

Interim Data From a Phase 1b Study of ALN-HTT02, an Investigational RNA Interference Therapeutic Targeting Exon 1 of Huntingtin for HTT-lowering in People with Huntington's Disease

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**Presented at the European Huntington's Disease Network (EHDN) Clinical Research Congress 2026, Krakow, Poland
October 22–24, 2026**





Disclosure for Sarah Tabrizi, MD, PhD

Conflict	Disclosure
Consultant	Anylam 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.

TO PATIENTS AND CAREGIVERS

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

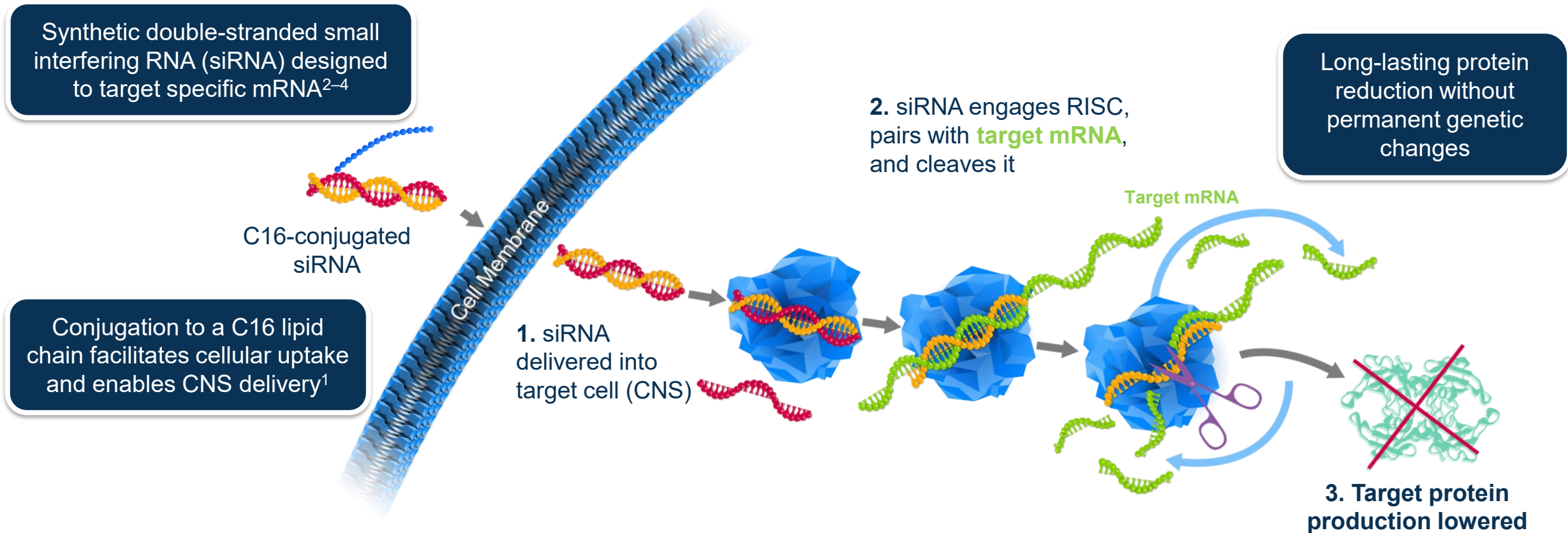
FUNDING

The ALN-HTT02 clinical program is being conducted as a partnership between Anylam Pharmaceuticals and Regeneron Pharmaceuticals, Inc.

Medical writing support provided by Paul Banks, PhD, of Oxford PharmaGenesis, part of the Klick Health family, was funded by Anylam Pharmaceuticals in accordance with Good Publication Practice guidelines.

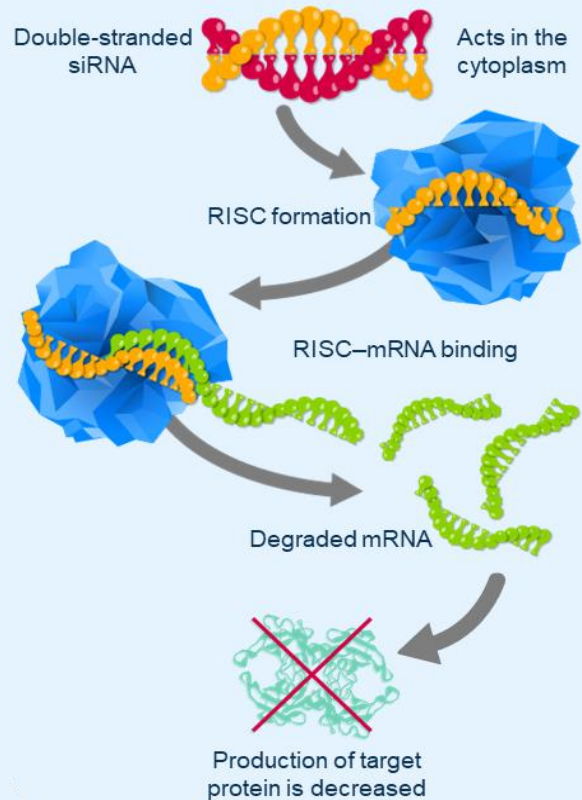
RNA Interference in the CNS

C16 Delivery Platform Enables RNAi Therapeutics to Reduce Production of Disease-Associated Proteins in the CNS¹



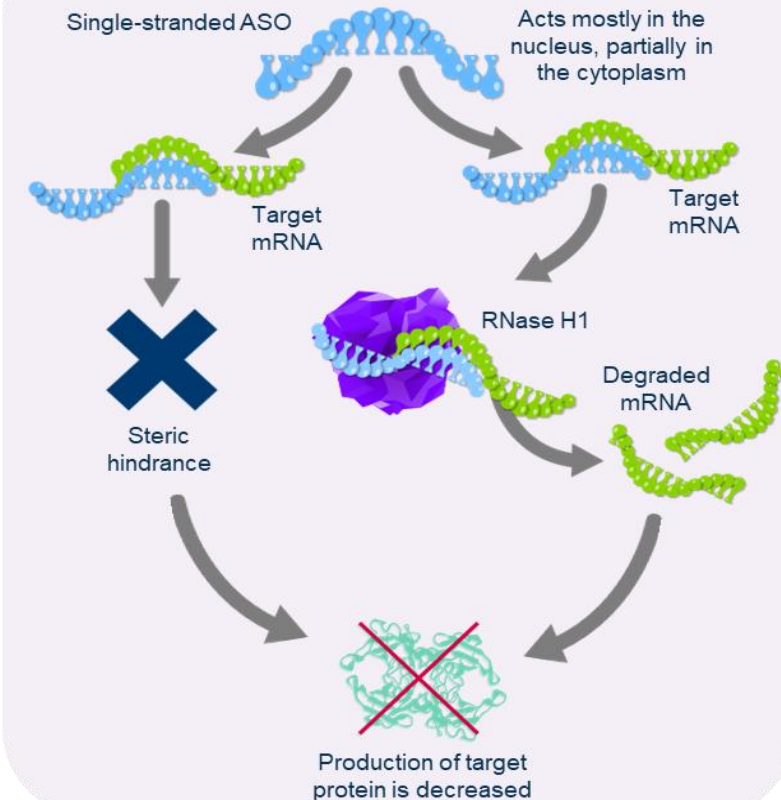
RNAi is Distinct from ASOs

RNAi¹⁻³



- RNAi has distinct chemistry and mechanism to the ASO class
- Catalytic mechanism provides potential for high potency and long duration of action, supporting infrequent administration
- Six approved products across rare and prevalent diseases
- No class-driven evidence of inflammatory effect or thrombocytopenia to date

ASO¹⁻³

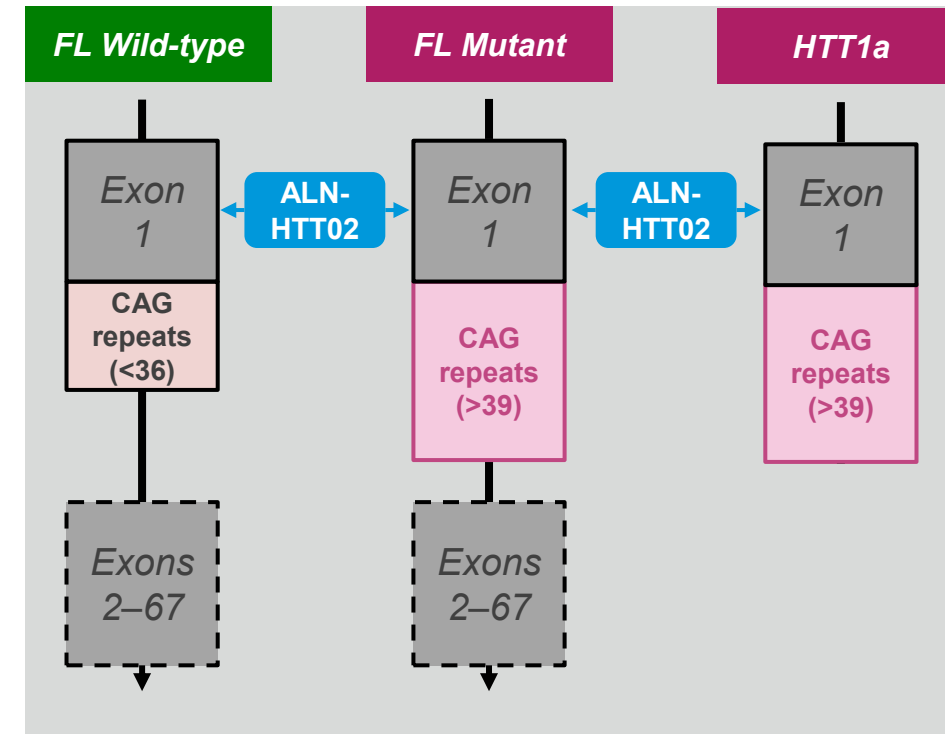


ALN-HTT02 Targets Exon 1 of HTT

Leveraging C16-siRNA Platform for CNS Delivery

- **ALN-HTT02 is an intrathecally administered investigational RNAi therapeutic for Huntington's disease (HD)**
 - ALN-HTT02 targets a conserved mRNA sequence within *HTT* exon 1
 - Designed to reduce the expression of all HTT protein species in the CNS, including HTT1a
 - No permanent changes: specific, genetic targeting that is reversible
- **ALN-HTT02 utilizes the C16-siRNA delivery platform to target the CNS**
 - This platform is being used across five ongoing clinical programs in over 250 participants, with a consistently favorable safety profile to date

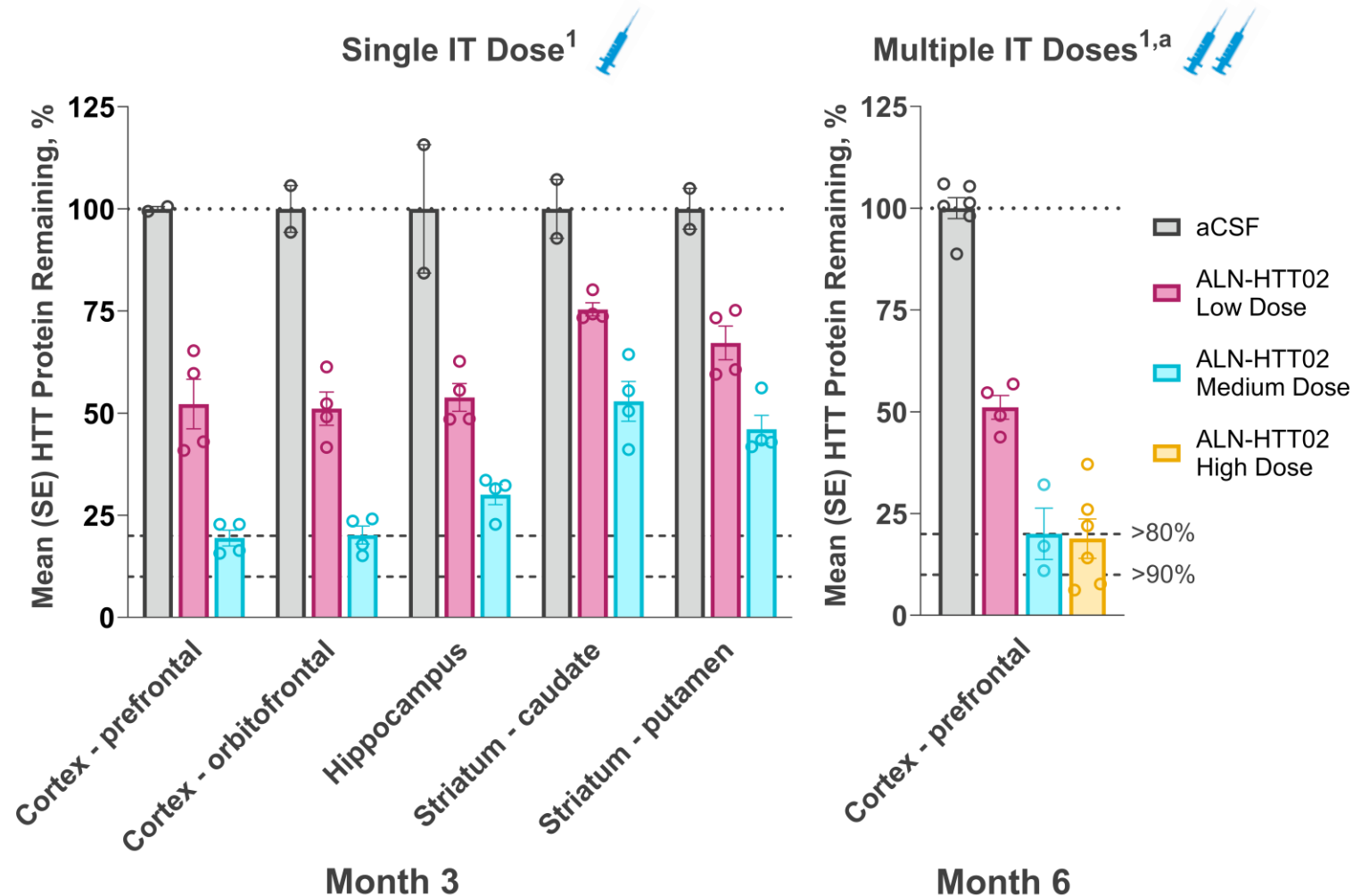
HTT Alleles in HD



ALN-HTT02 Durably Lowered HTT Throughout the Brain with an Encouraging Safety Profile in Non-Human Primates

- Across multiple NHP studies up to **12 months in duration**:^{1,2}

- No neurological abnormalities
- No changes in CSF inflammatory markers or neurofilament light chain (NfL)
- No histological changes
- No adverse findings, even after wtHTT-lowering >90%



HTT protein levels shown relative to aCSF-treated animals. ^aWell-dosed animals (ALN-HTT02 levels at >1000 ng/mL 24 h after dosing). aCSF, artificial cerebrospinal fluid; CSF, cerebrospinal fluid; HTT, huntingtin; IT, intrathecal; NfL, neurofilament light chain; NHP, non-human primate; wtHTT, wild-type HTT. 1. Sloan K *et al.* Oral Presentation at the European Huntington's Disease Network and Enroll-HD 2024 Meeting. September 12–14, 2024. Strasbourg, France (recording available online at EHDN.org). 2. Cantley W *et al.* Poster Presentation at CHDI HD Therapeutics Conference. February 23–26, 2026. Palm Springs, USA.

Phase 1b Study of ALN-HTT02 Ongoing in Adults with HD

Study Designed in Partnership with the HD Community

Phase 1b, Randomized, Double-Blind, Placebo-Controlled Trial



Study objective

- Evaluate the safety, tolerability, and PK/PD effects of single IT doses of ALN-HTT02



Key inclusion criteria

- Aged 25–70 years
- Genetically confirmed HD with >39 CAG repeats
- HD-ISS Stage 2 or early Stage 3

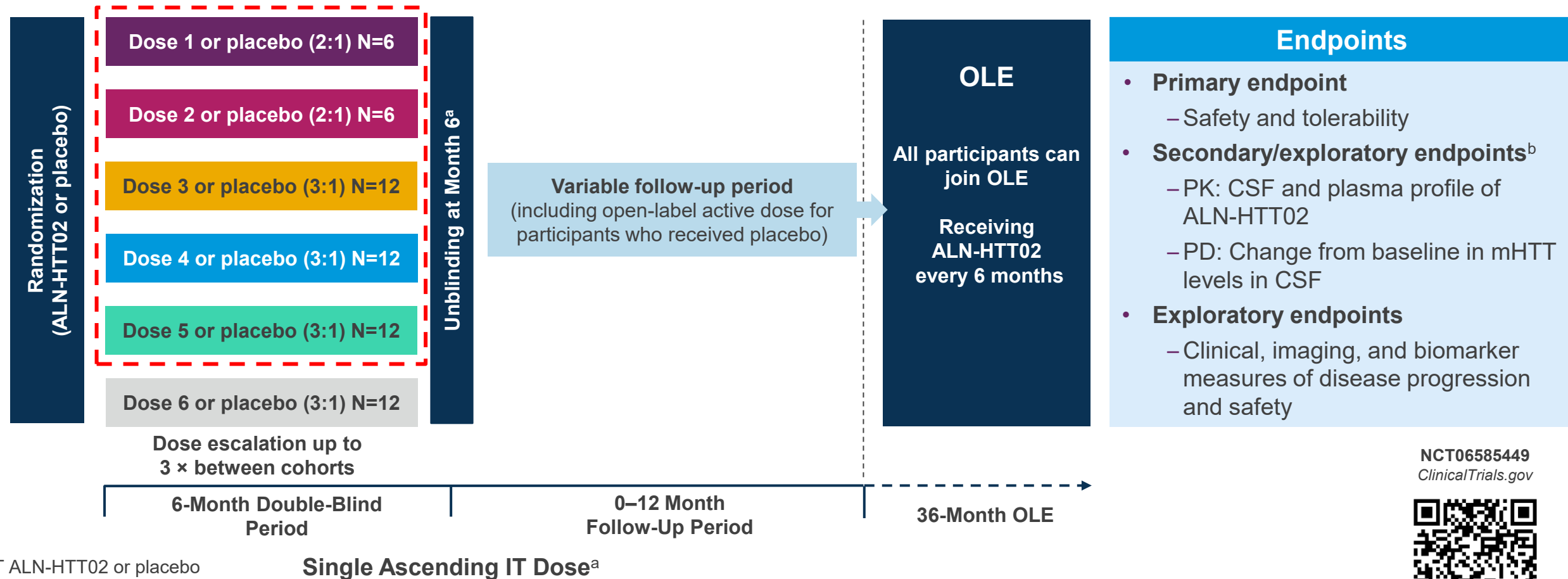
NCT06585449
ClinicalTrials.gov



Protocol reviewed and accepted by Enroll-HD CTC and endorsed by EHDN EC
Study ongoing in Canada, Germany, and the UK

Phase 1b Study of ALN-HTT02 Ongoing in Adults with HD

Study Designed in Partnership with the HD Community



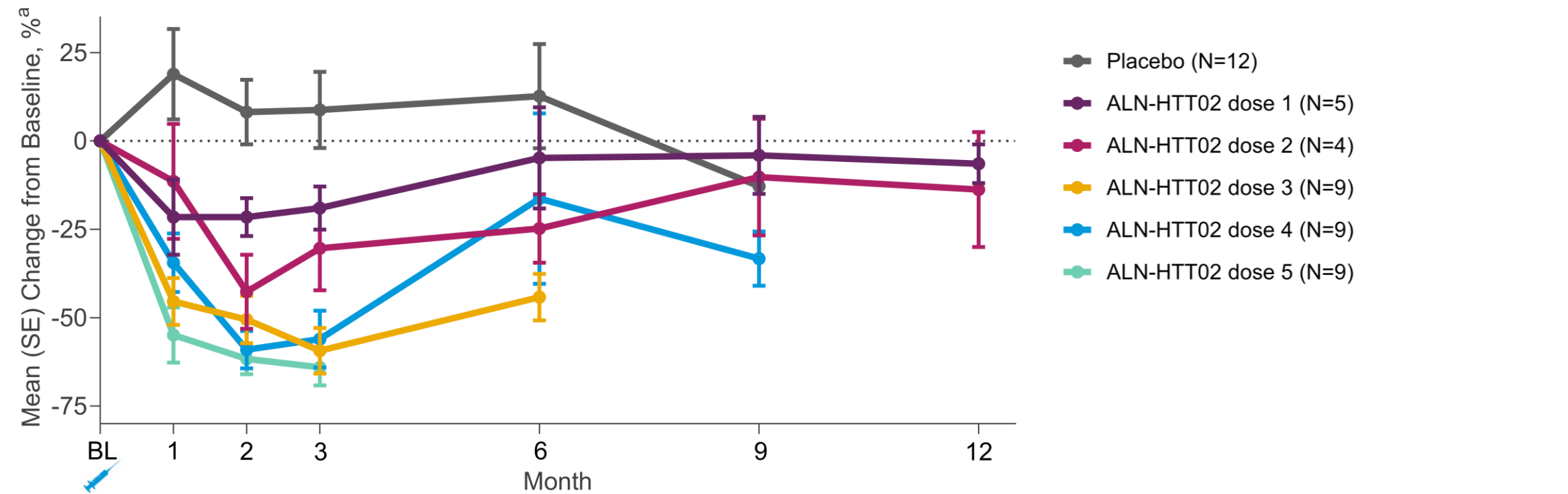
^aThe decision to proceed to the next dosing cohort is determined by the Safety Review Committee. Each cohort is unblinded after all participants in a cohort have reached Month 6. ^bPK and PD are secondary endpoints for single-ascending doses and exploratory for repeat doses. CSF, cerebrospinal fluid; CTC, Clinical Trial Committee; EC, Executive Committee; EHDN, European Huntington's Disease Network; HD, Huntington's disease; IT, intrathecal; mHTT, mutant huntingtin; OLE, open-label extension; PD, pharmacodynamic; PK, pharmacokinetic.

Baseline Patient Characteristics were Similar Across Cohorts

Demographic/Characteristic	ALN-HTT02 dose 1 or placebo (N=6)	ALN-HTT02 dose 2 or placebo (N=6)	ALN-HTT02 dose 3 or placebo (N=12)	ALN-HTT02 dose 4 or placebo (N=12)	ALN-HTT02 dose 5 or placebo (N=12)
Age, years, mean (SD)	52.2 (8.8)	54.7 (9.0)	45.4 (11.0)	51.3 (8.8)	49.9 (8.7)
Female, n (%)	1 (16.7)	2 (33.3)	8 (66.7)	5 (41.7)	6 (50.0)
White, n (%)	5 (83.3)	6 (100.0)	12 (100.0)	10 (83.3)	11 (91.7)
BMI, kg/m ² , mean (SD)	25.8 (4.4)	30.4 (4.3)	28.2 (6.2)	26.1 (4.6)	27.1 (4.9)
HD-ISS stage, n (%)					
2	1 (16.7)	4 (66.7)	7 (58.3)	4 (33.3)	6 (50.0)
3	5 (83.3)	2 (33.3)	5 (41.7)	8 (66.7)	6 (50.0)
Number of CAG repeats, mean (SD)	43.8 (1.6)	42.5 (2.0)	44.8 (4.0)	43.3 (2.1)	43.0 (1.8)
CAP100, mean (SD)	111.0 (23.0)	103.1 (4.5)	98.4 (14.0)	102.5 (8.2)	98.4 (11.8)
Total Functional Capacity, mean (SD)	12.2 (0.8)	12.0 (1.3)	12.5 (0.7)	11.8 (1.1)	12.2 (1.0)

Dose-Dependent CSF mHTT Reduction Demonstrated with SMCxPRO Assay

Up to 64% Mean Reduction at Month 3 and up to 80% Individual Reduction in CSF mHTT After a Single IT Dose of ALN-HTT02

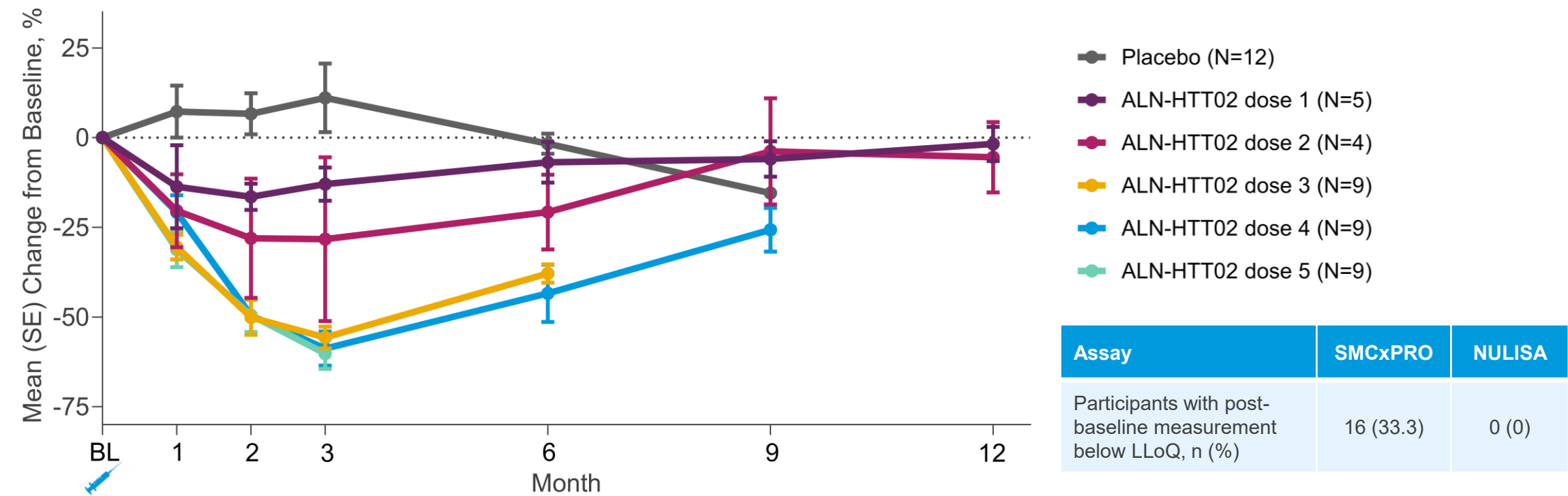


mHTT reduction	Placebo (N=12)	ALN-HTT02				
		Dose 1 (N=5)	Dose 2 (N=4)	Dose 3 (N=9)	Dose 4 (N=9)	Dose 5 (N=9)
Mean maximum observed, % (SD) ^b	2.9 (25.5)	35.6 (18.0)	45.5 (15.7)	52.9 (22.5)	65.7 (11.8)	64.8 (10.2)
Minimum individual, % ^b	-36.8	19.0	23.5	6.7	49.3	52.0
Maximum individual, % ^b	60.8	63.2	59.7	79.6	80.7	77.2

^{a,b}Post-baseline values reported as less than the LLoQ are set to LLoQ/2, which is the case for 16 participants in figure^a and 12 in table^b. LLoQ = 26.5 fM. BL, baseline; CSF, cerebrospinal fluid; IT, intrathecal; LLoQ, lower limit of quantification; mHTT, mutant huntingtin; SD, standard deviation; SE, standard error; SMC, single molecule counting immunoassay.

Dose-Dependent CSF mHTT Reduction Confirmed with Independent NULISA Assay

Up to 60% Mean Reduction at Month 3 and up to 83% Individual Reduction in CSF mHTT After a Single IT Dose of ALN-HTT02



mHTT reduction	Placebo (N=12)	ALN-HTT02				
		Dose 1 (N=5)	Dose 2 (N=4)	Dose 3 (N=9)	Dose 4 (N=9)	Dose 5 (N=9)
Mean maximum observed, % (SD) ^b	4.9 (13.2)	28.4 (15.0)	32.2 (26.2)	52.7 (16.2)	57.3 (13.5)	59.2 (12.5)
Minimum individual, % ^b	-16.4	14.1	0.9	14.9	37.0	38.1
Maximum individual, % ^b	21.1	53.7	57.2	66.8	76.6	83.0

We gratefully acknowledge the CHDI Foundation and Alamar Biosciences for establishing the NULISA assay, the Alnylam BioA team, Evotec, and Alamar Biosciences for enabling clinical sample testing. BL, baseline; LLoQ, lower limit of quantification; mHTT, mutant huntingtin; NULISA, NUcleic acid Linked Immuno-Sandwich Assay; SD, standard deviation; SE, standard error; SMC, single molecule counting immunoassay.

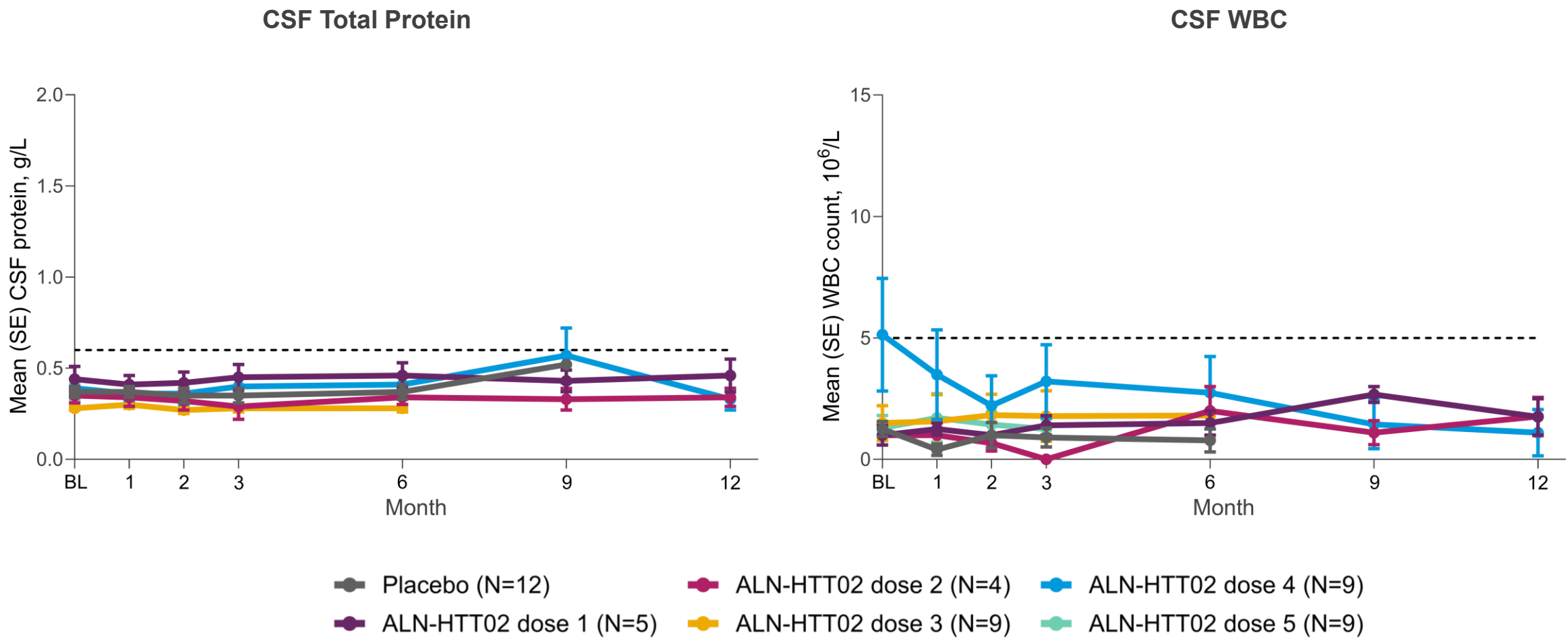
Blinded Safety Summary

Active and Placebo Participants Pooled Within Cohort Owing to Ongoing Blinded Study

Category	ALN-HTT02 dose 1 or placebo (N=6)	ALN-HTT02 dose 2 or placebo (N=6)	ALN-HTT02 dose 3 or placebo (N=12)	ALN-HTT02 dose 4 or placebo (N=12)	ALN-HTT02 dose 5 or placebo (N=12)
Duration of study drug exposure, months, mean (SD)	18.7 (2.3)	12.5 (3.7)	6.9 (0.9)	11.4 (0.3)	4.7 (0.5)
At least one AE, n (%)	6 (100.0)	6 (100.0)	10 (83.3)	11 (91.7)	12 (100.0)
At least one severe AE, n (%)	0	1 (16.7)	0	2 (16.7) ^a	0
Related to study drug	0	1 (16.7) ^b	0	0	0
Related to lumbar puncture	0	1 (16.7)	0	1 (8.3)	0
At least one serious AE, n (%)	0	0	0	4 (33.3) ^c	0
Related to study drug	0	0	0	0	0
Related to lumbar puncture	0	0	0	2 (16.7)	0
Death, n (%)	0	0	0	0	0
At least one AE of clinical interest, n (%)	1 (16.7) ^d	0	0	1 (8.3) ^e	0

Data shown for double-blind period as of September 10, 2026. ^aTwo severe AEs were reported: radius fracture and likely bacterial meningitis; both were also reported as serious AEs. ^bOne participant experienced headache; assessed as severe, non-serious; the event was resolved. ^cFour serious AEs were reported: acute myocardial infarction (resolved with sequelae), radius fracture (resolved), post-lumbar puncture syndrome (resolved), and likely bacterial meningitis (resolving). None was assessed as related to study drug. ^dOne patient had one mild event of asthenia assessed as mild, unrelated to study drug or lumbar puncture; the event was resolved. ^eOne patient had one mild event of feeling of imbalance not related to study drug or lumbar puncture; the event was resolved. AE, adverse event; SD, standard deviation.

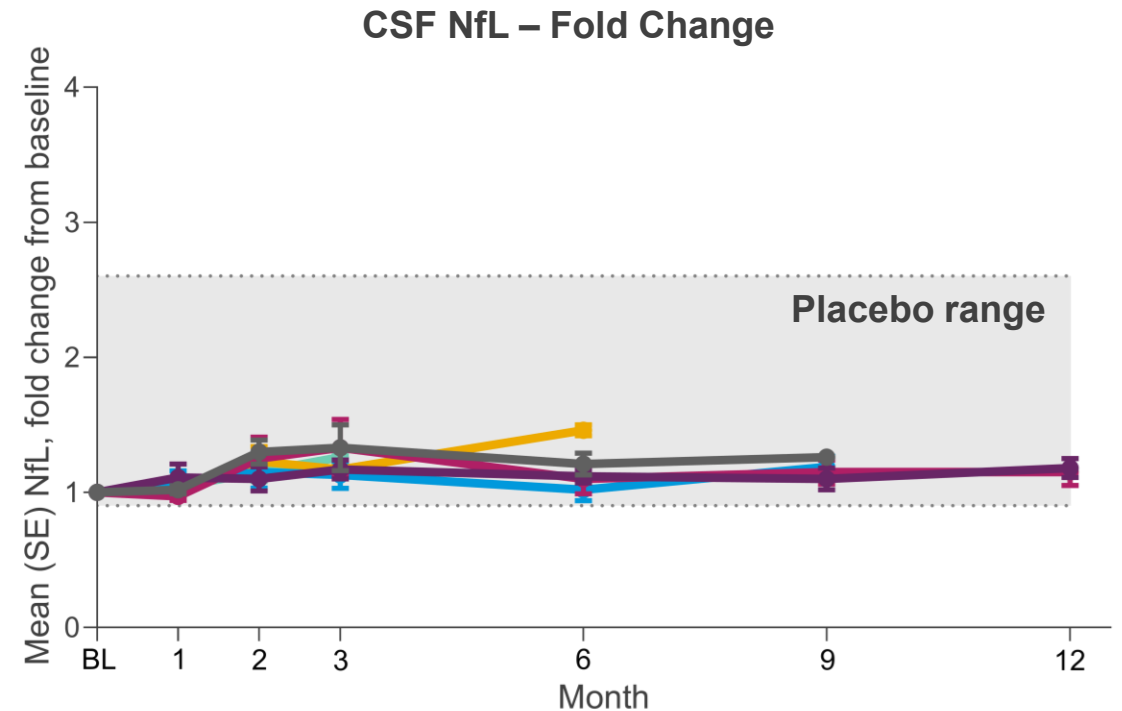
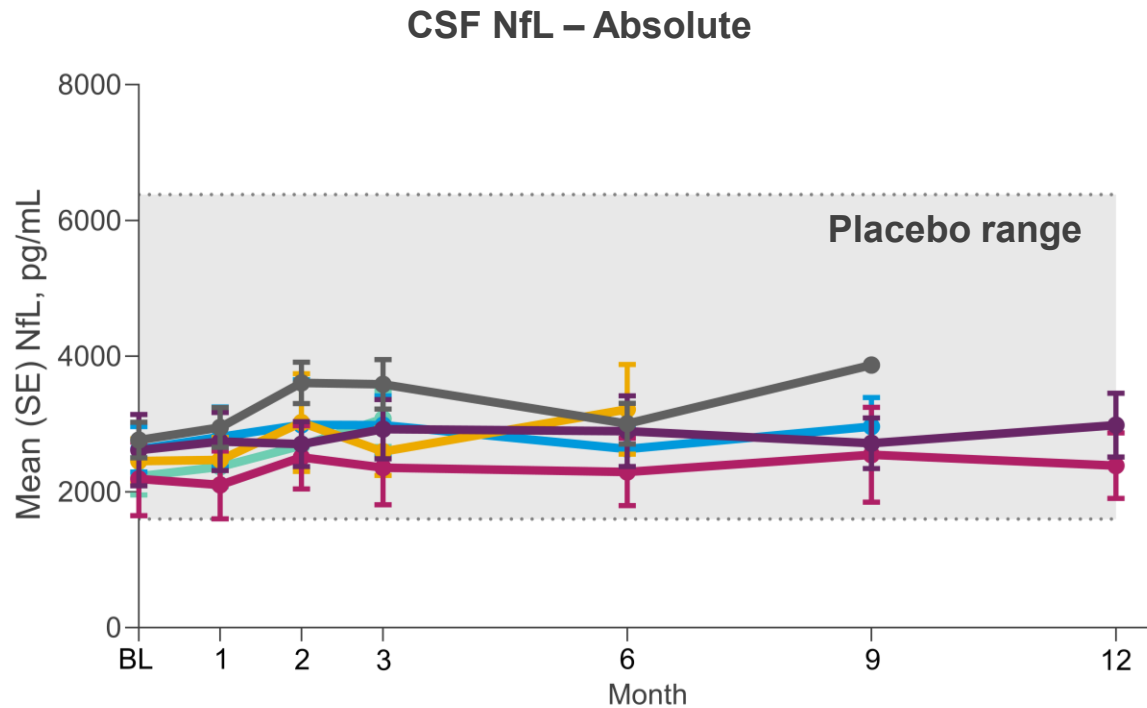
No Dose-Dependent Increases in CSF Inflammatory Markers



CSF total protein data from one participant in each of the dose 3 and dose 4 groups, and the 12-month data point from one participant in the dose 1 group, were excluded owing to suspected site input error. Dashed lines denote typical reference values. BL, baseline; CSF, cerebrospinal fluid; SE, standard error; WBC, white blood cell.

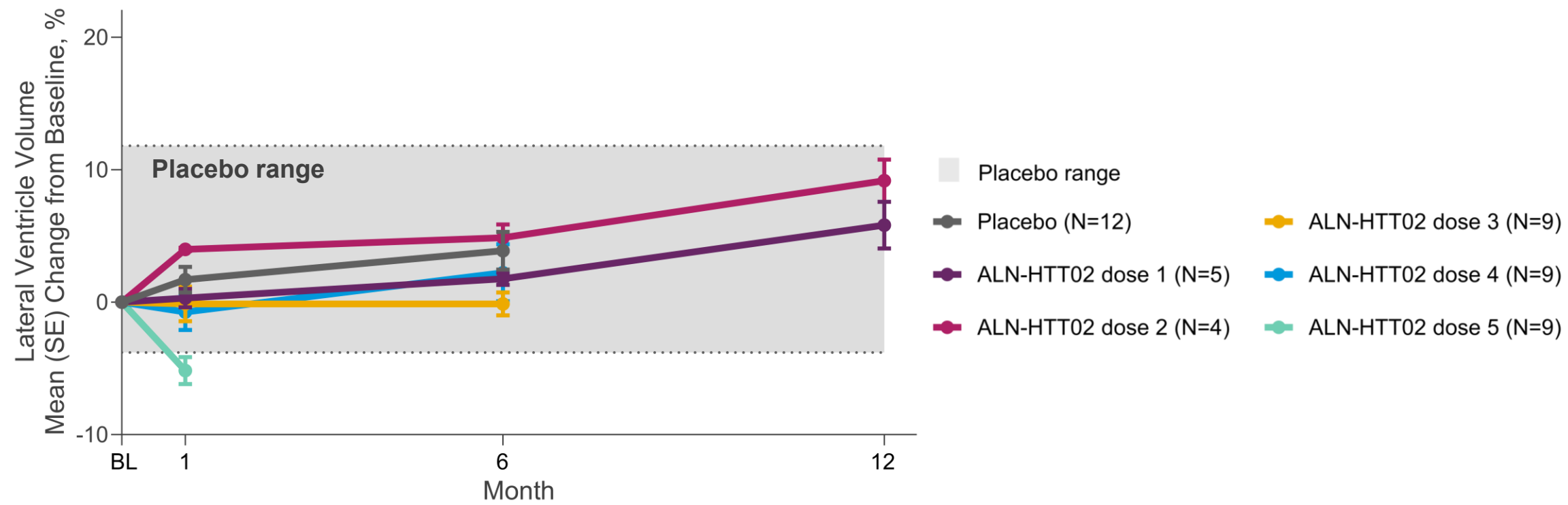
No Dose-Dependent Increases in CSF NfL

NfL is a Biomarker of Neuroaxonal Injury



No Dose-Dependent Increases in Ventricle Size

No Increases Beyond Placebo Range Despite Robust mHTT-Lowering



NULISA assay	Placebo (N=12)	ALN-HTT02 dose1 (N=5)	ALN-HTT02 dose 2 (N=4)	ALN-HTT02 dose 3 (N=9)	ALN-HTT02 dose 4 (N=9)	ALN-HTT02 dose 5 (N=9)
Mean maximum observed mHTT reduction, % (SD)	4.9 (13.2)	28.4 (15.0)	32.2 (26.2)	52.7 (16.2)	57.3 (13.5)	59.2 (12.5)

Shaded placebo range indicates maximum and minimum observed individual placebo values. BL, baseline; mHTT, mutant huntingtin; NULISA, NUCleic acid Linked Immuno-Sandwich Assay; SD, standard deviation; SE, standard error.



ALN-HTT02-001 Phase 1b Interim Results Summary

- **ALN-HTT02 is an investigational RNAi therapeutic utilizing the C16-siRNA platform, in development for treatment of HD**
 - ALN-HTT02 is designed to lower all forms of HTT protein in the CNS, including HTT1a
 - Robust, dose-dependent HTT-lowering with an encouraging safety profile in both NHP and adults with HD
 - To date, no evidence of CNS inflammation, NfL increases or ventricular enlargement with ALN-HTT02
- **Participants from this Phase 1b study are able to join the open-label extension, receiving ALN-HTT02 every 6 months**
 - Will further assess safety profile and potential efficacy trends of long-term HTT-lowering via RNAi
- **ALN-HTT02 will advance into a larger placebo-controlled study to assess its potential to slow HD progression in adults with HD**
 - Planned initiation in 2027; details will be forthcoming
 - Moving forward, ALN-HTT02 will use the name **brezosiran**

Thank you to the participants, their families, investigators, and study staff for supporting the ALN-HTT02-001 study

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

Thank you for the opportunity to share our work today



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