



January 22, 2026

ATTN: Brenda L. Reggettz, PharmD
Senior Regulatory Health Project Manager, Neurology 1

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
[REDACTED]
Beltsville, MD 20705-1266

RE: IND 167326 – PrP-lowering divalent siRNA 2439-exNA
Response to Information Amendment

Serial Number: 0009

Dear Brenda:

We previously submitted a trial protocol for pre-symptomatic prion disease patients, entitled “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.” FDA notified us on December 10, 2025 that this protocol may proceed provided that specific issues are addressed. I am writing today to supply you with an updated version of the protocol and consent form addressing FDA’s requests.

Specific page numbers corresponding to FDA’s requests are as follows (FDA feedback in **bold**, our responses in plain):

1. Revise your informed consent form (ICF) to clearly explain that you have not conducted the standard set of animal studies recommended by the International Conference on Harmonisation M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals and explain that this exception is being made because of the rarity and severity of the disorder, and because of the high penetrance of the genetic mutations leading to disease.

The revised Informed Consent Form, page 2, now states:

“This study's sponsor has not conducted the standard set of animal studies recommended by the International Conference on Harmonisation M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals. This exception is being made because of the rarity and severity of the disorder, and because of the high penetrance of the genetic mutations leading to disease.”

2. Revise the protocol as follows:

a. Amend the study stopping and dose escalation criteria to include the application of reasonable clinical judgment.

i. We do not agree with basing stopping or reporting criteria on an assessment of an adverse event's "relatedness" to the study drug, as it is often not clear to investigators during the course of a study which events are related to the study drug. Safety signals may not be identified until the study data is analyzed by the IMM or DSMB or after the study is completed.

ii. Any severe or serious adverse reaction should prompt an immediate safety assessment by the IMM to determine whether dosing may proceed in additional patients, and whether changes to the study protocol are needed, e.g., dosing adjustment.

The revised Protocol, page 52, now reads: "As shown above, if a severe, non-serious AE or an SAE is observed, the Investigator must report the SAE to the MSM via the Online Adverse Event Reporting System within 24 hours. For each review described above, the MSM will apply reasonable clinical judgment to determine whether dosing may proceed in additional participants or concerns are sufficient to satisfy a study stopping criteria."

b. Amend your cohort dose administration plan so that after sentinel dosing, the remaining study subjects in all cohorts should have doses administered with staggered timing and no two subjects should be dosed simultaneously.

The revised Protocol, page 12, now reads: "Assuming the MSM gives approval to advance, the second and third pre-symptomatic participants within a given dose level cohort will be treated, at least 1 day apart. Participants will never be dosed on the same day."

c. Add safety follow-up visits at Week 1 and Week 2.

The revised Protocol, page 31-32 (Schedule of Activities) now shows in-person visits at Week 1 and Week 2.

d. Serious adverse events are discussed in your protocol but not defined. Include the standard definition of serious adverse events in the protocol.

The revised Protocol, page 49-50, now includes the standard definition of SAEs, beginning with "A serious adverse event (SAE) is defined as an AE that meets any of the following criteria..."

e. Revise the eligibility criteria so that it specifies that all subjects will use highly effective methods of contraception.

The revised Protocol, page 44, now states "All subjects will use highly effective methods of contraception throughout trial participation" and describes these requirements in detail.

f. The inclusion criterion: “No symptoms of prion disease in the opinion of the investigator” is a vague inclusion criterion. Your inclusion criteria should be based on quantitative measure of performance, such as on the MRC-PDRS, or a normal neurological exam, etc.

The revised Protocol, page 25, now states the following inclusion criterion: “No symptoms of prion disease, as demonstrated by an MRC Score of 20, a MoCA score in the normal unimpaired range, and a normal neurological exam.”



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cc: IND 167326 Regulatory File