April 26, 2023

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/S004 & G210126/S004/A001
Trade/Device Name: Pediatric Influence of Cooling duration on Efficacy in Cardiac Arrest Patients
Dated: March 27, 2023
Received: March 28, 2023
CMS Category: B
Annual Report Due: May 26, 2023

Dear William Meurer:

The Food and Drug Administration (FDA) has reviewed the supplement to your Investigational Device Exemption (IDE) application to expand your pivotal study (P-ICECAP) for a significant risk device proposing the addition of 425 patients. Your submission was amended on April 14, 2023 to provide additional information supporting this change. FDA has determined you have provided sufficient data to support expansion of your human clinical study; this means that there are no subject protection concerns that preclude expansion of the investigation. Your supplement is therefore approved, and you may expand your study. Your investigation is limited to 40 US institutions and 500 US subjects.

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

1. A detailed interim report, formulated by the unblinded DSMB statistician, submitted to FDA and the DSMB after 400 subjects are enrolled and treated with at least 30 day follow up data. The purpose of this report is to identify otherwise unrecognized ongoing safety issues appropriate for informing stopping decisions as well as for monitoring the fidelity of designed enrollment and randomization patterns.

2. Detailed minutes for the DSMB meeting (open and closed sessions) following this interim report.

3. The interim report requested in item 1 above should include a comprehensive clinical report including at a minimum, adverse event information and appropriately supportive patient line-item data (e.g., temperature and outcomes data for each subject) on the first 400 subjects enrolled and treated with all follow-up information available. In addition, this report should include a detailed analysis of aggregate safety and effectiveness results for the pooled 400 subjects as well as further

stratification by targeted temperature management (TTM) device, by cooling duration arm, and by TTM plus cooling duration arm.

These staged conditions have been implemented so that FDA can continue to appropriately monitor study procedures and patient safety in this trial of a vulnerable pediatric population. .

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.

FDA will waive those requirements regarding prior approval of a supplemental IDE application for investigational sites (21 CFR 812.35(b)) provided that the total number of investigational sites does not exceed the limit identified in this letter. Under this waiver, the study may be initiated at new sites, up to the approved limit, and updated information required by 21 CFR 812.20(b) on participating investigators and associated Institutional Review Boards (IRBs) and the IRB approval documentation may be submitted all at once in your IDE annual progress report. You must, however, submit a supplemental IDE application, and receive FDA approval, prior to expanding the investigation beyond the site limit specified in this letter. In addition, you must maintain current records as required by 21 CFR 812.140 and submit reports as required by 21 CFR 812.150. If a reviewing IRB requires any significant changes in the investigational plan or in the informed consent that may increase the risks to subjects or affect the scientific soundness of the study, then this change must be submitted to FDA for review and approval prior to initiating the study at that investigational site (21 CFR 812.35). Minor changes requested by the IRB may be made without prior FDA approval. FDA also will waive the requirement for 6-month current investigator lists (21 CFR 812.150(b)(4)) provided that current investigator information is submitted every 12 months as part of the IDE annual progress report.

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.

Future correspondence concerning this application should be identified as an IDE supplement referencing the IDE number above, 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.

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,

Jaime Raben -S

Jaime Raben, PhD
Acting 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 (21) Study Design Considerations (SDC) and (1) Future Consideration are identical to those identified in the April 21, 2023 conditional approval letter:

Clinical/Protocol

1. In previous interactions, we stressed that a "zero hour" randomization arm was not synonymous with "normothermia." In Study Design Consideration 1 of our July 28, 2022 letter, we clarified that "we believe the issues involving 'normothermia' are not semantical, but rather they will be key to any eventual inferences of safety and effectiveness." You agreed and removed "normothermia" from various locations within P-ICECAP's IDE documents. From our review of the current Amendment, we note the following:

    a. In Section 2.1 (Rationale) of the revised protocol, you state:

        > There are a total of 10 possible treatment arms exploring 0 through 96 hours of cooling duration…The overarching goal of this project is to identify clinical strategies (duration of cooling) that will improve the neurobehavioral outcomes of children after OHCA.

    b. In Section 3.2 (Randomization and Allocation), you state:

        > 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.

    c. In Section 4 (Selection and Enrollment of Participants), you state:

        > At all participating sites, the usual clinical practice during the course of P-ICECAP for comatose pediatric OHCA survivors will be TTM to targets of 33-37 °C on arrival in the PICU; any definitive servo-regulated surface temperature control device may be used.

    d. In Section 4.1 (Inclusion Criteria and Rationale), you state:

        > All participants will be randomized within 6 hours of ROSC and after the initiation of targeted temperature management. Enrollment is defined as the time of randomization.

    e. On p. 1/27 of your most recent "Statistical Design and Power" analysis plan (18 February 2022), you clarify the following:

The 6-hour duration has been replaced with a no-additional cooling arm. (Some patients will receive cooling prior to randomizations). Any residual references to a 6-hour arm refer to a no-additional cooling or 0-hour arm.

f. In Section 5.1 (Interventions, Administration, and Duration) of the revised protocol, you state:

> Duration of cooling will be measured from the time that cooling is started as indicated by activation of a definitive cooling device (see 5.2 for definition) set to a target of 33°C (targets from 32- 34°C and maintained continuously prior to randomization also qualify as start of cooling.

Taken together, we believe that P-ICECAP's characterization of "0 hour" remains inappropriately inconsistent, confusing, and likely misleading. Furthermore, we are concerned that the substantial heterogeneity of subjects within the potentially key "0 hour" randomization arm as currently defined could be problematic and may jeopardize safety or effectiveness inferences. For example, it appears to us that the "0 hour" cohort could include subjects who have received:

- 120 hours of 36.8°C
- 6 hours of 33°C followed by 16 hours of rewarming and 98 hours of 36.8°C
- 1 hour of 32°C followed by 16 hours of rewarming and 103 hours of 36.8°C
- 2 hours of untargeted hypothermia followed by 4 hours of 34°C followed by 16 hours of rewarming and 100 hours of 36.8°C

Although pre-randomization temperature may confound all randomization arms, we believe the impact could be most pronounced on "0 hour" subjects, as all other subjects will be maintained at 33°C for at least 12 hours without temperature variability. Therefore, we strongly recommend that you revise the trial's documents throughout to more accurately characterize "0 hour" and to more consistently and clearly identify the limitations inherent to the "0 hour" randomization arm.

2. 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.

3. 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.

4. 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 <u>initial</u> 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.

5. As stated in approval condition 7 of our July 28, 2022 letter, 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

6. 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.

7. 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.

8. 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.

9. 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.

10. 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.

11. 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.

12. 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.

13. 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.

14. 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.

15. 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.

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

17. 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.

18. 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.

19. 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.

20. 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.

21. 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.

If you intend to propose changes to your study to address these Study Design Considerations you should submit an IDE supplement.

Future Considerations

You should also give serious consideration to the following, which FDA considers important for the interpretation of the final study results:

1. In your March 23, 2023, Amendment 4 to G210126/S002, you responded to Amendment 3's Approval Condition #1 with, *"FDA Requests more reassurance that interim safety reports will not lead to statistical bias... We have added additional clarifications to the Data Safety and Monitoring Plan (tracked version included) - that make it clear that the clinical investigators do not have access to the document portal used by the DSMB."* However, FDA's request asked you to identify and reconcile any impact[s] that knowledge of the 50-patient safety cohort's interim results may have on the otherwise- blinded trial's statistical analysis plan that includes a 150-patient, 3-arm burn-in period; if your opinion was that knowledge of the safety analysis's results would have no impact, we asked that you *"articulate your reasoning within the protocol and the Statistical Design and Power document."* We further reiterated our longstanding concern that if knowledge of interim results were not properly accounted for in the statistical analysis plan, trial conclusions could be rendered biased, thereby calling into question the importance of the knowledge to be gained from the trial. In a recent Submission Issue Request (Q230188), you provided additional detail specifically about the protocol's preservation of blinding of the trial leadership and investigators. In our feedback to you, we noted, *"You appear to believe that this approach to database firewalls addresses our previous concern that 'if knowledge of the interim results is not properly accounted for in the statistical analysis plan, it may significantly bias the trial conclusions.'"* We assume that your current response to Approval Condition #1 represents the totality of how you intend to *"articulate your reasoning within the protocol and the Statistical Design and Power document."* To the extent that the safety cohort's data have now already been collected and submitted for DSMB and FDA review, this response to the specifics of the Approval Condition is acceptable. However, please understand FDA remains concerned that your trial risks incurring unplanned knowledge by investigators of interim study results that in turn could affect subject enrollment processes as well as subject-specific implementation of randomized treatment interventions in your study, both of which could jeopardize our interpretation of overall study results. We recommend that your final report includes information as to whether subject enrollment was infact impacted by unplanned investigator knowledge of the interim study results and if so, the potential impact of this bias on final study outcomes.

The Future Consideration listed above is intended to remind you of the caution that may need to be exercised upon interpretation of the final study results. No response is necessary under this IDE, unless you wish to modify your device or study to address these concerns, in which case approval of an IDE supplement may be needed.

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.