D.
Johns Hopkins Hospital
Baltimore, MD

Thomas G. Brott, M.D.
Mayo Clinic
Jacksonville, FL

Henry Halperin, M.D.
Johns Hopkins Hospital
Baltimore, MA

Alfred Hallstrom, Ph.D.
University of Washington
Seattle, WA

John Marler, M.D.
National Institutes of Health
Rockville, MD

Normal S. Kato, M.D.
Cardiac Care Medical Group
Encino, CA

CALL TO ORDER

Panel Chair William H. Maisel, M.D., called the meeting to order at 8:05 a.m., to review a 510(k) submission for the Alsius Corporation CoolGard 3000/Alsius Icy Heat Exchanger Catheter Thermal Regulating System, K040429. **Panel Executive Secretary Geretta Wood** read the conflict of interest statement. She noted that Dr. Hallstrom was unable to attend and that Dr. Blumenstein would be participating in the meeting through a telephone conferencing connection. A limited waiver had been granted to Dr. Halperin for his interest in issues before the panel that could potentially be affected by the panel's recommendations, permitting him to participate in the panel's review and discussion but excluded him from voting.

OPEN PUBLIC SESSION

Terry Vanden Hoek, M.D., Associate Professor of Medicine at the University of Chicago School of Medicine, began by addressing the 2003 International Liaison Committee on Resuscitation (ILCOR) recommendations, noting that they came from a wide variety of international participants. The American Heart Association (AHA) had already recognized the possible beneficial use of hypothermia after cardiac arrest but there had been no knowledge about or consensus that this technique should be used in particular patient groups. ILCOR issued an advisory statement on this topic between the 2000 and 2005 guidelines publication date—an unusual event, he noted, reflecting a consensus that the weight of the evidence suggested that there was more that could be done to improve cardiac survival. That technique includes cooling subsets of patients to 32°C–34°C for 12 to 24 hours. He stressed how remarkable it is that there is any protocol

that improves survival from cardiac arrest, especially given that the mortality rate is 95%. Dr. Vanden Hoek underscored that the fact that so many different parties agreed on the ILCOR recommendations supports the value of the treatment. He ended his presentation by suggesting that the benefits of hypothermia in cardiac arrest patients may actually increase if the speed of cooling process is increased.

Mary Ann Peberdy, M.D., Associate Professor of Medicine and Emergency Medicine at the Virginia Commonwealth University, described current practice of providing mild hypothermia to cardiac arrest patients. Despite the international endorsements of this treatment, hypothermia is underutilized in the United States, with only about 13 percent of clinicians admitting to employing this technique following cardiac arrest. She asserted that there are various reasons why the technique is underutilized, primarily related to the cumbersome and imprecise nature of the current protocols—something to which she can personally attest. Dr. Peberdy said that clinical personnel seeking to carry out induction, maintenance, and reversal of mild hypothermia in a cardiac arrest patient very often must use somewhat crude and time-consuming methods and materials, including large plastic garbage bags with ice. These methods may not be necessarily safe, she noted, by introducing the possibility of inconsistent temperature control and the various problems associated with patients lying in wet beds, including the dangers associated with using a defibrillator in these less-than-optimal circumstances. These attempts can lead to “overshoot” of the desired target of 32°C–34°C, placing the patient at risk for further complications, and leading to a “ping-pong effect” in which the patient’s body temperature is unstable.

These difficulties has prompted many to seek out a more consistent way to

manage this protocol; however, she stressed that in the United States and overseas, hospitals and clinicians are reporting the value of providing mild hypothermia for cardiac arrest patients. Dr. Peberdy added that many emergency medical personnel report seeing striking differences between those patients who receive this therapy and those who do not. Currently, an independent board of scientists and clinicians (National Registry of CardioPulmonary Resuscitation) are tracking and collecting data on the use of this technique and care for patients after the restoration of spontaneous circulation (ROSC).

A number of panel members raised questions about Drs. Vanden Hoek's and Dr. Peberdy's presentations. Dr. Brinker asked Dr. Peberdy if she currently uses this device; she said no because the FDA has not approved it for this indication, and her hospital is reluctant to use devices off-label. Dr. Vander Hoek said that the University of Chicago Hospital has used the cooling catheter device for cardiac arrest patients. Dr. Marler asked why it would be so difficult to conduct a study looking at a comparison between the use of ice bags and cooling catheters. Dr. Peberdy answered that it would not be particularly difficult, but that very few hospitals are currently using this hypothermia therapy, so the comparisons would not be meaningful.

SPONSOR PRESENTATION

Ken Collins, B.Sc. (Med.), M.B.B.S., M. Biomed., Executive Vice President of Regulatory, Clinical, Quality and Research and Development for Alsius Corporation, began the sponsor's presentation. Dr. Collins reviewed the time line for the sponsor's 501(k), noting that this FDA panel was meeting in response to Alsius' appeal of the agency's request for randomized control trial the 501(k). He covered ILCOR's

2003 published recommendation for the use of mild hypothermia, specifically that “unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest should be cooled to 32°C–34°C for 12 to 24 hours when initial rhythm was ventricular fibrillation.” This was the basis for the new indication of use for the CoolGard 3000 System. Predicate devices include the CoolGard 3000 System (cleared for use in the induction, maintenance, and reversal of mild hypothermia in neurosurgery, rewarming in cardiac surgery, and fever control in cerebral infarction/intracerebral hemorrhage) and the Thermorite model HC-83 Hypo/Hyperthermia unit. The CoolGard System is approved and widely used for cardiac arrest patients in Canada and the European Union.

Dr. Collins reviewed the sponsor’s submitted clinical data, including a review of the literature, a meta analysis, the Alsius IDE Feasibility Study, and an analysis of the cardiac arrest patient registry at the Allgemeines Krankenhaus (AKH), the Emergency Department at the Vienna General Hospital in Austria. He then described current methods used to cool cardiac arrest patients and the risks and challenges associated with those methods. Dr. Collins asserted that the Alsius device can produce the desired hypothermic effects in patients in a much more precise manner and without the risks associated with wet surfaces and imprecise control. The CoolGard 3000 System is a heat exchange system that pumps saline to and from the catheter in a closed loop with temperature control, cooling at a rate of 0.05–1.5°C per hour. The Icy Catheter is an 8.2 French catheter inserted in the femoral vein, with the cooling end predominantly in the inferior vena cava. Balloons are mounted on the shaft of the catheter. He noted that cardiac arrest is a significant public health issue and is particularly lethal with a survival rate for all rhythms of only 8.4 percent, according to a survey of 35 community hospitals

in the United States, done by Rhea, et al.

Dr. Collins covered the meta-analysis included in the 510(k), which has since been published in *Critical Care Medicine* (Crit Care Med 2005; 33:414-418). They looked at three studies in the meta-analysis: the Hypothermia after Cardiac Arrest Study (HACA) of March 1996–January 2001, a randomized controlled study at various international centers that did not use the CoolGard System; the Bernard Study of September 1996–June 1999, an Australian multicenter randomized controlled hypothermia study that did not use the CoolGard System; and the Hachimi-Idrissi Study, undertaken over six months in 2000 and 2001, a single-center randomized controlled feasibility study that did not use the CoolGard System. He presented statistical analysis from the three studies that illustrated how mild hypothermia was shown to have clear benefits for comatose survivors of cardiac arrest.

Dr. Collins also described the IDE G000207 that was included in the 510(k) materials, a noncontrolled feasibility study of 13 patients in the United States enrolled over an 18-month period in 2001 and 2002. The inclusion criteria for the patients were in line with what the sponsor believed would be required in a randomized trial, including a primary cardiac arrest with return of spontaneous circulation in less than 60 minutes from the onset of advanced coronary life support (ALCS), where the Glasgow Coma Scale (GCS) is less than 8 and the post-resuscitation systolic blood pressure (SBP) was more than 90. The 30-day survival was 69 percent and the adverse event profile was consistent with the HACA study, the meta-analysis, and the AKH registry data set, he said.

Dr. Collins then presented the AKH patient data, an ongoing data collection involving data from a randomized control trial and the patient registry. The selection

criteria (data specifically from the 510(k) data set) included patients who were comatose survivors of cardiac arrest, with primary successful cardiopulmonary resuscitation, with ROSC arrival in the emergency department. The patients were all older than 18 years and had survived at least 24 hours with nontrivial resuscitation times (>1 minute). He noted in the baseline data that the GCS score of 3 on admission was more common in the device group than the control group (89 percent versus 62 percent) and the average ROSC was longer in the device group (25±16), indicating that the device group included a patient population at greater risk of death. Thirty-day unadjusted survival statistics reveal that 69 percent of the device group survived, while 58 percent of the control group survived; he said that the confidence interval of 95 percent is “near significant.” Dr. Collins also covered various propensity analyses that were done to create better match comparisons between cohorts; he said that these analyses, along with logistic regression analyses, produced highly significant results, suggesting significant benefit from use of the device.

Dr. Collins asserted that the efficacy outcome with these patients is also the primary safety outcome; in other words, efficacy is survival. The AKH registry data has shown significant improvement in survival, as well as survival with good neurological outcome, with the Alsius CoolGard System.

Fritz Sterz, M.D., Professor of Internal Medicine, University of Vienna, Austria, continued the presentation. The cardiac arrest patient registry began in 1995 at the Vienna General Hospital, and continues with approximately 2,500 patients. Dr. Sterz presented safety data from the 510(k) submission, noting that they selected patients who most closely matched the device patients for the best comparison. Therefore, control patients were selected to match the inclusion criteria for the CoolGard System patients:

ventricular fibrillation on presentation, presumed cardiac cause of arrest, comatose on arrival, ≤ 4 minutes of no-flow, and no hemodynamic instability, with survival of ≥ 24 hours. He presented the adverse effect data, comparing the normothermia group with those receiving hypothermia. He noted three highlights: there was increased incidence of renal failure in the hypothermia group (2 percent versus 15 percent); more bradycardia events in the hypothermia group (5 percent versus 8 percent); and pancreatitis episodes that appeared only in the hypothermia group (0 percent versus 6 percent). However, these side effects were resolved with rewarming, he said, and there were no major differences between the complications in their trial and the HACA trial.

Dr. Risto O. Roine, M.D., Ph.D., Associate Professor of Neurology, University of Helsinki, continued the sponsor's presentation by presenting an overview of the Cerebral Performance Categories Scale used in the HACA trial. He noted that it was very similar to the other outcomes scales used in resuscitation evaluation, and has been recommended as reporting guidelines by the AHA for cardiac arrest since 1991; it has also been used in most written reviews and most major resuscitation research published trials since 1990. He added that it is considered a more relevant measurement for cognitive outcome than the GCS or the modified Rankin score used in stroke research.

Dr. Roine noted that the use of mild hypothermia induction for cardiac arrest has been adopted for all national and local guidelines in Finland. In fact, all five university hospitals in the country use the Alsius CoolGard 3000 for endovascular cooling. In Helsinki, more than 90 percent of all eligible out-of-hospital ventricular fibrillation (VF) cardiac arrest patients are cooled; 48 patients received this treatment in 2004 with the Alsius device. Of the patients entered into the European Registry Council-HACA registry

in Finland in 2004, 72 percent are still alive and living at home. He noted that this is considerably higher than when he did his thesis on this topic in 1993.

Dr. Collins wrapped up the sponsor's presentation by reminding the panel that the product is already market approved for three different temperature management indications.

QUESTION AND ANSWERS

Dr. Page asked why there were only 13 patients in the U.S. feasibility study for the CoolGard. Dr. Collins says technology is evolving very rapidly, and they had difficulty securing informed consent for inclusion in the clinical trial, as there was considerable resistance to this in the community. Panel members asked about patient shivering and whether patients were treated with sedatives and paralytic drugs. Dr. Collins said that all patients shiver, but this was not an issue in the comatose survivors. Dr. Sterz noted that patients, after ROSC, will typically receive sedatives from the ambulance service professionals, depending on their awareness, and, as standard treatment, they will be assessed for sedative and paralytic drug requirements in the ambulance and in the emergency room.. But most patients do arrive unconscious, with no sedatives having been used. The sponsors said that they did not believe shivering was related to the increased renal failure in the hypothermia patients listed in the AKH safety trial.

Dr. Somberg asked the sponsors questions about the Austrian registry, specifically, the time from cardiac event to resuscitation and the time from cardiac event to cooling. Dr. Sterz said the chain of survival is very short once patients enter the

emergency unit, but typically about 20 minute elapse from emergency call to ambulance delivery at the hospital; they do have rapid resuscitation in Austria. The Panel also discussed with the sponsor the use of rapid infusion of saline; Dr. Sterz noted that is an integral part of the treatment effort for patients in the Austrian registry. The Panel also expressed concerns as to how the control group is constituted. Alsius approached Dr. Sterz for use of his data, and the statistician on staff wrote a prospectus on how the control group could be extracted. There were also questions about whether there were complications such as excessive vascular complications, hitting an artery or a nerve, pulmonary emboli, having to withdraw the catheter early. The sponsors reported not having seen any emboli or problems with vein punctures or placing the catheter. There were the usual complications that appear with use of a central line.

The Panel asked the sponsors to elaborate on the differences between surface cooling and endovascular cooling of patients, given that the randomized data presented is related to surface cooling: are there data showing that cooling faster is better; in the registry, why were some patients cooled and some not; and why were some patients cooled with endovascular therapy and others surface cooled? Dr. Sterz answered that this is explained by the fact that Alsius came to his group asking them to use the endovascular device, and then other companies came asking them to use their surface cooling device; however, Dr. Sterz said that he has agreed with these additional companies not to present their data. He added that the surface cooling devices and the endovascular cooling devices are comparable in survival rates in his data base. The Panel expressed concern that they did not have access to data in the registry that might help to understand the efficacy and safety of the device.

Dr. Weisfeldt asked about the incidence of acute renal failure, and confirmed with the sponsor that the definition was a 0.5 mg increase in serum creatinine. The sponsor noted that it resolved itself within seven days. The Panel also wanted to confirm with the sponsor that this was not seen in the HACA trial, with surface cooling.

FDA PRESENTATION

Richard Felten, M.S., FDA Team Leader for the 510(k), began the FDA's presentation by providing the panel with an overview of the currently granted indications for use of the Alsius CoolGard 3000: patients with cerebral infarction and intracerebral hemorrhage who require fever reduction, and who require access to the central venous circulation and are intubated and sedated; cardiac surgery patients who need to achieve or maintain normothermia during surgery and during recovery and intensive care; and neurosurgery patients who need to have mild hypothermia induced, maintained, and reversed during surgery and recovery and intensive care. The requested indication is for use in "the induction, maintenance and reversal of mild hypothermia in the treatment of unconscious adult patients with spontaneous circulation after out-of-hospital cardiac arrest when the initial rhythm was ventricular fibrillation."

Julie Swain, M.D., cardiovascular surgeon and advisor to the FDA, discussed the clinical trial data submitted by Alsius in support of the new indication for use of the device. She said that the FDA clinical issues with data submitted by Alsius, namely, the meta-analysis data, the specific Alsius data, the safety data, as well as concerns about the applicability of non-US data. She noted that the inclusion criteria differs in each of the three studies and the AKH registry, and she expressed concern about the inclusion of in-

house cardiac arrest patients in the registry.

Dr. Swain noted, as well, that cooling and rewarming techniques and times differed among the studies and the registry, and that the success endpoints are different. She also questioned the design differences among the studies and the registry, noting that in the Bernard paper, patients were added at the end of the initial study because the endpoint was not significant. Dr. Swain also went over the problems with the data used by the AKH registry, including the lack of complications, and possible bias in the patient selection process. She also brought up the fact that patients who died within 24 hours were excluded from the AKH registry—a group she felt should have been included. She added that none of these studies were powered to detect differences in an individual adverse events, so those looking at the data do not have the power to determine whether and adverse event was significant. As well, there were no prespecified safety endpoints in these studies.

Dr. Swain said that the sponsor still needs to prove that the method of cooling does not affect the patients' outcomes, either by efficacy or by safety. She finished her presentation by asserting that questions still remained about the safety and efficacy of surface cooling for the proposed indication; about whether the surface cooling data can be used to support the safety and effectiveness of endovascular cooling for the proposed indication; about the limitations of the AKH registry; and the risk/benefit profile of the device.

Yihua Zhao, Ph.D., Division of Biostatistics, FDA/CDRH/OSB, reviewed the sponsor's data sources, including the main data set and the AKH Registry. Dr. Zhao reviewed the sponsor's meta-analysis, noting that each of the studies used different

survival and neurological endpoints, patient cohorts, external cooling devices, and target temperatures. Therefore, she said, combining the three randomized control trials was a questionable choice. Even if the studies were similar, the Agency would recommend the following four steps whenever a Bayesian analysis is performed: use of prior information should always be agreed upon in advance by the sponsor and the FDA; comparability among studies should be agreed upon by clinicians; the use of Bayesian hierarchical models is recommended; and simulations are strongly recommended to assess operational characteristics of the study design and to control Type I errors.

Dr. Zhao said that the AKH registry data presented the following concerns: the CoolGard and normothermia patient groups were not comparable at baseline; it is inappropriate to make any direct treatment comparisons on effectiveness endpoints; the extent of the imbalance between the two groups may not be completely understood because there were variables that were not measured, and might have proved to be important in predicting outcome; and treatment comparison could have been improved via propensity score analysis. She finished her presentation by summarizing her findings, noting that using the current propensity score model, only the endpoint of “survival to 30 days and good neurological recovery” is marginally statistically significant between the CoolGard group and the normothermia group.

Ronald M. Lazar, Ph.D., Professor of Clinical Neurology, Departments of Neurology and Neurological Surgery, Columbia University College of Physicians and Surgeons, spoke on what constitutes a good neurological outcome. He covered the postanoxic encephalopathy continuum, cerebral events categories, and the literature related to neurological outcomes of out-of-hospital cardiac arrests after hypothermia

treatment, cited by the sponsor in support of the device.

Dr. Lazar noted that the sponsor has suggested that patients are “just glad to be alive,” however the Roine study (JAMA. 1993;269:237-242) suggests that this is not necessarily the case. This study showed that 48 percent of patients having experienced VF resuscitation efforts over 2 ½ years had suffered moderate to severe deficits in such areas as manual dexterity, memory, calculations, skilled motor movement, attention, initiation, planning, motivation, and significantly, depression. He questioned the sponsor’s use of the CPC scale, noting that CPC score of 2—considered “moderate cerebral performance”—would place patients into a category where they could not dress themselves easily and could not take public transportation, and would be eligible for Social Security support. Those struck by cardiac arrest are not all necessarily elderly people at the end of their working lives, he added, but they would be essentially disabled and unable to care for themselves. He suggested that brain function measurement in a clinical trial should be performed by clinical neuroscience specialists who are unaware of the treatment, and that neural endpoints should be obtained in the acute period, at discharge, and at longer term follow-ups to ensure meaningful patient outcomes.

PANEL QUESTIONS AND ANSWERS

The panel expressed interest in the CPC score of 2 and the use of the word “hemiplegia.” Dr. Brott asked Dr. Sterz whether there were patients listed as having a CPC score of 2 in the HACA trial hemiplegic *and* judged to be independent; he answered, yes.

Dr. Brinkler asked Dr. Swain whether she could be more specific in her rejection

of the AHA's recommendation for hypothermia. Dr. Swain said that the FDA is simply analyzing the data, and is not necessarily looking at what an organization may think about the data; however, she added that these studies don't meet level of evidence the Cardiovascular Division typically asks for from the sponsors of other devices. There are not two good randomized trials showing efficacy of this device. She added that she has no ethical qualms about doing a normal randomized control trial against normothermia.

Dr. Somberg asked Dr. Zhao about why they required the relatively high confidence level of 97.5 percent. She said that this was a more conservative because the sponsor offered multiple endpoints, and study's success criteria was not clearly defined.

OPEN COMMITTEE DISCUSSION

Dr. Maisel moved the panel on to considering the two primary reviews of the sponsor's submitted material.

Dr. Somberg submitted a copy of his written review for the record, but also discussed it during this period. He reiterated the FDA Circulatory Systems Devices Panel meeting of September 21, 2004, in which the panel decided that the standard of care for cardiac arrest was not hypothermia in the United States. The panel also decided that endovascular techniques for hypothermia raised a different set of safety issues than surface induced hypothermia, and felt that a randomized trial would be needed to evaluate an intervention. He noted that Alsius believes that the CoolGard 3000 should be approved for an additional indication based on its similarity to a predicate device and the assertion that the use of hypothermia in the treatment of comatose survivors of cardiac arrest due to VF has been established in randomized control trials. His review of the

sponsor's materials follows:

1. He does not believe a predicate device for the CoolGard 3000 exists.
2. As reported in the September 2004 panel meeting, there is no consensus for hypothermia as standard of care for cardiac arrest with VF.
3. Even without these previous concerns, an evaluation of potential liver toxicity and possible infection must be done for endovascular hypothermia. These are problematic from other studies, but are not evaluated by the CoolGard studies. The guidelines must also have protocol information on such issues as shivering and neurovascular blocking drugs.
4. One disturbing part of the sponsor's analysis was that all patients who died within 24 hours were excluded; an analysis of these patients would have been appreciated. In addition, the monitoring was inadequate; the registry records were in German and it appears the monitor did not read German. Supplemental materials reveal that selection of patients and interventions may not allow adequate comparisons. As well, much of the data presented by the sponsor are not comparable to the situations in the United States, making comparisons difficult. Toxicity levels reported in supplemental materials is disturbingly high.

Dr. Brott began his review of the sponsor's materials by noting the importance of the treatment and need for treatment of cardiac arrest patients. He expressed concern that there was a lack of depth in the sponsor's submission regarding the various features of hypothermia.

Dr. Brott discussed the clinical data presented in the materials. In the Bernard study, he noted there was no objective criteria presented as to how patients were rated to

have fulfilled the primary outcome. The second study was larger and more rigorous, but he was very concerned to learn about the hemiplegic issues related to patients being rated CPC scale categories 1 and 2. The third study, did not explicitly discuss good neurological recovery. These previous studies were the randomized trials.

He does not believe, as is stated in the sponsor's materials, that mild hypothermia is the standard of care for cardiac arrest with VF, noting that colleagues at the Mayo Clinic, Cincinnati, Kaiser, and other sites have not reported using hypothermia in cardiac arrest. Dr. Brott questioned why this data has not produced any changes in the standard of care in the United States.

He agreed that the September 2004 advisory panel's concurrence that the randomized trials, while producing interesting results, were not sufficient support for an application of a particular device. Dr. Brott said that he agreed with the specific limitations in the AKH registry data, but he was troubled by the significant differences at baseline, and could not make significant inferences on this data set. Regarding the 13-patient feasibility study, of the surviving nine patients, two were in a persistent vegetative state, and two were severely disabled; he noted that no statements regarding safety and efficacy of the catheter. He also noted that the sponsor did not provide the panel with information beyond technical complications; he would have liked more safety information on endovascular manipulation. He said that up until this meeting he believed the CPC was an acceptable scale, but he is concerned about the fact that a patient with complete hemiplegia could be considered independent. Dr. Sterz, at this point, assured Dr. Brott that there were no hemiplegic patients in the study placed into CPC category 2. He appreciated this assurance, but pointed out that these categories could be improved if

a detailed inventory of daily life activities is first done with each patients. This is more useful than simply a categorical scale, and could be a more appropriate secondary endpoint.

Dr. Maisel opened the floor for panel members' additional comments and questions.

Dr. Brinker asked what percent of patients in either group (control or active) had various procedures, and whether they were excluded from analysis if they had experienced an adverse event consequent to one of those procedures. Dr. Sterz answered that there was no difference in either group, and no patients were censored. Dr. Brinker agreed with the two previous reviewers that the information on hypothermia efficacy is on less firm grounds than he would have liked, and he would have liked to have seen a truly randomized trial comparing this device with normothermic care.

Dr. Page said that he was impressed by the international bodies' recommendation of hypothermia as the standard of care. He believes that it is not standard of care in the United States because there are no tools, outside of plastic garbage bags, to perform this procedure. He expressed a desire for additional safety data, but the fact that there is a four-fold increase in survival with good neurological status is compelling.

Dr. Halperin noted that his hospital has incorporated hypothermia in coronary care with positive results, in response to Drs. Sterz's and Bernard's studies. He raised the issue as to whether it is hypothermia itself, or the way hypothermia is achieved, that provides the benefit. He believes that hypothermia itself provides the positive results. The major downside of the CoolGard device is the complication profile, however the hypothermia procedure does seem to offer some hope to these patients.

Dr. Blumenstein expressed dissatisfaction with the sponsor's data, and said that a randomized clinical trial is essential in this situation. The endpoint in such a trial could be a "bad thing," or a condition in which a patient has no substantial chance of improvement.

Dr. Kato noted that, increasingly, surgeons realize that hypothermia is not necessarily myocardially or neurologically protective, and that keeping the patient warm is often preferable. He expressed disappointment with sponsor for not performing a randomized clinical study, and suggested that one must be done in this case.

Dr. Weisfeldt said that he also believes the device needs a prospective randomized trial for safety relative to surface cooling. He then addressed the core issue of whether clinicians should deliver hypothermia to these patients. A study to determine whether or not to use hypothermia in these case would be very difficult because of the concern for establishing and maintaining clinical equipoise. He suggested that further examination of the current studies might produce additional helpful information to help the Panel understand them better and draw clearer conclusions about the use of hypothermia.

Dr. Maisel noted that the ILCOR recommendations are noteworthy, even with the flawed data. While hypothermia is not the standard of care following cardiac arrest in the United States, surface cooling, at least, seems to be a reasonable treatment option. The device has the potential for being easier to implement in an emergency care situation. But he expressed concern about the leap from surface cooling to endovascular cooling, especially given that the safety issues have not been clarified in endovascular cooling. A randomized trial may be difficult, but he is comfortable that a study looking at the two

cooling methods would be ethical. Panel members suggested that patients who died before 24 hours and were excluded should be inserted back into the analysis; Dr. Sterz said that he did not believe it would effect the data, but he would attempt it.

Dr. Halperin addressed the issue of standard of care, noting that the AHA is the “keeper of the guidelines” for cardiac treatment in the United States, not ILCOR. The AHA will produce a statement on hypothermia treatment in the guidelines at end of this year, which, he suggested, may explain why hypothermia for cardiac arrest has not been widely adopted by the U.S. health care community.

SPONSOR COMMENTS

Dr. Maisel asked the sponsors to address the panel about why patients who died within 24 hours were excluded from the analysis and to clear up some of the panels’ statistical questions. Dr. Collins noted that the starting number of patients for the study was 1,882; this includes all CoolGard 3000 and control patients. There were 206 deaths by 24 hours, 1 who received CoolGard 3000 treatment and 205 normothermic patients. The odds ratio with these deaths excluded was 1.61; the odds ratio with the death included was 2.17. The simple survival outcomes are as follows: patients who died within 24 hours and removed from the data set, the CoolGard patients survival proportion was 43/62, and the normothermic patients’ proportion was 695/1,191; with the deaths left in, the CoolGard proportion was 43/63, and the normothermic proportion was 695/1,396. Dr. Collins asserted that it was more conservative for Alsius to remove the deaths at 24 hours than to keep them in. The actual 30-day survival numbers for the years 2001–2003 were as follows: with the device, 43/63; normothermic, 56/118.

Dr. Maisel opened the floor to Panel members with questions for the FDA or the sponsor. Panel members asked for further clarification on the subset of patients that may have received treatment with the CoolGard 3000. Dr. Sterz addressed this and described the decision process used to place patients in the control group. Dr. Marler expressed uncertainty as to whether or not the data shows that patients will truly receive benefit from the device, and that a clinical trial is probably the way to proceed.

RECOMMENDATIONS/FDA QUESTIONS

Question 1: Please discuss whether you believe the data provides reasonable assurance of safety for the proposed indication. In your discussion, please specifically address whether:

- a. The manner in which the data was collected (prospective registry) provides adequate assurance that the rates of adverse events noted in the submission are representative of what might be expected in actual clinical practice.**
- b. The data adequately address the risks and potential concerns of intravascular cooling mentioned at the September, 2004 Panel Meeting, including bleeding, clotting, DIC, and ventricular fibrillation.**
- c. The increased rates of early pancreatic and renal injury raise any new or specific concerns.**

The Panel was in general agreement that the sponsor had not presented sufficient safety data to ensure the safety of the endovascular device for this clinical indication. Most Panel members requested that more data be provided on safety endpoints, such as bleeding complications, acute pancreatitis, renal insufficiency, thrombosis, infection and sepsis, recurrent cardiac events, and device mechanical failures. Some members suggested that more knowledge about the impact of cooling on patients with heart disease was needed, as well. Several Panel members indicated that the most appropriate way to collect this information was through a randomized controlled study comparing intravascular cooling with surface cooling; a number of members stressed that the groups must be comparable. Dr. Page gave an endorsement to the concept of hypothermia, and

suggested that the current data could be analyzed more closely, but that he did not believe they would ever be able to get a randomized trial. Dr. Brinkler raised the issue, however, of the comparability of the two groups in the registry if the registry data was reanalyzed.

Question 2: Please discuss whether you believe the data provides reasonable assurance of effectiveness for the proposed indication. In your discussion, please specifically comment on whether the issue of non-randomized data was adequately addressed by the propensity analysis.

The Panel highlighted the difficulties in interpreting the sponsor's effectiveness data, noting that interpretation was limited by the method in which data were collected, specifically with the registry study. Dr. Maisel and others praised what was done with AKH registry but acknowledged its limitations given that it was not randomized. The Panel also expressed doubt as to whether hypothermia in general had been proven to be a beneficial therapy for cardiac arrest patients. They also were not convinced that surface cooling data could be applied to endovascular cooling devices and techniques. Again, several Panel members suggested that a randomized control trial was the best way to understand questions related to effectiveness; however, some members recognized that the extreme lethality of cardiac arrest could change the design of any randomized trial undertaken.

Question 3: Taking into account all pertinent clinical information available as well as your responses to the above questions, please comment on whether you believe the data provides an overall risk/benefit ratio which supports marketing clearance of the device in the United States for the proposed indication.

The Panel was in near consensus that the sponsor's data did not reach an acceptable risk-to-benefit ratio threshold to support a marketing clearance; however, a couple of Panel members believed that the data were close and suggested some promise for its use, specifically Drs. Page and Halperin. Dr. Weisfeldt offered a qualified no, stating that if the safety concerns were met he would be in favor of the device.

Question 4: If you believe that the data currently submitted is adequate and sufficient to support marketing clearance:

a. Please comment on what specific elements should be included in the labeling to accurately reflect the risks, benefits, and proper use of the device including any modifications to the proposed:

i. indications for use statement (IFU),

ii. contraindications,

iii. warnings/precautions, and

iv. instructions for use.

For the latter, please comment on what specific rates of cooling, duration of cooling, optimal target temperature(s), rewarming rates, and optimal time to initiation of therapy are supported by the data or whether the general treatment guidelines proposed by the sponsor (32-34°C for 12-24 hours) are sufficient for labeling purposes.

b. Please comment on whether you believe a post-market study should be required and if so, what the critical components and design of that study should be.

The Panel noted that because they had reached a near-consensus on Question 3, they could provide no significant specific recommendations regarding labeling changes and a post-market study. Some of the Panel members did comment that the labeling was somewhat verbose and confusing, however, and that they should mention the use of fluids and paralytics.

Question 5: If you do not believe that the data presented today met the threshold for marketing clearance, please discuss what additional type and amount of clinical data would be required to meet this level of assurance. In your discussion please comment on:

a. The appropriate endpoints (including assessment scales and timing of assessments) which should be used to evaluate the effectiveness of endovascular cooling catheters for this indication.

b. Whether a randomized controlled trial (RCT) would specifically be required and if so, what the appropriate control group(s) would be. If not, please comment on what other types of trial design would be adequate.

c. Whether, due to the potential differences in standard of care between the international community and the United States, data collected in the U.S. would be required.

a. The Panel felt that additional clinical data would be required to reach a marketing threshold, and that endpoints assessed at 3 or 6 months would be adequate. The Panel expressed general consensus that a scale, such as the CPC scale, might be sufficient if the patient categories were supported by detailed inventories of living activities and quality of life. The Panel suggested that cognitive endpoints should be included as secondary endpoints. They stated that the collection of safety endpoints as discussed earlier was also vital.

b. Most of the Panel believed that a random clinical trial is required to support a marketing application, either a 3-arm study with endovascular cooling, surface cooling, and normothermia, or a 2-arm study with surface cooling as a control. Such studies could encourage hospitals to use this device as well as offer positive publicity among the general public about the use of hypothermia in cardiac arrest.

c. Panel members agreed that any future trial should include U.S. sites; if foreign sites are used in addition, they must share similar “chain of survival” characteristics and times with the other sites.

OPEN PUBLIC SESSION

There were no comments made during the open public session. Dr. Maisel asked **Industry Representative Michael C. Morton** if he had any comments. Mr. Morton stressed that industry and FDA must work together on the 510(k) process, and that he appreciated the efforts of the sponsor. He praised the FDA reviewers for their concise presentation. **Consumer Representative Linda Mottle, MSM-HAS, RN, CCRP**, noted that the device of this type is certainly needed, but she concurred with the Panel that the

data was not strong enough. She encouraged the sponsor to conduct the recommended trials and move forward with the device.

ADJOURN

Dr. Maisel thanked the participants and adjourned the meeting at 2:30 p.m.

I certify that I attended this meeting of the Circulatory System Devices Advisory Panel Meeting on March 17, 2005, and that these minutes accurately reflect what transpired.

Geretta Wood
Executive Secretary

I approve the minutes of this meeting as recorded in this summary.

William H. Maisel, M.D.
Chairperson

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