

Update on the ALN-HTT02-001 Ph1b study of brezosiran, in development for Huntington's Disease (HD)

Dear Huntington's Disease Community,

Alnylam is presenting initial Phase 1b clinical trial results for ALN-HTT02, an investigational treatment for Huntington's disease at the 2026 European Huntington's Disease Network (EHDN) Clinical Research Congress in Krakow, Poland. Moving forward, ALN-HTT02 will be developed under the name brezosiran (bre-ZOH-sir-an).

How the Investigational Therapy, Brezosiran, May Work

Brezosiran uses RNA interference (RNAi) technology to reduce the production of the huntingtin (HTT) protein that causes Huntington's disease. By targeting Exon 1 of HTT, a specific upstream part of the HTT mRNA (messenger RNA) molecule, brezosiran is designed to potentially reduce all forms of HTT protein in the brain. This approach reduces the production of both the full-length mutant HTT protein as well as a shorter form of the mutant HTT protein called HTT1a, which has been shown in preclinical research to contribute to disease progression. Brezosiran is an investigational product and is not approved by any health authority around the world. The safety and efficacy of brezosiran have not been established.

Initial Key Phase 1b Study Results for ALN-HTT02 (Brezosiran) in Huntington's Disease

- The ongoing Ph1b trial includes adults with genetically confirmed Huntington's disease, Aged 25–70 years, in HD-ISS (Huntington's Disease Integrated Staging System) Stage 2 or early Stage 3. Data from the first 48 subjects is being presented.
- In the Phase 1b trial, the investigational product, Brezosiran, was administered as an injection into the fluid around the spinal cord (called an "intrathecal injection). Researchers observed dose-dependent reductions in mutant HTT proteins.
- Brezosiran was generally well tolerated, and researchers saw no related signs of brain inflammation or nerve cell damage.

What Happens Next?

Additional research is needed to understand the longer-term safety profile and potential efficacy of brezosiran.

- Existing participants from the Phase 1 study are able to transition into an ongoing Ph1b open-label extension (OLE) study in which they will receive brezosiran once every six months for up to three years. This study will continue to evaluate

brezosiran's ability to lower HTT protein and safety profile over time. The OLE study will also explore potential efficacy trends over time.

- While the Ph1b OLE is running, Alnylam plans to also begin a larger, placebo-controlled efficacy study to assess its potential to slow progression in adults with Huntington's disease. This study will test whether lowering all forms of HTT with brezosiran can slow the progression of Huntington's disease. Alnylam intends to initiate the study in 2027, pending alignment with regulators, and will share more information with the community soon.

Collaboration with the Community

Progress is only possible through collaboration with the Huntington's disease community. Alnylam remains committed to listening to and learning from people with Huntington's disease, families, caregivers, advocacy organizations, healthcare professionals, and researchers.

Thank you for your continued partnership and support of Huntington's disease research.

Sincerely,

The Alnylam Patient Advocacy and Clinical Development Team