IND 159898

REMOVE FULL CLINICAL HOLD

Jaideep Kapur, MBBS, PhD
Eugene Meyer III Professor of Neuroscience
University of Virginia School of Medicine
409 Lane Road, 3012D
Charlottesville, VA 22908

Dear Dr. Kapur:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ketamine hydrochloride and levetiracetam.

We also refer to your amendment dated May 16, 2025, which provides a complete response to our January 13, 2022, letter which cited the reasons for placing this IND on clinical hold and the information needed to resolve the clinical hold issues.

We have completed the review of your submission and have concluded that the clinical trial may be initiated.

We have the following comments and recommendations, however, regarding your study protocol:

1. The proposed pH limit for levetiracetam injection (60 mg/mL) does not meet the USP monograph limits for levetiracetam injection (5.0 – 6.0). We recommend updating the proposed limit to align with the USP monograph.

2. We acknowledge your justification for collecting two plasma samples and using a PK/PD modeling approach to evaluate the exposure–response relationship for levetiracetam and ketamine. Based on the cited literature, the use of sparse sampling to characterize levetiracetam PK appears reasonable. However, the meeting package does not include sufficient information to assess whether this approach is also appropriate for characterizing ketamine PK. Therefore, we recommend that you ensure the proposed sampling strategy is suitable for adequately describing the PK of ketamine.

3. Revise the Exception from Informed Consent (EFIC) Plan and protocol to clarify processes pertaining to providing the legally authorized representative (LAR) or family member an opportunity to object to study participation:

a. Revise the EFIC Plan to clearly state that any immediately available LAR or family member will be asked if they object to study participation. As written, the process for providing the LAR or family member the opportunity to object may not sufficiently meet this EFIC requirement if those individuals do not realize they have an opportunity to decline participation.

b. Add to Section 6 of the protocol, “Study Enrollment Procedure,” a statement that the clinical or study team will give any immediately available LAR or family member an opportunity to object to the trial.

c. Add to the Enrollment Flow Diagram shown in Section 6.6 of the protocol the step where the LAR or family member is given the opportunity to object to the research.

4. Revise the Community Consultation plan described in the EFIC Plan:

   a. The “Content” section of the community consultation plan continues to state that the community will be informed that “informed consent will not be possible.” During community consultation, communities should be informed that you are proposing that informed consent will not be obtained for most (or all) research subjects and should include an explanation as to why consent is not feasible. Revise the “Content” section of the plan to clarify these points to ensure communities understand that the consultation is an opportunity for communities to provide input on your proposal.

   b. The content of community consultation should include the informed consent document (ICD), a description of the therapeutic window that will be used to contact the subject's LAR or family member, a description of the attempts that will be made to contact the subject's LAR to obtain consent, or, if no LAR is available, a family member to provide an opportunity to object to the subject’s enrollment in the trial. Revise the “Content” section of the community consultation plan to expand on the content that will be shared during the community consultations. Refer to Question 59 in the FDA Guidance Exception from Informed Consent Requirements for Emergency Research for details.

5. Revise the ICD to address the following requirements under 21 CFR 50.25(a):

   a. Provide a clear statement that the study involves research and clearly identify the interventions that are experimental (i.e., clearly identify that ketamine is not standard of care for status epilepticus). See 21 CFR 50.25(a)(1).

b. Disclose alternative courses of treatment that might be advantageous to the subject or that they would likely receive if not part of the research. This disclosure must include a description of the current medically recognized standard of care. See 21 CFR 50.25(a)(4).

6. We remind you that you must promptly submit to your IND and to Public Docket number 95S-0158 any IRB-approved materials used during public disclosure to the communities in which the clinical investigation will be conducted (i.e., the Community Consultation) and the materials used to disclose the study results (including the demographics of the research population) following completion of the clinical investigation. Materials for the Public Docket should be submitted to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. Please include the IND/IDE number on the materials submitted. [see 21 CFR 50.24(a)(7)(ii) and (iii); 21 CFR 312.54(a); and 21 CFR 812.47(a)]

7. If the subject is discharged to a long-term care facility, you may consider including a transfer order that, if an LAR is identified, the KESET research team will be contacted to provide information about the trial.

If you have any questions, contact Tina Chhabra, Regulatory Project Manager, at Tina.Chhabra@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Emily Freilich, MD
Director
Division of Neurology 1
Office of Neuroscience
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

EMILY R FREILICH
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