December 6, 2021

Michael A. Carome, M.D.
Director
Public Citizen's Health Research Group
1600 20th Street, NW
Washington, DC 20009

RE: Public Citizen Letter, Established Status Epilepticus Treatment Trial (ESETT)

Dear Dr. Carome:

Thank you for your June 8, 2021, letter requesting that the Office for Human Research Protections (OHRP) and the US Food and Drug Administration (FDA) conduct a compliance oversight investigation into the completed clinical trial entitled Established Status Epilepticus Treatment Trial (ESETT), clinicaltrials.gov number NCT01960075, and its review and approval by responsible institutional review boards (IRBs).

In your letter, you identify what you describe as fundamental flaws in the trial's design and assert that it appears the risks to subjects enrolled in ESETT were not minimized or reasonable in relation to anticipated benefits of the trial. You also express concerns "that the responsible IRBs that reviewed and approved ESETT lacked the professional competence and knowledge among their membership necessary to ascertain the acceptability of the trial."

OHRP and FDA discussed the issues raised in your letter, and this serves as a response for both FDA and OHRP regarding the issues noted above. As described below, FDA determined that the design and oversight for ESETT were appropriate and that no further action is warranted.

Regulatory Framework

FDA's regulations applicable to IRBs at 21 CFR part 56 are similar to the Department of Health and Human Services (HHS) regulations at 45 CFR part 46, with some differences due to the FDA's mission and statutory authority. FDA and HHS regulations detail requirements for IRB functions and operations, IRB review of research, expedited review procedures, criteria for IRB approval, and IRB recordkeeping, among others. FDA and HHS regulations for informed consent at 21 CFR part 50 are also similar; however, HHS regulations do not have a provision regarding the Exception From Informed Consent (EFIC) for Emergency Research that is found in FDA's regulations (21 CFR 50.24). Instead, HHS has provided a waiver of the applicability of certain requirements for obtaining and documenting informed consent for emergency research that meets the strictly limited conditions outlined in the "Secretarial Waiver of Informed Consent Requirement in Certain Emergency Research."

FDA's surveillance inspection program selects IRBs for inspection using a risk-based site selection approach, which includes consideration of whether an IRB has oversight responsibility for trials conducted under an EFIC per 21 CFR 50.24. Additionally, FDA's inspectional procedures involve evaluation of the IRB's written

procedures and records to determine the IRB's compliance with 21 CFR Parts 50 and 56, including 21 CFR 56.107 concerning IRB membership. FDA has established compliance program procedures specifically for the Agency's inspections of IRBs with oversight of trials conducted under 21 CFR 50.24. These FDA procedures include evaluating whether the IRB has written procedures for reviewing EFIC trials, whether those procedures were followed, and whether the IRB found and documented that the trial satisfies the criteria in section 50.24, approved the informed consent document, reviewed the plan for contacting family member(s) and legally authorized representatives, reviewed the plans for the community consultation and public disclosure process, and confirmed that an independent data monitoring committee was established.

Agency Review

FDA has considered the concerns raised in your letter. FDA's Center for Drug Evaluation and Research (CDER) staff in the Office of New Drugs, Office of Neuroscience, Division of Neurology 2 (Division), reexamined the relevant documentation from its initial review of the investigational new drug (IND) application and subsequent submissions from the sponsor.

During this reexamination, the Division reviewed the clinical trial protocol to confirm that the trial design and care to be provided to research subjects were appropriate. The Division also reexamined the dosing in all weight categories and confirmed that dosing was within the standard of care guidelines published by the Neurocritical Care Society and by the American Epilepsy Society (Brophy S, 2012[1]; Glauser T, 2016[2]). The design of the trial, including the specific allowance for rescue medication before the 60-minute assessment for the primary endpoint, allowed the clinical investigators to apply the current standard of care in determining treatment both during and after the trial intervention. Finally, upon reexamination, the Division also determined that the higher incidence of status epilepticus in Blacks than Whites based on epidemiologic studies (Shorvon S, 2020[3]) was appropriately reflected in the percentage enrollment of Black subjects in ESETT.

Overall, the Division found that the concerns described in your letter, which largely centered on trial design, had been carefully considered and appropriately addressed during the initial review of the ESETT protocol prior to trial initiation.

Also, CDER staff in the Office of Scientific Investigations (OSI) within the Office of Compliance reexamined the relevant documentation from OSI's consultation on the initial IND submission. OSI had been consulted by the Division at the time of the initial IND submission to review the submission for compliance with 21 CFR 50.24 regulatory requirements, in accordance with internal procedures. At all stages of review, OSI determined the plans for community consultation and public disclosure were adequate.

Further, in light of your letter, OSI has reexamined the inspection history of the IRBs involved with the review and approval of ESETT. OSI concluded there were no objectionable conditions or practices with respect to IRB oversight regarding exception from informed consent requirements for ESETT (21 CFR 50.24) and IRB membership (21 CFR 56.107).

Conclusion

After careful reexamination and review, FDA has determined the design of ESETT was appropriate and the

[1] Brophy GM et al. Guidelines for the Evaluation and Management of Status Epilepticus. Neurocritical Care 17:3-23, 2012.
[2] Glauser T et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Currents 16 (1) 48-61, 2016.
[3] Shorvon S, Sen A. What is status epilepticus and what do we know about its epidemiology? Seizure: European Journal of Epilepsy 75: 131-136, 2020.

IRBs responsible for oversight of ESETT met applicable regulatory requirements for this trial. Therefore, no further action is warranted.

Sincerely,

Jacqueline A. Corrigan-curay -S

Digitally signed by Jacqueline A. Corrigan-curay -S
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Jacqueline Corrigan-Curay, M.D., J.D.
Principal Deputy Center Director
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U.S. Food and Drug Administration

CC: Jerry Menikoff, M.D., J.D., Director, OHRP
Rachel. L. Levine, M.D., Assistant Secretary for Health, HHS
Francis Collins, M.D., Director, NIH
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