

ALN-HTT02, a Novel C16-siRNA Conjugate for HTT-lowering in the CNS

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Relevant Disclosures for Kevin Sloan, PhD

Conflict	Disclosure
Employee	Alnylam Pharmaceuticals
Shareholder	Alnylam Pharmaceuticals

ALN-HTT02

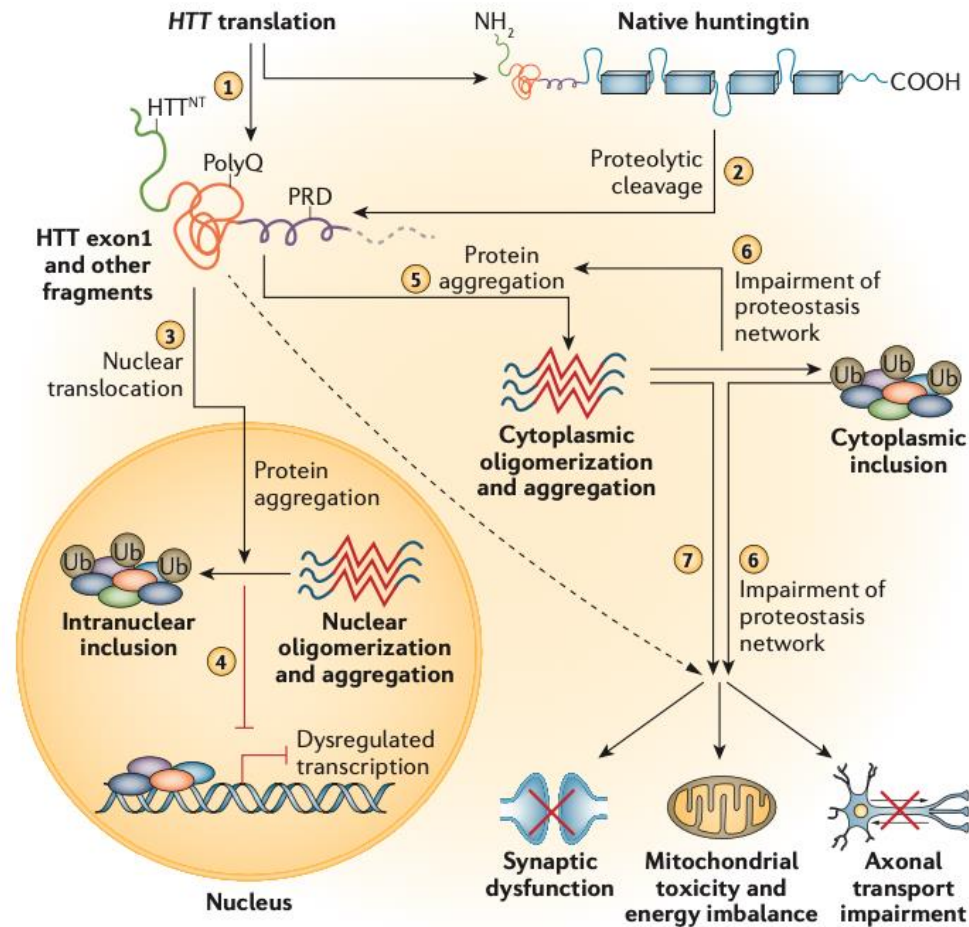
- ALN-HTT02 is an investigational drug being studied for the treatment of Huntington's disease. ALN-HTT02 is not approved by any health authority, and the safety and efficacy of ALN-HTT02 have not been established.
- The ALN-HTT02 clinical program is being conducted as a partnership between Alnylam Pharmaceuticals and Regeneron Pharmaceuticals, Inc.

TO PATIENTS and CAREGIVERS:

- No information in this presentation constitutes medical advice. If you have any specific medical questions, you should seek the advice from your treating physician.

HTT is a Genetically Validated Target for Huntington's Disease¹

No approved disease-modifying treatments exist, reflecting a critical unmet need²



- **Huntington's disease (HD) is progressive and fatal, driven by mutant huntingtin (HTT)^{1,3}**
 - Toxic, broadly disruptive gain of function
 - CAG repeat expansion; somatic instability
 - Protein aggregation
 - Widespread neurodegeneration
- **Both full-length mutant HTT and shorter exon 1 splice isoforms likely contribute to disease pathology²**
- **Investigative HTT-lowering approaches may offer potential to alter the course of HD progression^{1,4}**
 - Safety and extent of achievable clinical benefit have yet to be elucidated
 - Early efforts limited by therapeutic platform challenges

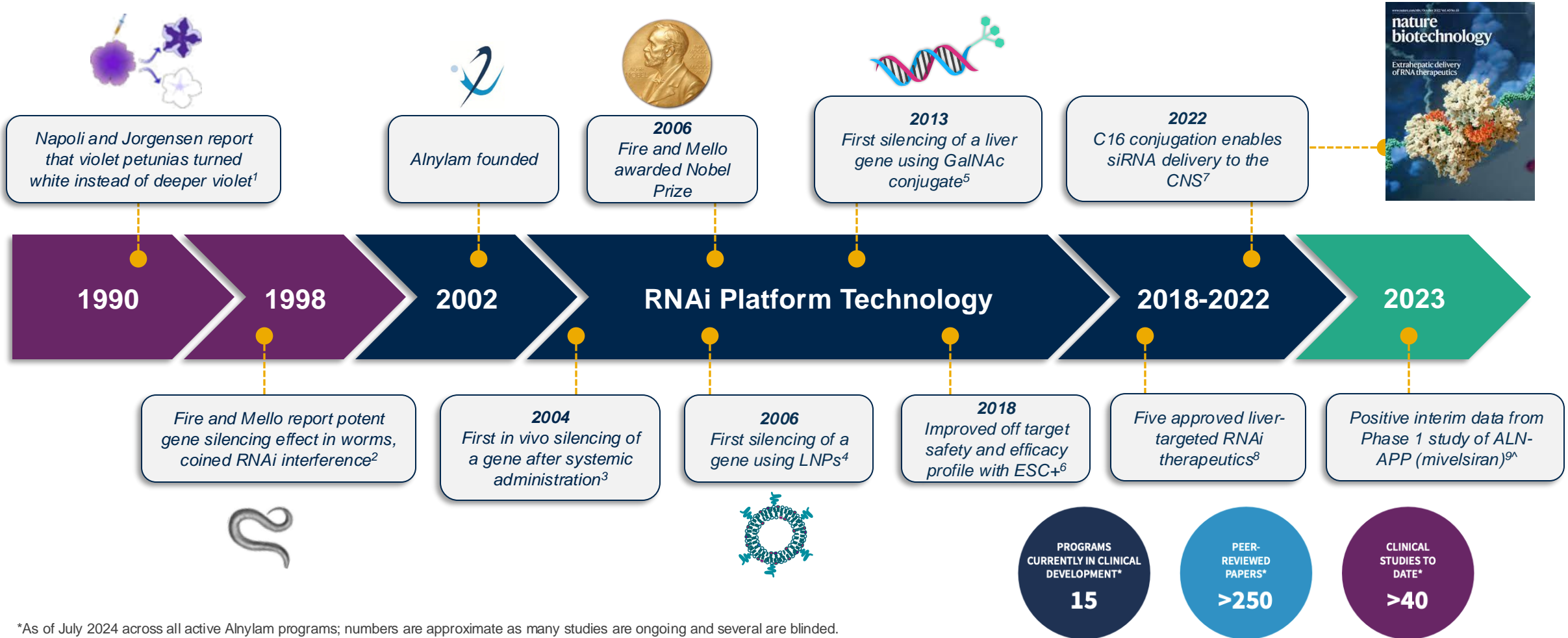
Figure: Bates GP, et al. Huntington disease. *Nat Rev Dis Primers*. 2015. Springer Nature. <https://www.nature.com/articles/nrdp20155>. Reprinted with permission from Springer Nature.

CAG, cytosine-adenine-guanine; HD, Huntington's disease; HTT, huntingtin.

1. Tabrizi SJ, et al. *Lancet Neurol*. 2022;21(7):645-658. 2. Sampaio C. *Parkinsonism Relat Disord*. 2024;122:106049. 3. Bates GP, et al. *Nat Rev Dis Primers*. 2015;1:15005. 4. Ferguson MW, et al. *J Cent Nerv Syst Dis*. 2022;14:11795735221092517.

Anylam has Pioneered Development of RNAi Therapeutics

Over 20 years of platform learning & optimization



*As of July 2024 across all active Anylam programs; numbers are approximate as many studies are ongoing and several are blinded.

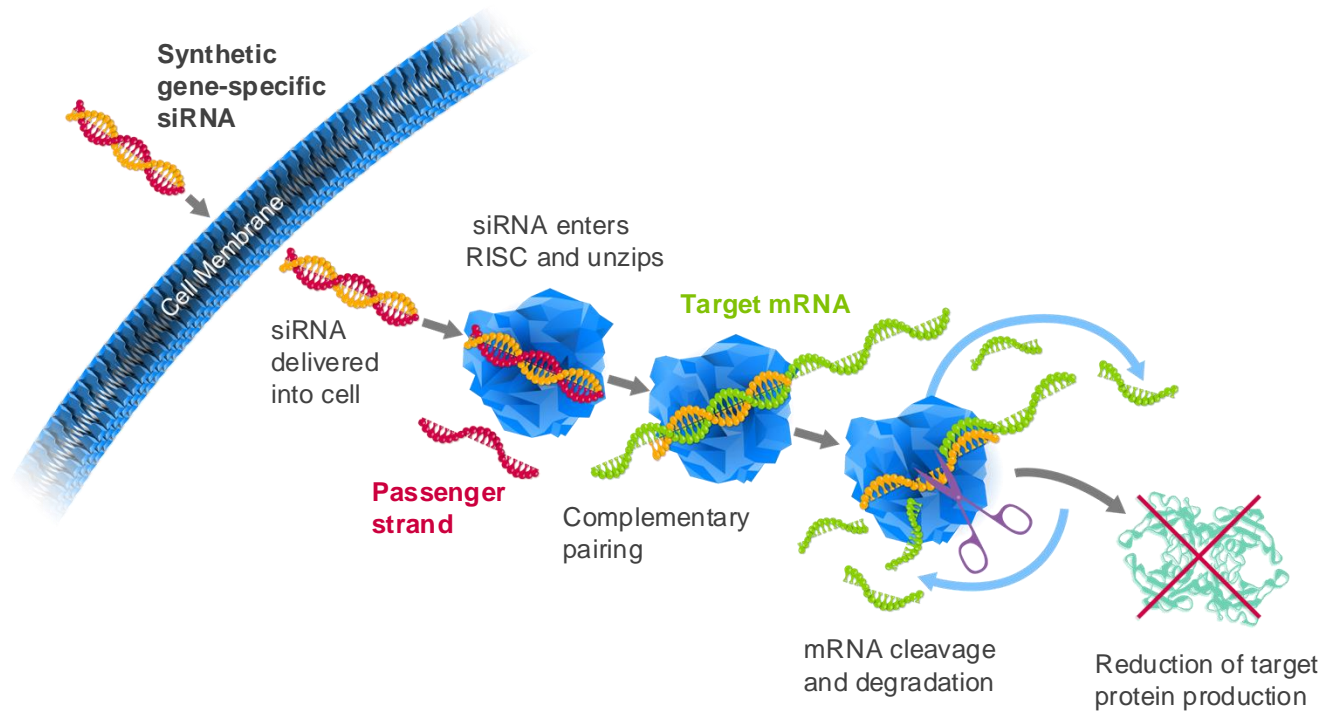
ᵃMivelsiran is an investigational drug being studied for the treatment of Alzheimer's disease and cerebral amyloid angiopathy.

C16, 2'-O-hexadecyl; CNS, central nervous system; ESC+, enhanced stabilization chemistry plus; GalNAc, N-acetylgalactosamine; LNP, lipid nanoparticle; RNAi, RNA interference; siRNA, small interfering RNA.

1. Napoli C, et al. *Plant Cell*. 1990;2(4):279-289. 2. Fire A, et al. *Nature*. 1998;391(6669):806-811. 3. Soutschek J, et al. *Nature*. 2004;432(7014):173-8. 4. Zimmermann TS, et al. *Nature*. 2006;441(7089):111-4. 5. Manoharan M. Delivery strategies for RNA interference (RNAi) based therapeutics. 246th American Chemical Society National Meeting; September 8-12, 2013; Indianapolis, IN. 6. Foster DJ, et al. *Mol Ther*. 2018;26(3):708-717. 7. Brown KM, et al. *Nat Biotechnol*. 2022;40(10):1500-1508. 8. An G. *J Clin Pharmacol*. 2024;64(1):45-57; 9. Cohen S et al. Interim Phase 1 Part A Results for ALN-APP, the First Investigational RNAi Therapeutic in Development for Alzheimer's Disease. Alzheimer's Association International Conference (AAIC). July 2023. Amsterdam, Netherlands.

RNA Interference Harnesses an Endogenous Process to Lower Expression of Disease-Associated Proteins

RNAi Mechanism of Action^{4,a}



- RNAi is a **natural biological process** to regulate gene expression¹
- Synthetic small interfering RNAs (siRNAs) designed to **specifically degrade mRNA** encoding a disease-associated protein¹
- **Catalytic mechanism**, repeatedly reducing target protein expression while leaving DNA intact¹
- RNAi therapeutics have demonstrated **potent and durable efficacy**, supporting infrequent dosing regimens, with **acceptable safety profiles**^{2,3}
- RNAi therapeutics are a unique class of genetic medicine; **distinct from antisense oligonucleotides**¹

^aImage created by Alnylam Pharmaceuticals from data published in Jadhav *et al.* 2024⁴

mRNA, messenger RNA; RNAi, RNA interference; siRNA, small interfering RNA.

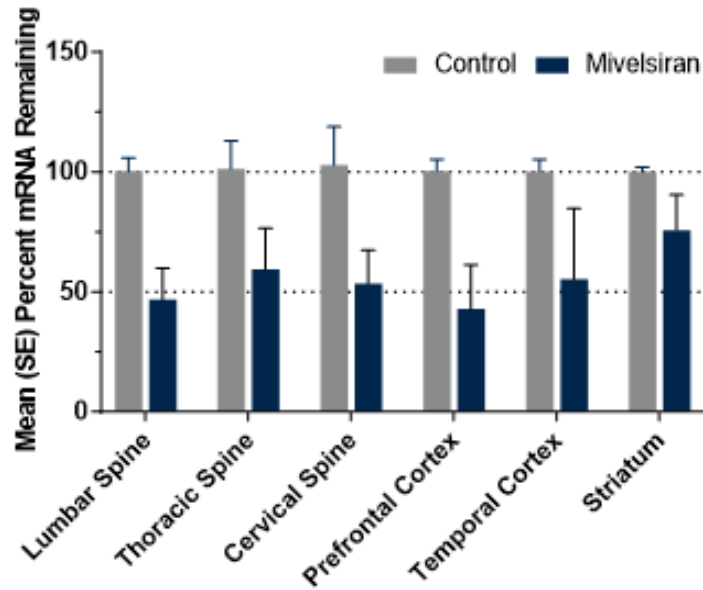
1. Niemietz C, et al. *Molecules*. 2015;20(10):17944-17975. 2. An G. *J Clin Pharmacol*. 2024;64(1):45-57. 3. Aagaard L, Rossi JJ. *Adv Drug Deliv Rev*. 2007;59(2-3):75-86. 4. Jadhav V et al. *Nature Biotechnol* 2024;42:394-405.

First Translation of RNAi in the CNS

Preclinical and Phase 1 data of C16-siRNA demonstrate robust lowering of target protein expression with encouraging safety in Alzheimer's disease

Preclinical Results with APP-lowering siRNA^{1,2}

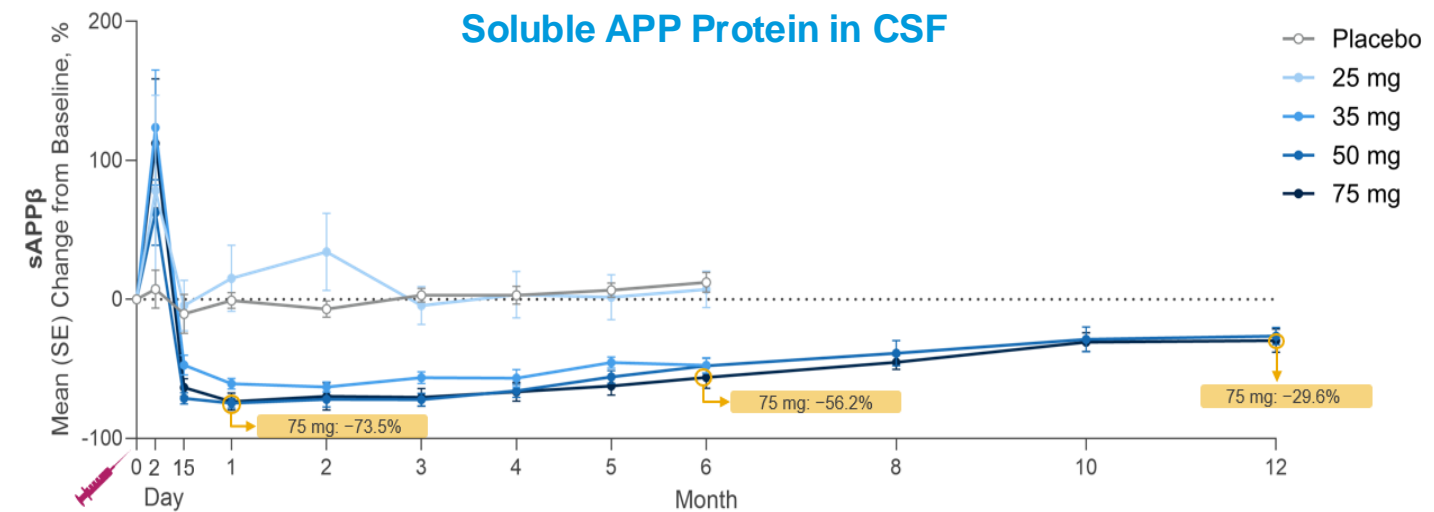
- IT dosing of siRNA enables delivery to the CNS
- C16 conjugation enables widespread siRNA distribution and durable target engagement



3 months post single IT dose in NHPs

Interim Phase 1 SAD Results of Mivelsiran in Early-Onset AD³

- Rapid, robust reductions in target protein levels observed through Month 12
- Majority of AEs are mild or moderate and nonserious
- CSF safety biomarkers, routine lab assessments, and exploratory NfL data all show no significant abnormalities



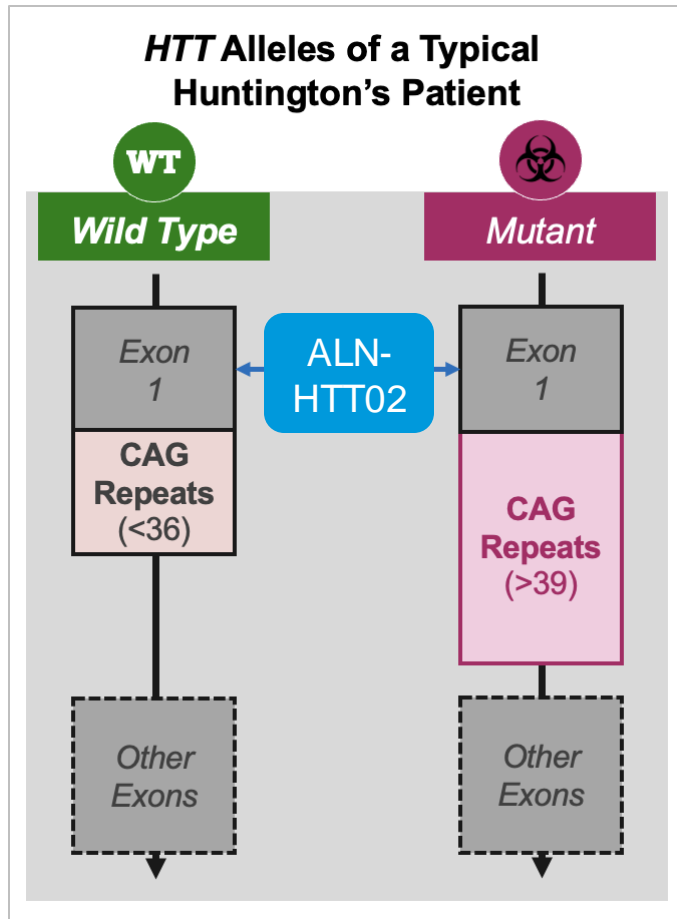
12 months post single IT dose in humans

1. Brown KM, et al. *Nat Biotechnol.* 2022;40(10):1500-1508. 2. Kurz J, et al. Oral presentation presented at the Alzheimer's & Parkinson's Diseases Conference (ADPD), March 28–April 1, 2023, Gothenburg, Sweden. 3. Deering R, et al. Oral Presentation at the International Cerebral Amyloid Angiopathy (ICAA) Conference, October 15–17, 2024, Munich, Germany.

AD, Alzheimer's disease; AE, adverse event; APP, amyloid precursor protein; C16, 2'-O-hexadecyl; CNS, central nervous system; CSF, cerebrospinal fluid; IT, intrathecal; mRNA, messenger RNA; NfL, neurofilament light chain; NHP, non-human primate; RNAi, RNA interference; SAD, single ascending dose; sAPP, soluble amyloid precursor protein; siRNA, small interfering RNA.

ALN-HTT02 is an Investigational RNAi Therapeutic Designed to Reduce HTT Protein Expression in the CNS

Leveraging a Clinically-Validated C16-siRNA Delivery Platform



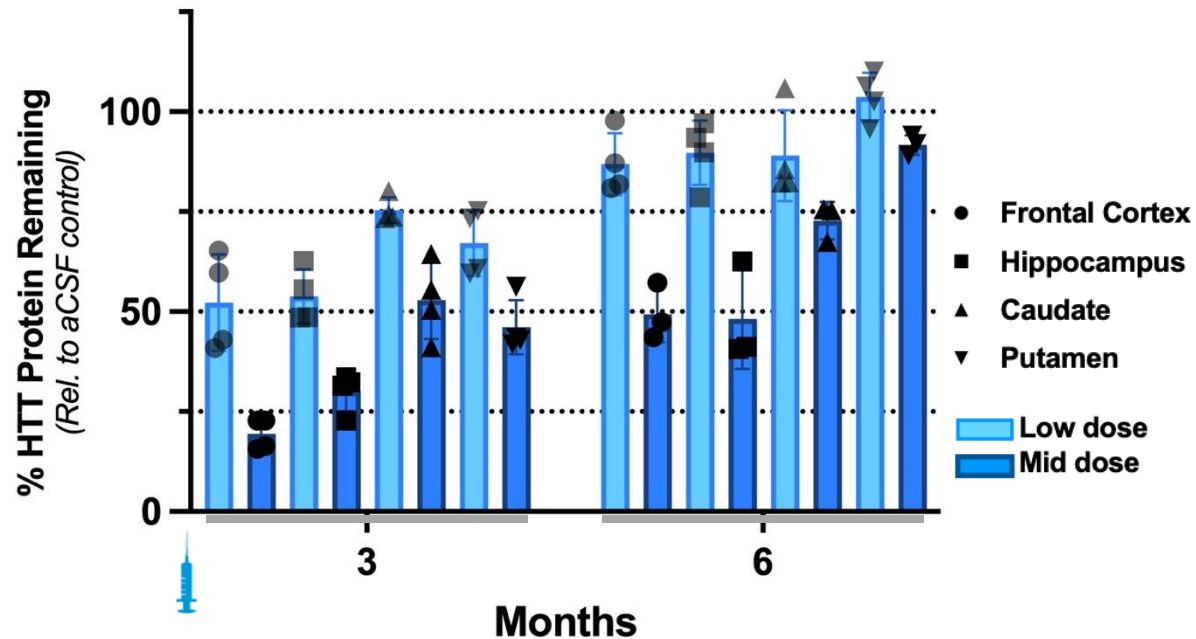
Therapeutic hypothesis

- ALN-HTT02 targets a conserved mRNA sequence **within exon 1**
- Designed to reduce expression of **all** HTT protein species
 - *mHTT (full-length), mHTT (exon 1), wtHTT*
- By reducing **all** forms of mHTT protein containing expanded polyglutamine tracts, ALN-HTT02 has the potential to limit toxic gain of function activities and alter the course of HD progression

Single Dose of ALN-HTT02 Demonstrates Broad CNS Distribution and Durable HTT-Lowering in NHP¹

PK/PD Profile Consistent with Prior RNAi Experience in the CNS

Single IT Dose of ALN-HTT02

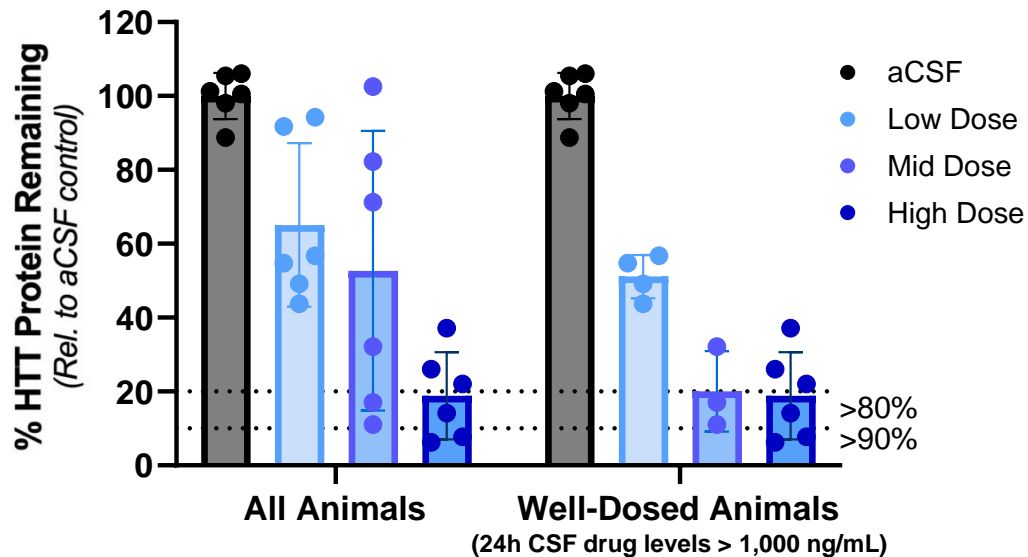


- Observations following a **single dose** of ALN-HTT02:
 - **Widespread distribution** across CNS regions
 - **Durable** HTT-lowering, supporting infrequent dosing in the clinic
 - **Encouraging safety profile through 6 months**
 - No in-life neurological abnormalities
 - No elevations in CSF NfL
 - No elevations in CSF total protein

HTT-Lowering via Multiple Doses of ALN-HTT02 is Well Tolerated in NHP¹

Safety Profile Supports Continued Development

Multiple IT Doses of ALN-HTT02 (Q3M for 6 Months)



PD data from frontal cortex at 6M

- Observations following **multiple doses** of ALN-HTT02 at 3 dose levels:

- **Encouraging safety profile through 6 months**
 - No in-life neurological abnormalities
 - No adverse CSF parameter changes
 - No adverse microscopic findings
- ALN-HTT02 has been evaluated in 4 independent NHP studies to date
 - **No adverse findings, even after deep HTT-lowering (>90%)**

A Phase 1b Study of ALN-HTT02 in Adult Patients with HD¹

Placebo-controlled single ascending dose study evaluating safety, tolerability, and PK/PD

Study population

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

Endpoints

Primary endpoint

- Safety and tolerability

Secondary endpoints

- PK: CSF and plasma profile of ALN-HTT02
- PD: Change in mHTT levels in CSF

Exploratory endpoints

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

Dose (Administered IT)	Randomization	Single Ascending Dose ^a	Open-label ^b (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

a. The decision to proceed to the next dosing cohorts is determined by the Safety Review Committee

b. After all patients in the double-blind cohort have reached Month 6, cohort is unblinded and placebo-treated patients may receive a single open-label dose of ALN-HTT02

Study initiating in the UK & Canada; additional countries planned

Protocol reviewed and accepted by Enroll-HD CTC and endorsed by EHDN EC



clinicaltrials.gov

Summary

- Alnylam's clinically-validated siRNA platform may offer a new approach for HTT-lowering in the CNS
- ALN-HTT02 is an investigational RNAi therapeutic designed to durably lower all forms of mHTT, including exon 1 fragments
 - *Potential to optimize depth and duration of HTT-lowering via clinical dosing regimens to maximize efficacy while preserving safety*
- wtHTT-lowering in the CNS appears well tolerated in NHPs after IT dosing with ALN-HTT02
 - *Findings demonstrated in multiple independent studies, even with deep HTT-lowering*
- A Phase 1b study of ALN-HTT02 in people with Huntington's disease is currently initiating¹

If you are seeking additional scientific information related to Alnylam therapeutics, US HCPs may visit the Alnylam US Medical Affairs website at RNAiScience.com. Non-US HCPs should contact medinfo@alnylam.com.

C16, 2'-O-hexadecyl; CNS, central nervous system; CSF, cerebrospinal fluid; HD, Huntington's disease; HTT, huntingtin; IT, intrathecal; mHTT, mutant huntingtin; NHP, non-human primate; PD, pharmacodynamic; RNAi, RNA interference; SAD, single ascending dose; siRNA, small interfering RNA; wtHTT, wild-type huntingtin.

1. ClinicalTrials.gov. NCT06585449. Available from: <https://clinicaltrials.gov/study/NCT06585449> (Accessed Oct 16, 2024).



Thank you to the patients, their families, investigators, and study staff for participation in the ALN-HTT02-001 study

Thank you to our collaborators and HD advocacy groups for ongoing advice and support of the program

Thank you to the HSG 2024 organizers for the opportunity to share our work

