May 26, 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
Trade/Device Name: Pediatric Influence of Cooling duration on Efficacy in Cardiac Arrest Patients
Dated: April 23, 2021
Received: April 26, 2021
CMS Category: B
Annual Report Due: One Year from the Date of This Letter

Dear William Meurer:

The Food and Drug Administration (FDA) has reviewed your Investigational Device Exemption (IDE) application regarding your pivotal study (P-ICECAP) for a significant risk device. While FDA identified some outstanding issues in your application, FDA has determined you have provided sufficient data to support initiation of a human clinical study; this means that there are no subject protection concerns that preclude initiation of the investigation. Your application is therefore approved with conditions, and you may begin your investigation using a revised informed consent document which corrects deficiency number 2 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.

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:

1. Your study does not have halting (stopping) rules. Halting rules are important to allow the study to pause to consider adverse events prior to continuing treatment that has not been shown to be safe. Your treatment protocol currently includes a plan to treat pediatric out-of-hospital cardiac arrest subjects with hypothermia up to 96 hours. This duration of hypothermic treatment has not been demonstrated to have a

known safety/risk profile. In order to improve the likelihood of an acceptable benefit and possible risk ratio, it is important that untried, high risk treatments are carefully measured. Therefore, considering the risks (hemorrhage, infection, skin injury, neurological worsening), please develop halting rules that will allow the DSMB and FDA to review adverse events that may suggest the study is unsafe, before further treatments of other subjects ensue. If the adverse event(s) that lead to halting are reviewed and found to be within the expected parameters of the study, then the DSMB and FDA may conclude that the study can proceed. Alternatively, the DSMB or FDA may conclude that the study may need to be fully stopped.

2. Please address the following issues related to the Consent for Clinical Research Study and Authorization to Disclose Health Information document:

   a. Although your Study Information Packet contains all the required elements of informed consent, this consent document that will be signed by the parent/guardian/LAR does not include all the required elements of informed consent. To address this deficiency, we recommend that the parent/guardian/LAR be required to read the Study Information Packet before being asked to sign the consent document (i.e., the Study Information Packet will be an integral part of the Informed Consent Document). We also recommend adding a statement to the consent document confirming that the parent/guardian/LAR has read and understands the Study Information Packet. For example, under the heading, "Statement of Legally Authorized Representative," we suggest you add the following statement below the first paragraph and above the text "I want my child to participate in this study (Yes/No):

      " *I have read and understand the information presented in the Study Information Packet. (Yes/No).*"

      If you do not choose to make this suggested change, please submit a revised consent document that includes all the required elements of informed consent under 21 CFR 50.25(a), that are currently found in your Study Information Packet.

   b. Under the heading, Who Decides Which Group Your Child Will Go In?, the document states "cooling times are assigned <u>mostly</u> by chance." Please remove the word "mostly".

   c. Under the heading, What Are the Possible Benefits of the Study?, the document states "the study <u>will</u> help doctors learn how long to cool children." Given that this outcome is not guaranteed, please change the word "will" to "may." In this section, the document also states that "It will also help doctors learn whether to cool patients at all." Given that you do not have a normothermia control group, we do not agree with this statement and recommend removing this sentence.

   d. Please make the following revisions to the Study Information Packet:

      i. Under the heading, "What is this document"?, please revise the first paragraph to reflect that the parent/guardian/LAR is required to read this document as part of the informed consent process. You may consider the following (or similar) language:

         "Your child has the opportunity to participate in a research study called the Pediatric Influence of Cooling Duration on Efficacy in Cardiac Arrest Patients (P-ICECAP) Study.

This document will give you some additional information about P-ICECAP to help you understand the details of the study and whether you would like your child to participate in the study. In addition to information about the study, the last page lists contact information for people connected to the study. You can contact them at any time you have questions or concerns."

ii. Under the heading, "What is involved in the study?, the document states that the "duration of cooling each participant receives is determined mostly at random." Please remove the word "mostly."

iii. Under the heading, "What are the risks of the study?, please include the risks of thrombosis (as identified in your IDE application).

3. You have proposed the P-ICECAP study as a consented study, obtaining consent from subjects or their parent/guardian/legally authorized representative (LAR) within 6 hours following application of standard of care (SOC) therapeutic hypothermia treatment (cooling via site specific cooling devices). This approach to consent is acceptable as long as the current SOC at the study site is therapeutic hypothermia. Because informed consent needs to be obtained prior to the research intervention, specifically the duration of therapeutic hypothermia, the sites that will be permitted to enroll subjects in the P-ICECAP study need to have demonstrated that they have previously established therapeutic hypothermia protocols as the SOC treatment in pediatric cardiac arrest subjects, prior to being asked to participate in the study, and for reasons other than participating in P-ICECAP trial. As such, at these sites informed consent would be obtained within the first 6 hours of the application of the SOC cooling therapy (consistent with the shortest dosing duration in the study of 6 hours) and before randomization to the research intervention.

   At sites currently identified for the P-ICECAP study that have indicated that they currently utilize normothermia as SOC for pediatric cardiac arrest (e.g., see the letter from UC Davis Medical Center) and/or will begin using therapeutic hypothermia specifically to participate in the P-ICECAP study (e.g., see Mattel Children's Hospital at UCLA), the change in treatment from normothermia to therapeutic hypothermia is considered a research intervention. Obtaining informed consent before the hypothermia intervention will not be feasible and as such, in order to include these sites in the P-ICECAP trial, your study would need to be performed under 21 CFR 50.24, Exception from Informed Consent Requirements for Emergency Research (EFIC).

   As such, under the proposed consented P-ICECAP study, FDA will require that any study admitted into the P-ICECAP trial submit verification to you that therapeutic hypothermia is the established SOC therapy for pediatric cardiac arrest at their site, and for reasons other than their desire to participate in the P-ICECAP trial. Ensuring that SOC therapy has been established at all sites may also ensure that patients are not put at increased risk of learning curve issues due to study site inexperience with this procedure. FDA has approved up to 40 centers and will entrust you to include only those sites that meet the criteria established above. Ambiguous responses from sites such as "*Currently our site utilizes [X-Systems] for controlled temperature management*" (e.g., see University of Arizona Tucson letter) will not be acceptable. Only clear indications of an established hypothermia protocol for pediatric cardiac arrest, other than the desire to participate in the P-ICECAP trial, will be acceptable. Please acknowledge your understanding of this requirement prior to enrolling into the P-ICECAP study (an e-mail to the lead

reviewer, Catherine Wentz, is sufficient to acknowledge your understanding prior to enrollment. However, please provide your full response to this condition of approval in your response to this letter).

In your submission that responds to the deficiencies listed above, please identify your response as an amendment to G210126 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.

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.

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.

FDA believes the study design provided in your submission is adequate and may support a future marketing approval or clearance, if it is successfully executed and meets its stated endpoints without raising unforeseen safety concerns.

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.

Your response should be identified as an IDE amendment referencing G210126, 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.

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.

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:

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).

Statistical

4. 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.

5. 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.

6. 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.

7. 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.

8. 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.

9. In the posterior distribution, Y_i is defined as the final response for each subject. However, according to the longitudinal analysis, Y_i is the imputed 12 month response based on 3 month data. We recommend you clarify whether Y_i is the observed or imputed 12 month data. Additionally, the $y_{i,3}$ 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.

10. 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.

11. 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.

12. 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.

13. 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.

14. 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.

15. 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.

16. 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.

17. 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.

18. 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.

<u>Other</u>

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

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.