ALN-HTT02: Phase 1b Study

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The safety and efficacy of ALN-HTT02 are currently being investigated in clinical studies and have not been evaluated by US Food and Drug Administration or any health authority.

If you are seeking additional scientific information related to Alnylam medicines, you may visit the Alnylam US Medical Affairs website at RNAiScience.com.

SUMMARY

- The safety, tolerability, PK, and PD of ALN-HTT02 in adults with Huntington's disease are being evaluated in an ongoing, randomized, double-blind, placebo-controlled, single ascending dose, phase 1b study (NCT06585449).[1,2]
- ALN-HTT02 is an investigational 2'-O-hexadecyl (C16)-conjugated RNAi therapeutic that targets a conserved mRNA sequence within exon 1 to reduce the expression of all HTT protein species in the CNS, including mHTT (full-length), mHTTa (exon 1), and wtHTT.[2,3] The therapeutic hypothesis for ALN-HTT02 suggests that the reduction of all mHTT protein that contain expanded polyglutamine tracts has the potential to limit toxic gain-of-function activities and alter the course of Huntington's disease progression.[2]

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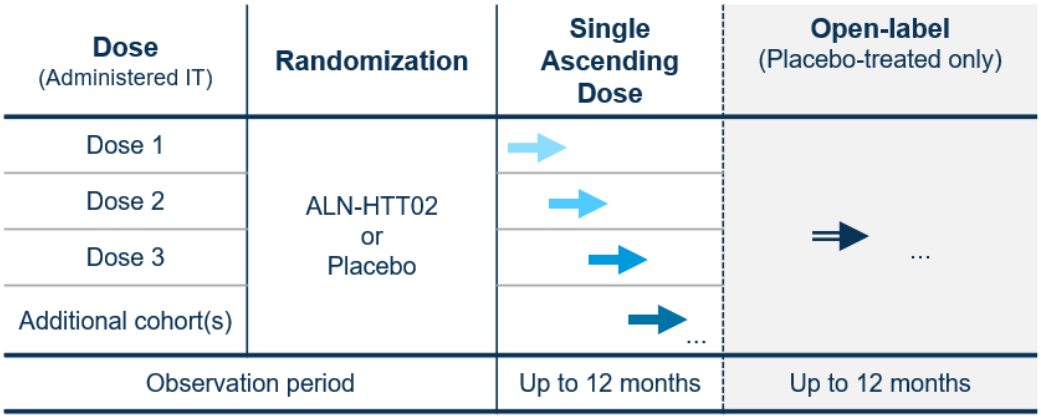
STUDY DESIGN

The phase 1b study of ALN-HTT02 is an ongoing, randomized, double-blind, placebo-controlled, single ascending dose study designed to evaluate the safety, tolerability, PK, and PD of ALN-HTT02 in adult patients with Huntington's disease.[1,2] Enrolled patients will be randomized to receive IT injections of ALN-HTT02 or placebo in single ascending doses during a double-blind period of up to 12 months (**Figure 1**). The decision for a patient to proceed to the next dosing cohort will be determined by the Safety Review Committee. After all patients in the double-blind cohort have reached Month 6, the cohort will be unblinded and placebo-treated patients may receive a single open-label dose of ALN-HTT02. The open-label dose observation period for patients initially randomized to placebo will last up to 12 months.[2]

Figure 1. ALN-HTT02 Phase 1b Study Design.[2]



Abbreviations: IT = intrathecal.
From Sloan et al.[2]

The primary endpoint will assess the safety of ALN-HTT02 through the frequency of adverse events.[1,2]

Secondary endpoints include[1]:

- Change from baseline in levels of mHTT in CSF
- Concentrations of ALN-HTT02 in plasma
- Concentrations of ALN-HTT02 in CSF
- Concentrations of ALN-HTT02 in urine

Exploratory endpoints include[2]:

- Clinical, imaging, and biomarker measures of disease progression and safety

Key study inclusion criteria are[2]:

- Age 25-70 years with >39 CAG repeats
- HD-ISS Stage 2 or early Stage 3

Key study exclusion criteria are[1]:

- Significant structural or degenerative neurologic disease other than Huntington's disease at screening
- Primary or secondary immune compromise at screening due to infections, medical conditions, or chronic therapies
- ALT or AST >2× ULN
- eGFR <45 mL/min/1.73m^2 at screening
- Received an investigational agent within the last 1 year or 5 half-lives (if known)

The trial is listed as recruiting as of February 28, 2025.[1]

ABBREVIATIONS

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CAG = cytosine-adenine-guanine; CNS = central nervous system; CSF = cerebrospinal fluid; eGFR = estimated glomerular filtration rate; HD-ISS = Huntington's Disease Integrated Staging System; HTT = huntington; IT = intrathecal; mHTT = mutant huntingtin; mRNA = messenger ribonucleic acid; PD = pharmacodynamics; PK = pharmacokinetics; ULN = upper limit of normal; wtHTT = wild-type huntingtin.

Updated 20 October 2025

REFERENCES

1. Alnylam Pharmaceuticals: A Study to Evaluate ALN-HTT02 in Adult Patients With Huntington's Disease. Available from: https://clinicaltrials.gov/study/NCT06585449. Accessed February 28, 2024.
2. Sloan K. ALN-HTT02, a novel C16-siRNA conjugate for HTT-lowering in the CNS. Presented at: European Huntington's Disease Network (EHDN) and Enroll-HD Congress; September 12-14, 2024; Strasbourg, France.
3. Sloan, K. ALN-HTT02, an investigational RNAi therapeutic targeting Exon 1 of HTT in Phase 1 development for Huntington's disease. Presented at: CHDI Huntington's Disease Therapeutics Conference; February 24-27, 2025; Palm Springs, CA, USA.