March 2026

Dear Prion Disease Community,

We are writing to provide an update on our Phase 1/2a clinical trial of ION717 in people with prion disease, PrProfile. Based on preliminary analysis of data from our Phase 1/2a PrProfile clinical trial of our investigational medicine, ION717, in people with prion disease (PrProfile; NCT06153966), Ionis will expand the trial in the following two ways:

1. An additional dosing regimen (Regimen 3) will be tested in approximately 20 additional people with symptomatic prion disease. Unlike those previously enrolled in PrProfile, participants in Regimen 3 will not receive a placebo and will receive only ION717 during the trial.[1]
2. The open-label extension period will be extended from 70 weeks to 142 weeks to allow for continued evaluation of ION717 for a more extended period of time.[1]

Review of data from early-stage clinical trials, such as PrProfile, is customary and used to inform appropriate next steps. The decision to expand PrProfile is based on a review of interim data showing an encouraging safety and tolerability profile, and that ION717 is engaging with its target biology (i.e., prion protein).

Ionis recently updated the trial information available at clinicaltrials.gov to reflect these changes. No other changes to the study design have been made (e.g., eligibility criteria, outcome measures). As the trial expands to include additional participants, Ionis has updated the estimated date for the primary study endpoint to approximately February 2027. This date is subject to change, as it is based on our initial estimate for completing enrollment.[1]

No new clinical sites will be added, and it is possible that not all current PrProfile clinical sites will participate in Regimen 3 enrollment. Ionis will update individual clinical site status on clinicaltrials.gov as they become activated to enroll participants as part of this expansion.[1]

Ionis expresses its sincere appreciation to all individuals with prion diseases, their caregivers, and families who have and continue to participate in the PrProfile study. Ionis looks forward to collaborating with our clinical trial investigators and their staff to identify and enroll additional participants into the Regimen 3 arm of PrProfile. We will provide further updates in the future.

Sincerely
The Ionis ION717 team

Below is additional information you may find useful

<u>Where can someone interested in participating in PrProfile go for more information?</u>

A person's doctor should be their primary source of information on health-related topics, including clinical trials. You can also find more information about PrProfile online here: https://clinicaltrials.gov/study/NCT06153966.

How does this impact people currently enrolled in PrProfile?

The trial's Open-Label Extension Treatment Period has been extended to allow for continued evaluation of ION717 for a longer period of time.[1] Study participants should direct questions they have to their study doctor and site staff.

What does this mean about the safety and efficacy of ION717?

The preliminary data show an encouraging safety and tolerability profile that support expanding PrProfile to test an additional dosing regimen. These preliminary data are not sufficient to establish the safety, tolerability, or efficacy of ION717 as a treatment for prion disease.

What dose(s) of ION717 are being studied in PrProfile?

Ionis has not disclosed the specific dose(s) of ION717 being studied in PrProfile.

What did Ionis present at the Prion 2025 conference?

Ionis recently presented an update on the Phase 1/2a clinical trial of ION717 (PrProfile) at the Prion 2025 conference in Brazil. This presentation included information about how participants in the trial were randomized in the Double-Blind Treatment Period (ION717 followed by placebo or placebo followed by ION717), a list of assessments and tests being conducted in the study, confirmation that the study database to date had been locked to support an initial analysis, and an intention to share additional information in 2026.[2]

When will Ionis share data from PrProfile with the prion disease community?

We understand there is significant interest among the prion disease community in seeing preliminary data from our clinical trial. A review of preliminary data from PrProfile supported expanding the study to explore an additional ION717 dosing regimen. Ionis will share data from PrProfile at future medical and scientific conferences. We anticipate that to occur after the study reaches its updated Primary Study Completion date, now projected to be approximately February 2027.[1]

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The CJD Support Group Network Australia and the CJD International Support Alliance provide community resources and support to those affected by prion disease. For more information about Ionis, visit www.ionis.com or email padvocacy@ionis.com.

References: 1. Profile: A Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ION717. https://clinicaltrials.gov/study/NCT06153966. Published December 1, 2023. Updated March 17, 2026, 2. Keynote Lecture - An Antisense Oligonucleotide Designed to Lower Prion Protein. Presented by Rob Pulido. Prion 2025 Conference. November 6, 2025. Buzios, Brazil

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