

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.

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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

INDEX

[Study Design](#) – [Abbreviations](#) – [References](#)

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

Dose (Administered IT)	Randomization	Single Ascending Dose	Open-label (Placebo-treated only)
Dose 1	ALN-HTT02 or Placebo		 ...
Dose 2			
Dose 3			
Additional cohort(s)		 ...	
Observation period		Up to 12 months	Up to 12 months

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 include¹:

- 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 include²:

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

Key study inclusion criteria are²:

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

Key study exclusion criteria are¹:

- 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/1.73m² 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 = huntingtin; 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.