



IND 167326

REMOVE PARTIAL CLINICAL HOLD

Broad Institute of MIT and Harvard
Attention: Eric V. Minikel, PhD
Director, Prion Therapeutic Science
415 Main Street
Cambridge, MA 02142

Dear Eric Minikel:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for PrP-lowering divalent siRNA 2439-exNA.

We also refer to your amendments dated January 22, 2026, and February 2, 2026, which provide a complete response to our April 11, 2025, letter which cited the reasons for placing the protocol titled “An open-label, single ascending dose study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of intrathecally administered PrP-siRNA in healthy adult patients at genetic risk for prion disease,” on clinical hold, and the information needed to resolve the clinical hold issues.

We have completed the review of your submissions and have concluded that you may proceed with the proposed study because your protocol, as amended, has addressed the deficiencies in the stopping criteria, cohort dose administration plan, safety follow-up, and eligibility criteria. In addition, you have adequately revised your informed consent form. Please note that if you submit a new protocol that raises the same concern and have not submitted or do not include in that protocol submission the data previously requested to address the concern, that protocol may be placed on clinical hold until the data necessary to address the concern are provided.

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

Clinical Pharmacology:

1. We acknowledge your plan of collecting CSF and blood samples to characterize the pharmacokinetics and pharmacodynamics of single doses of PrP-siRNA as secondary objectives in both pre-symptomatic and symptomatic prion disease protocols. However, we note that the relevant sections of your protocols (e.g., section 6.1 - schedule of activities, study schedule) do not specify the blood sampling plan for PK characterization of PrP-siRNA. You should update your protocols clearly stating the time points for blood collection for PK assessment.

Clinical/Statistics

2. We acknowledge that your efficacy outcome measures are exploratory and not intended to demonstrate substantial evidence of effectiveness. However, given the rarity of the disease, we encourage you to maximize utility of any data collected by minimizing missing data, pre-specifying even exploratory hypotheses, planning to control family-wise error, and adjusting your analyses for known prognostic variables. You should use exact tests that do not rely on asymptotic distributions.

If you have any questions, contact Brenda Reggett, PharmD, Regulatory Health Project Manager, by email at [REDACTED]

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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