July 28, 2022

University of Michigan
William Meurer
Associate Professor Emergency Medicine and Neurology
Taubman Center B1-354F
1500 E. Medical Center Drive
Ann Arbor, Michigan 48130

Re: G210126/S002/A002
Trade/Device Name: Pediatric Influence of Cooling duration on Efficacy in Cardiac Arrest Patients
Dated: June 29, 2022
Received: June 30, 2022
CMS Category: B
Annual Report Due: May 26, 2023

Dear William Meurer:

The Food and Drug Administration (FDA) has reviewed the amendment to your Investigational Device Exemption (IDE) supplement regarding your pivotal study (P-ICECAP) for a significant risk device proposing revisions to the P-ICECAP clinical protocol including the replacement of the 6 hour cooling duration arm with a "zero- hour" additional cooling arm. You have proposed to proceed with a staged approach for the P-ICECAP study. You have not fully addressed the issues cited in our June 16, 2022 letter, and in particular, you have not provided sufficient detail in your protocol to adequately describe the staged trial and the proposed interim safety analyses. Your supplement therefore remains approved with conditions, and you may implement that change in your study using a revised informed consent document which corrects deficiency numbers 2b and 4-7. Your investigation is limited to 40 US institutions and 50 US subjects.

Your IDE application has been approved with conditions as a staged study. You may request approval to expand enrollment in your study when you have submitted the following:

1. Detailed interim safety reports submitted to FDA and the DSMB after every 10 subjects enrolled and treated (with at least 30 day follow up data). The purpose of these reports is to identify otherwise unrecognized ongoing safety issues appropriate for informing stopping decisions.

2. Detailed minutes for the DSMB meetings (open and closed sessions) following each interim safety report.

3. A comprehensive clinical report (including at a minimum, adverse event information, and temperature and outcomes data for each subject) on the first 40 subjects enrolled and treated (with all follow-up information available).

These staged conditions have been implemented to address the concerns outlined in our March 25, 2022 conditional approval letter.

You must also obtain institutional review board (IRB) approval before implementing this change in your investigation as required by 21 CFR 812.35(a) because FDA believes this change affects the rights, safety, or welfare of subjects.

Approval Conditions

This approval is being granted on the condition that, within 45 days from the date of this letter, you submit information correcting the following issues:

Clinical Protocol

1. In our Conditional Approval letter dated March 25, 2022, we requested that a normothermia control arm be added to the study design, and in the absence of this requested control arm, your proposed study would be conditionally approved as a staged trial with enhanced FDA oversight of safety. In your Amendment 1, you maintained the decision not to add a normothermia control arm, and our June 16, 2022 approval therefore included, among others, a condition that you update the protocol "to include the new staged aspect of the trial, the required interim analyses, and details regarding these interim analysis intended to address the outstanding safety concerns related to this study design." Although the general approach you have now delineated in the current protocol (version 2, Section 9.12 Staged Approval and Interim Analyses for Safety) appears adequate, it lacks the necessary rigor and detail regarding the specifics of the interim analyses. For example, the text states, "Each of these [interim safety] reports will include the most up-to-date information, and data on participants from ." (*sic*), and therefore we are unclear as to the proposed format and extent of data to be presented to us. Similarly, you state, "Serious adverse events…will be summarized by allocation and listed at the participant level. The report will include a listing of all serious adverse events attributable to a definitive cooling device by allocation and listed at the participant level," and thus it is unclear to us if you intend to submit detailed listings of all serious adverse events (SAEs) irrespective of cooling device-relatedness. In this regard, we also note that your protocol does not refer to any processes involving investigators for the assignment of SAEs' device-relatedness, nor does it include a Clinical Events Committee charged with such a task. Furthermore, it appears that you have not modified the

draft Statistical Design Report to incorporate either the staged nature of enrollment or the firewalls, if any, needed to maintain the intended blinding in the setting of iterative interim reports. Therefore, we again request that you update the protocol and all other related documents to properly include the new staged aspect of the trial, the required interim analyses, and details regarding these interim analyses intended to address the outstanding safety concerns related to this study design.

2. Your response to Approval Condition #2 from our letter dated June 16, 2022 is incomplete. The revised primary objective of P-ICECAP is acceptable, and we acknowledge that you have revised some language in your protocol to incorporate this change. However, the protocol and informed consent document (ICD) retain language implying that this trial will demonstrate that hypothermia is superior to normothermia. Please address the following:

    a. Specifically, the protocol includes the following: 1) the statement, "*If the treatment effect of cooling is increasing across duration, for at least some set of durations, then this provides evidence of the efficacy of cooling versus no cooling. This would confirm the Therapeutic Hypothermia After Pediatric Cardiac Arrest Out-of-Hospital Trial (THAPCA-OH) results of a strong trend for therapeutic hypothermia resulting in better neurobehavioral and survivor outcomes than normothermia*" (page 12); 2) the language in the paragraph on page 18 that starts with "*If the optimal duration of therapeutic hypothermia…*" implies that this trial will conclusively change care and answer the question about whether hypothermia is superior to normothermia; 3) the protocol states, "*an increasing treatment effect across some set of durations would imply efficacy of cooling versus no cooling*" (page 38); and 4) the protocol states, "*If increasing durations of cooling are associated with an increasing treatment benefit in at least one part of the duration-response curve, then this would demonstrate that cooling is effective versus no cooling in improving neurological outcomes*" (page 38-39). This information is misleading. Please correct the language we have identified as being misleading and also please carefully review your protocol to ensure that there is no remaining text that suggests that your trial will be able to identify whether hypothermia is superior to normothermia.

    b. The "Key Information" of the ICD states, "*This study compares cooling children for shorter or longer lengths of time, or just preventing fever, to learn if any are better*." This statement may be misleading as it suggests that the study may answer the question of the superiority of normothermia. Please revise this sentence. You may consider the following or similar language:

        "*This study compares cooling children for shorter or longer lengths of time to try to learn what duration is best*."

3. Your response to Approval Condition #3 from our letter dated June 16, 2022 is not acceptable. We acknowledge your revisions to the protocol regarding exclusion of pregnant people; however, the pregnancy testing may be conducted for research purposes only. As such, please remove the word "clinically indicated" from the statement "Participants of childbearing potential cannot be randomized until a *clinically indicated* pregnancy test is negative."

Informed Consent

4. Approval Condition #7 from our letter dated June 16, 2022, regarding the risks identified in the informed consent document, requires additional attention. The revised risk section in general is acceptable; however, you appear to refer to the THAPCA-OH trial when stating "The cooled group appeared to recover better and more survived, but the study wasn't large enough to know for sure." As noted in the publication of the results of this trial, a larger trial "might" have identified a smaller intervention effect. (Moler et al., 2015). Please replace the word "wasn't," in this sentence with the words "may not have been."

5. Regarding Approval Condition #9 from our letter dated June 16, 2022, while we acknowledge your revisions to include both the Celsius and Fahrenheit scales in some sections of the ICD, the Fahrenheit temperature was not added to the following sections: "How long will my child be cooled?", "What are the alternatives to participation?", and "What are the alternatives to participation?". Please carefully review your protocol and add the corresponding Fahrenheit temperatures to all sections of the ICD.

6. Regarding Approval Condition 12(b) from our letter dated June 16, 2022 related to the "More Detailed Information" section of the informed consent document, we acknowledge your revisions to the "What are the possible benefits of the study?" section of the ICD. However, we also note that the subsection does not describe what the possible benefit may be. In addition, the sentence "Being part of this study may help children in the future if doctors learn how long to control body temperature after an out-of-hospital cardiac arrest" may imply that P-ICECAP will provide data to support the duration of both hypothermic and normothermic TTM. Please revise this sentence, and you may wish to consider the following or similar language:

   > *"Your child may or may not directly benefit from being in the study. Your child may have better brain function after their cardiac arrest if the temperature management they are assigned to results in better outcomes than the other temperature management assignments. However, your child may not benefit if a much different length of cooling turns out to result in better outcomes, or if maintaining bodies at a normal temperature turns out to be better. Being part of this study may help children in the future."*

7. We acknowledge you have removed language from the protocol that suggests subjects randomized to zero-hour cooling will have therapeutic hypothermia. However, we identified the statement "When ready to leave the hospital, typically well after the period of cooling is complete…" on page 10 of the ICD. Please correct this sentence as necessary to be consistent with the fact that subjects randomized to the zero-hour cooling arm will not receive therapeutic hypothermia. Additionally, please carefully review your informed consent document for any other statements that may imply this fact and make all necessary revisions.

In your submission that responds to the deficiencies listed above, please identify your response as an amendment to G210126/S002 and reference the date of this letter. As we render only one decision per application, if you include additional changes beyond the scope of these deficiencies with your response, such changes may raise new issues that impact our decision.

In order for your study to serve as the primary clinical support for a future marketing approval or clearance, FDA has provided additional study design considerations as an attachment to this letter. These recommendations do not relate to the safety, rights or welfare of study subjects and they do not need to be addressed in order for you to conduct your study. You are reminded that prior to implementing any significant modifications to the approved investigational protocol you must obtain FDA approval, and, if appropriate, IRB approval for the changes.

Your response should be identified as an IDE amendment referencing G210126/S002, and must be submitted following eCopy guidelines to:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
IDE Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

The Federal Food, Drug, and Cosmetic Act (the Act), as amended by section 1136 of the Food and Drug Administration Safety and Innovation Act (FDASIA), authorizes FDA to require an electronic copy (eCopy) for certain types of submissions. An eCopy is an exact duplicate of a paper submission, created and submitted on a CD, DVD, or other electronic media, accompanied by a single paper copy of your signed cover letter. This authorization applies to the original, amendments, supplements, and reports, as applicable, for your submission type.

For more information about FDA's eCopy program, including the technical standards for an eCopy, refer to the guidance document, "eCopy Program for Medical Device Submissions" at https://www.fda.gov/media/83522/download. In addition, we strongly encourage you to visit FDA's eSubmitter website at https://www.fda.gov/industry/fda-esubmitter/cdrh-esubmitter-program in order to develop an eCopy in accordance with the technical standards prior to sending it to FDA.

Please note that the above condition(s) of approval should be satisfied within 45 days from the date of this letter or we may take steps to propose withdrawal of approval of your IDE application.

If you would like a meeting or teleconference with the review team and management to discuss your planned approach for responding to the deficiencies in this letter, please submit your request for feedback as a Submission Issue Q-Submission (Q-Sub). Please submit a valid eCopy of the Submission Issue Q-Sub to the address listed above. The eCopy must be accompanied by a single paper copy of your signed cover letter. Your submission should reference this IDE, identify the specific deficiencies you wish to discuss, and indicate your preferred feedback mechanism (i.e., email, meeting or teleconference). For additional information regarding Q-Subs, please refer to the Guidance for Industry and FDA Staff on Medical Devices: Requests for Feedback and Meetings for Medical Device Submissions at https://www.fda.gov/media/114034/download. FDA's guidance represents FDA's proposed approach to this issue.

If you have any minor clarification questions concerning the contents of the letter, please contact Catherine P. Wentz at 301-796-6339 or Catherine.Wentz@fda.hhs.gov.

Sincerely,

Nicole G. Ibrahim -S

Nicole Ibrahim, Ph.D.
Director
DHT2B: Division of Circulatory Support,
Structural and Vascular Devices
OHT2: Office of Cardiovascular Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Enclosure
Additional Recommendations and Considerations

ADDITIONAL RECOMMENDATIONS AND CONSIDERATIONS

The recommendations and/or considerations below do not relate to the safety, rights or welfare of study subjects and they do not need to be addressed in order for you to conduct your study.

Study Design Considerations

FDA suggests the following additional modifications to your clinical protocol for your consideration (please note this list of study design considerations (SDC) contains the same SDCs identified in the June 16, 2022 conditional approval letter with the following exceptions – 1) you were able to sufficiently address SDCs 3, 6, 7, 8, 9, and 27 from the June 16, 2022 list of SDCs; 2) Study design considerations 5 and 10 were combined (now SDC 6) and revised based on your June 29, 2022 response to these SDCs; and 3) two new SDCs were identified based on our review of your June 29, 2022 amendment (identified as SDCs #1 and #2 below). Please consider addressing the following concerns:

Clinical/Protocol

1. You have appropriately modified the Primary Objectives (Section 1.1) to address our concern that the study is incapable of "demonstrating efficacy of hypothermia versus no cooling" because it does not include a normothermia control arm as we have recommended. You have also modified the introductory overview of the Study Design (Section 3) to reflect the fact that there is no "zero hour (normothermia)" enrollment arm within the trial. However, the protocol has not been properly updated throughout to reflect these fundamental clarifications to study design and objectives. For example;

    - In Section 2.2, you cite "the need for further studies to determine 1) whether therapeutic hypothermia is superior to controlled normothermia and 2) duration of target temperature management as high priorities for pediatric CA resuscitation research." You then go on to claim, "The P-ICECAP trial's innovative study design will answer these two questions," but it will not address the first.

    - Section 3.2 continues to indicate that "Participants will be potentially randomized over the course of the trial to the following possible durations of cooling (in h): 0, 12, 18, 24, 36, 48, 60, 72, 84 and 96."

    Please revise the protocol and all associated documents to ensure that the objectives and procedures of the study are unambiguous and consistent to all readers of the documents. We strongly advise that you perform a detailed proof-reading of your revised documents prior to re-submission to FDA, as we believe the issues involving "normothermia" are not semantical, but rather they will be key to any eventual inferences of safety and effectiveness. In this regard, we point out that you, too, have highlighted the importance of a discrete "normothermia" benchmark: "The meaning of the TTM is unclear. To many, the 36°C group resembles normothermia, and the lack of benefit compared to 33°C is interpreted as lack of overall benefit from cooling beyond using advanced temperature control devices to prevent hyperthermia. To many others, however, using advanced cooling devices to maintain a target of 36°C is still cooling, albeit to a higher temperature (a lower dose of cooling)… This reinforced the importance of having another study like the Influence of Cooling duration on

Efficacy in Cardiac Arrest Patients (ICECAP) to more robustly confirm efficacy of cooling or to restore sufficient uncertainty in the larger clinical community to permit a future trial with a normothermic control arm."

2. Section 5.1 (Interventions, Administration, and Duration) of the protocol has been revised to state,

   > *"The intervention will be random allocation to duration of cooling after cardiac arrest, inclusive of a duration of no additional cooling where the participant is set to a normothermic target after randomization...In P-ICECAP, after the allocated duration of cooling is completed, controlled rewarming will be performed. Slow rewarming to a temperature of 36.8°C will occur over approximately 16 hours for those participants assigned to cooling durations greater than zero."*
   >
   > And,
   >
   > *"Participants assigned to no additional cooling will have their target set to normothermia after randomization. Duration will be 120 hours from the time the device is set to a normothermic target."*

   It is unclear to us if the overall duration of target temperature management for subjects will vary depending upon the cooling arm assignment. For example, will a "no additional cooling" subject be considered to have received 120 hours of managed temperature (at normothermia), while a "12-hour" cooling subject will be considered to have received 28 hours of managed temperature (12 hours hypothermia + 16 hours to normothermia)? Please clarify the metric of overall intervention duration; if the durations will vary as a function of treatment arm assignment, please discuss whether such treatment-group differences will confound the study results.

3. The proposed primary effectiveness measure of P-ICECAP is a composite of the average Vineland Adaptive Behavior Scales–Third Edition (VABS-3) at 12 months and survival at 12 months. Specifically, you propose to measure VABS-3 scores (which can range from 20-140) among surviving subjects, consistent with the published VABS-3 manual. You additionally propose to assign a VABS-3 score of "0" to non-surviving subjects. It is not clear to us if this VABS-3/mortality composite represents a previously un-implemented use of the VABS-3 scale for a clinical trial, nor if this proposed composite has been previously tested and/or validated. While we agree with you that "for out of hospital cardiac arrest, the primary outcome measure must concurrently account for survival rate and neurobehavioral functioning among survivors," we do not agree that you have provided an adequate justification for why death should be considered 20 points below the lowest attainable neurocognitive score in the ordinal VABS-3; the appropriateness of adding the interval value of 20 to the outcome of death is unclear to us. Importantly, P-ICECAPS's proposed secondary endpoint metrics related to neurological outcome (Pediatric Cerebral Performance Category (PCPC) and Pediatric Resuscitation after Cardiac Arrest (PRCA)) and ICECAP's primary outcome measure (modified Rankin Scale (mRS)) all incorporate death as part of the unadjusted scales. You state that the added 20-point margin assigned to non-survivors will prevent "excessively reward[ing] a cooling duration, in the setting where this duration primarily improves survival only by transitioning patients from death to severe neurobehavioral impairment." Clinically, however, the difference with VABS-3 = 20, and death may very likely not truly reflect an "additional" neurobehavioral impairment

equivalent to 20% of the age- corrected standardized mean (100). We acknowledge the example scenario (in which mortality and lower-score mortality diverge substantially) you provided in your statistical analysis plan that you believe justifies your proposed approach. However, you also state, "This example is extreme, as we do not expect recovery and mortality to diverge nearly this much." Accordingly, we are concerned that your trial design risks assigning undue statistical value to survival with poor neurological outcome as compared to death, and that this fact may jeopardize clinical interpretability of your trial. Therefore, please better clarify why you believe your modification to the VABS-3 metric (i.e., its conversion into a composite with survival) is justified for this trial in which you expect mortality to be 45-55%. In so doing, we recommend that you consider modifying your primary effectiveness measure to be the similar to the approach used in THAPCA-OH, for which favorable outcome was defined as 12-month survival with VABS-2 score ≥ 70 , as this approach would seem to better align clinical and statistical results in P-ICECAP.

4. You state that you will exclude individuals with pre-existing conditions that may confound the outcome determination. However, you do not delineate those specific conditions individually. For example, you plan to use a 3-month Vineland Adaptive Behavioral Scale (VABS-3) to predict 12-month outcomes and cite Somlene et al (2019) to support this approach. Although this article is not overt in clarifying the factors that impact the ability for 3-month data to predict 12-month outcome, it is clear that pre-cardiac arrest neurological status is a confounder. However, you do not exclude individuals with pre-cardiac arrest neurodevelopmental disorders. In order to allow consistency in recruitment, and confidence in outcome analysis based on the 3-month outcome data, it is important to have as clear inclusion and exclusion criteria as possible. If there are specific conditions known to impact the outcome determination, these conditions should be specified and delineated in the exclusion criteria. Please consider making the appropriate revisions to the exclusion criteria.

5. Although you are free to make the proposed protocol revisions as outlined in this Amendment, FDA is concerned that they may risk jeopardizing safety and/or effectiveness inferences at the conclusion of the study. Specifically, the first primary objective of your study is "[t]o determine whether increasing durations of cooling are associated with better outcomes or recovery, implying efficacy of hypothermia versus no cooling." The fundamental eligibility criterion related to that objective had previously been, "Eligibility will require that a core temperature of <34° C be obtained by 240 minutes after cardiac arrest ROSC." This criterion is now changed in your modified protocol, and FDA is concerned that the heterogeneous enrollment characteristics related to disparate initial temperature management strategies may ultimately confound the results, thereby potentially making the study uninterpretable with regard to this primary objective. To try to address our concern, you may want to consider pre-specifying initial target-temperature subgroups and/or require enrollment caps for subjects not initially cooled to 34 degrees within 6 hours.

6. As stated in Approval Condition #7 above, we identified a statement in the informed consent document that still suggested that subjects randomized to zero-hour cooling will have therapeutic hypothermia. Please carefully review all your trial-related documents and ensure that neither the protocol nor the ICD have any remaining language that implies that all subjects will be cooled.

Statistical

7. As you have amended the protocol (G210126/S002) to replace the 6-hour cooling arm with a no-additional cooling arm, we recommend you discuss whether the initially proposed dose-response curve for different cooling durations still applies.

8. Multiple imputation is proposed as part of the missing data strategy. We recommend you provide additional mathematical details for the multiple imputation method, including the regression models and predictor variables to be used. The predictor variables should be chosen either because they are correlated with the missing variable, the reason for missingness, or both.

9. According to the statistical analysis plan (SAP), you plan to use multiple imputation as well as longitudinal modeling to predict 12-month outcomes in the primary endpoint analysis. It is unclear whether or how these two methods will be used together in the analysis. We recommend you clarify this issue. In addition, please clarify whether multiple imputation will be used in the sensitivity analysis and/or the primary analysis.

10. In the dose-response model, different regions of the model appear to be connected into one long formula (page, "P-ICECAP Statistical Design D 5"), and the end of the formula is cutoff by the paper margin. We recommend you provide the mathematical formula of the U-shaped dose-response model in a clear format.

11. In Figure 1 (illustration of the U-Shaped Model), the cooling durations 6, 12, 18, 24, 36, 48, 60, 72, 84, and 96-hours are shown as d=1,…,10. Please note that as the durations are not equally spaced, it is not appropriate to use 1,…,10 to represent these time durations in the figure. We recommend you use the actual duration in plots of the dose response curves.

12. You provided prior distributions for parameters used in the dose-response curve. We recommend you provide additional rationale regarding the choice of the prior distributions such as the mean of the baseline response, width of the plateau, etc.

13. In the posterior distribution, $YYYY$ is defined as the final response for each subject. However, according to the longitudinal analysis, $YYYY$ is the imputed 12-month response based on 3-month data. We recommend you clarify whether $YYYY$ is the observed or imputed 12-month data. Additionally, the $yyYY$,3 in the posterior distribution is noted as the longitudinal modeling with 3 months while it appears to be the observed 3 months response in the longitudinal analysis section.

14. It appears that you plan to calculate the posterior probabilities that the mean response on dose dd is greater than a dose of 6 hours. However, the mathematical formula presented in the SAP shows an unconditional probability. We recommend you provide a clear definition for probability that the mean response on each dose d is greater than the mean response with dose of 6 hours.

15. You plan to estimate two parameters of target dose. However, target dose is not clearly defined. We recommend you clarify whether the target dose is the maximum effective dose or the shortest duration of cooling that provides the maximum treatment effect (as defined in the study objective). In addition, the probability of being the maximum effective dose for different cooling durations share

one common notation $PPPP(MMMMMM)$. We recommend you use an appropriate notation with an index for different cooling durations. Please note that the notation for Pr(ED95) has the same issue.

16. During the response adaptive randomization, subjects will be randomized in block sizes of 10. It is unclear how this blocked randomization is used in the response adaptive randomization (RAR) design setting. We recommend you provide a detailed description of this block randomization process as well as the overall randomization algorithm.

17. The trial may stop accrual for expected success if $PPPP(MMMMMM) > 0.95\ fffPP\ dd = 96\ hPP$. However, according to the SAP, d varies from 1 to 10. We recommend you clarify.

18. A primary study objective is to determine, in pediatric comatose survivors of out-of-hospital cardiac arrest (OHCA), the shortest duration of cooling that provides the maximum treatment effect as determined by the primary endpoint. We recommend you clarify whether the target dose or maximum effective dose is consistent with this study objective.

19. In the simulation, the aim 2 is defined as "determination of the shortest duration that provides maximum treatment effect is clinically defined by selecting an ED95 that is within 1 or 2 durations of the true ED95". It appears that ED95 is considered the target dose in this context. Please confirm.

20. The operating characteristics are presented in Table 3. However, the meaning of the column heads are not clear. We recommend you provide a clear interpretation of the column heads for Table 3.

21. In the secondary outcome analysis, you mention that "continuous secondary outcomes (change in PCPC from baseline to 12 months and PRCA at 12 months) will be analyzed in a similar nature as the primary outcome", which implies Bayesian methodology. However, you further provided regression model and significance testing for these outcomes. We recommend you clarify the method that will be used for these endpoints.

22. We were unable to locate a clear study objective for the secondary outcome analysis. We recommend you clarify the statistical significance discussed in the secondary outcome analysis section.

You may propose changes to address these Study Design Considerations as part of your submission (IDE amendment) that responds to the approval with conditions deficiencies provided in this letter. If you intend to propose changes to your study to address these Study Design Considerations, in the absence of a response to deficiencies, you should submit an IDE supplement.

If you would like FDA's feedback on your plans for addressing any additional recommendations and considerations, please submit a Pre-Submission. Your submission should reference this IDE, identify the specific Study Design Considerations and/or Future Considerations you wish to discuss, and indicate your preferred feedback mechanism (i.e., email, meeting or teleconference). Additional information regarding Pre-Submissions is available in the Guidance for Industry and FDA Staff on Medical Devices: Requests for Feedback and Meetings for Medical Device Submissions at https://www.fda.gov/media/114034/download.