August 3, 2021

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/A001
Trade/Device Name: Pediatric Influence of Cooling duration on Efficacy in Cardiac Arrest Patients
Dated: July 9, 2021
Received: July 12, 2021
CMS Category: B
Annual Report Due: May 26, 2022

Dear William Meurer:

The Food and Drug Administration (FDA) has reviewed the amendment to your Investigational Device Exemption (IDE) application regarding your pivotal study (P-ICECAP) for a significant risk device. You have corrected the deficiencies cited in our May 26, 2021 approval with conditions letter. Your application is therefore approved, and you may continue your investigation after you have obtained institutional review board (IRB) approval. Your investigation is limited to 40 US institutions and 900 US subjects.

We would like to point out that approval of an IDE application does not ensure that the results of this investigation will provide a reasonable assurance of the safety and effectiveness of your device or assure a determination of clearance/approval for your premarket submission.

Your study may meet the definition of an applicable clinical trial, which requires mandatory registration and results information submission to http://www.clinicaltrials.gov. Please see the final rule "Clinical Trials Registration and Results Information Submission" (81 FR 64982; Sept. 21, 2016) and 42 CFR Part 11. For information on informed consent requirements related to applicable clinical trials set forth in 21 CFR 50.25(c), please see "Guidance for Sponsors, Investigators, and Institutional Review Boards Questions and Answers on Informed Consent Elements, 21 CFR 50.25(c)" at https://www.fda.gov/media/82634/download.

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.

FDA acknowledges that your investigation will include foreign sites. FDA does not have jurisdiction over foreign sites; therefore, you may proceed at those foreign sites at your discretion. We encourage you however, to follow a uniform protocol at the domestic and the foreign investigational sites. Please note that FDA will accept data from studies conducted outside the United States if you demonstrate that the data are adequate to support a premarket submission (e.g., an IDE, or a marketing application or submission). Section 812.28 of the IDE regulation provides the requirements for studies conducted outside the United States that began on or after February 21, 2019, and are submitted in support of a premarket submission. For additional information please refer to the FDA Guidance "Acceptance of Clinical Data to Support Medical Device Applications and Submissions", available at: https://www.fda.gov/media/111346/download.

For studies conducted outside the United States that began before February 21, 2019, and are submitted in support of a premarket approval (PMA) application, FDA will accept the data if the data are valid and the investigators have conducted the studies in accordance with the "Declaration of Helsinki" or the laws and regulations of the country in which the study is conducted, whichever afford greater protection to the human subjects. If the country's standards are used, you must state in detail any differences between the country's standards and the "Declaration of Helsinki" and explain why the country's standards afford greater protection to the human subjects.

Furthermore, to export a device that is not in commercial distribution in the U.S. you must comply with Section 802 of the Federal Food, Drug and Cosmetic Act (the act). Detailed information regarding export requirements for investigational devices is available at: https://www.fda.gov/medical-devices/exporting-medical-devices/exporting-unapproved-devices.

For clarification regarding FDA decisions and recommendations for IDEs, please refer to the FDA guidance "FDA Decisions for Investigational Device Exemption Clinical Investigations: Guidance for Sponsors, Clinical Investigators, Institutional Review Boards, and Food and Drug Administration Staff," available at: https://www.fda.gov/media/81792/download.

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.

FDA encourages sponsors to collect clinical trial data in accordance with the Guidance for Industry: Evaluation and Reporting of Age-, Race-, and Ethnicity-Specific Data in Medical Device Clinical Studies (https://www.fda.gov/media/98686/download) and to enroll patients that would reflect the demographics of the affected population with regard to age, sex, race and ethnicity. Reference is made to 21 CFR 812.25(c) regarding description of patient population and to 21 CFR 814.15(b)(1) with regard to the need for data, including foreign data, to be applicable to the U.S. population and U.S. medical practice. We recommend that you include a background discussion of prevalence, diagnosis and treatment patterns for the type of disease for which your device is intended. This should include age-, sex-, race-, and ethnic-specific subgroup prevalence, identification of proportions of women and minorities included in past trials for the target indication, and a discussion of your plan to address any factors identified or suggested, which may explain potential for under-representation of women, minorities, and specific subgroups, if applicable. We recommend that you include a summary of this information in your protocol and investigator training materials. Consideration should be given to enrollment of investigational sites where recruitment of needed populations for study can be more easily facilitated.

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

Information to help you understand the function and duties of a sponsor, titled, "Sponsor's Responsibilities for a Significant Risk Device Investigation," is available at: https://www.fda.gov/medical-devices/device-advice-investigational-device-exemption-ide/sponsors-responsibilities-significant-risk-device-investigations-nov-1995. Additionally, information which you should provide to participating investigators, titled, "Investigators' Responsibilities for a Significant Risk Device Investigation," is available at: https://www.fda.gov/medical-devices/device-advice-investigational-device-exemption-ide/investigators-responsibilities-significant-risk-device-investigations-nov-1995.

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.

Background regarding the assigned CMS category and the process for requesting re-evaluation of the category is provided in guidance: "FDA Categorization of Investigational Device Exemption (IDE) Devices to Assist the Centers for Medicare and Medicaid Services (CMS) with Coverage Decisions," which is available at https://www.fda.gov/media/98578/download. Additional information about Medicare coverage related to Investigational Device Exemption (IDE) studies is available at https://www.cms.gov/Medicare/Coverage/IDE/index.html.

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. Study Design Considerations 1-3 and 6-21 are repeated from FDA's letter issued on May 26, 2021.

Clinical

1. 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.

2. 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.

3. Currently your informed consent form indicates that enrollment is expected to occur over 5 years. Your protocol ("Brief Synopsis") indicates that the study will continue over 7 years. Since follow-up is only out to 1 year, we are unsure as to why there is a 2-year gap between the duration of expected enrollment (5 years) and study completion (7 years). We recommend you clarify and make any necessary corrections to your documents (informed consent and/or protocol).

4. The P-ICECAP study is an adaptive allocation clinical trial designed to determine if increasing durations of induced hypothermia are associated with better neurobehavioral outcomes and to identify the optimal duration of induced hypothermia for neuroprotection in comatose survivors of childhood cardiac arrest. Your study design does not include a normothermia control arm. Induction of hypothermia for cardiac arrest in the pediatric population has a Class 2a recommendation from the American Heart Association (AHA) (level of evidence B-NR), and a recent study (THAPCA) evaluating cooling to mild hypothermia in pediatric cardiac arrest demonstrated no difference in any of the outcome measures (e.g., including survival and neuro outcome) as compared to the normothermia control arm. Accordingly, and consistent with prior recommendations, FDA suggests you consider including a normothermia arm for the P-ICECAP study.

5. You proposed protocol revisions as outlined in Amendment G210126/A001 to permit sites to practice their current temperature management protocol to the institution's target until consent is obtained. FDA is concerned this change 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, we recommend you consider pre-specifying initial target-temperature subgroups and/or require enrollment caps for subjects not initially cooled to 34 degrees within 6 hours.

<u>Statistical</u>

6. 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.

7. 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.

8. 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.

9. 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.

10. 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.

11. In the posterior distribution, Yi is defined as the final response for each subject. However, according to the longitudinal analysis, Yi is the imputed 12-month response based on 3-month data. We recommend you clarify whether Yi is the observed or imputed 12-month data. Additionally, the yi,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.

12. It appears that you plan to calculate the posterior probabilities that the mean response on dose d 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.

13. 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 $Pr(Max)$. 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.

14. 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.

15. The trial may stop accrual for expected success if $Pr(Max) > 0.95\ for\ d = 96\ hr$. However, according to the SAP, d varies from 1 to 10. We recommend you clarify.

16. 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.

17. 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.

18. 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.

19. 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.

20. 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.

Other

21. We recommend you provide FDA with the DSMB Charter and membership when available.

If you intend to propose changes to your study to address these Study Design Considerations 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.