

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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Conclusions

- **ALN-HTT02 is an investigational RNA interference (RNAi) therapeutic for Huntington’s disease (HD) designed to lower all forms of huntingtin (HTT) protein, including HTT1a, in the central nervous system (CNS).**
- **ALN-HTT02 provides robust, dose-dependent lowering of mutant huntingtin (mHTT) and has an encouraging safety profile in adults with HD, with no evidence of CNS inflammation, neurofilament light chain (NfL) increases, or ventricular enlargement.**
- **Phase 1b study participants are able to join the open-label extension, receiving ALN-HTT02 every 6 months, which will allow further characterization of the 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; initiation is planned for 2027.**
- **ALN-HTT02 will henceforth use the name brezosiran.**

Background

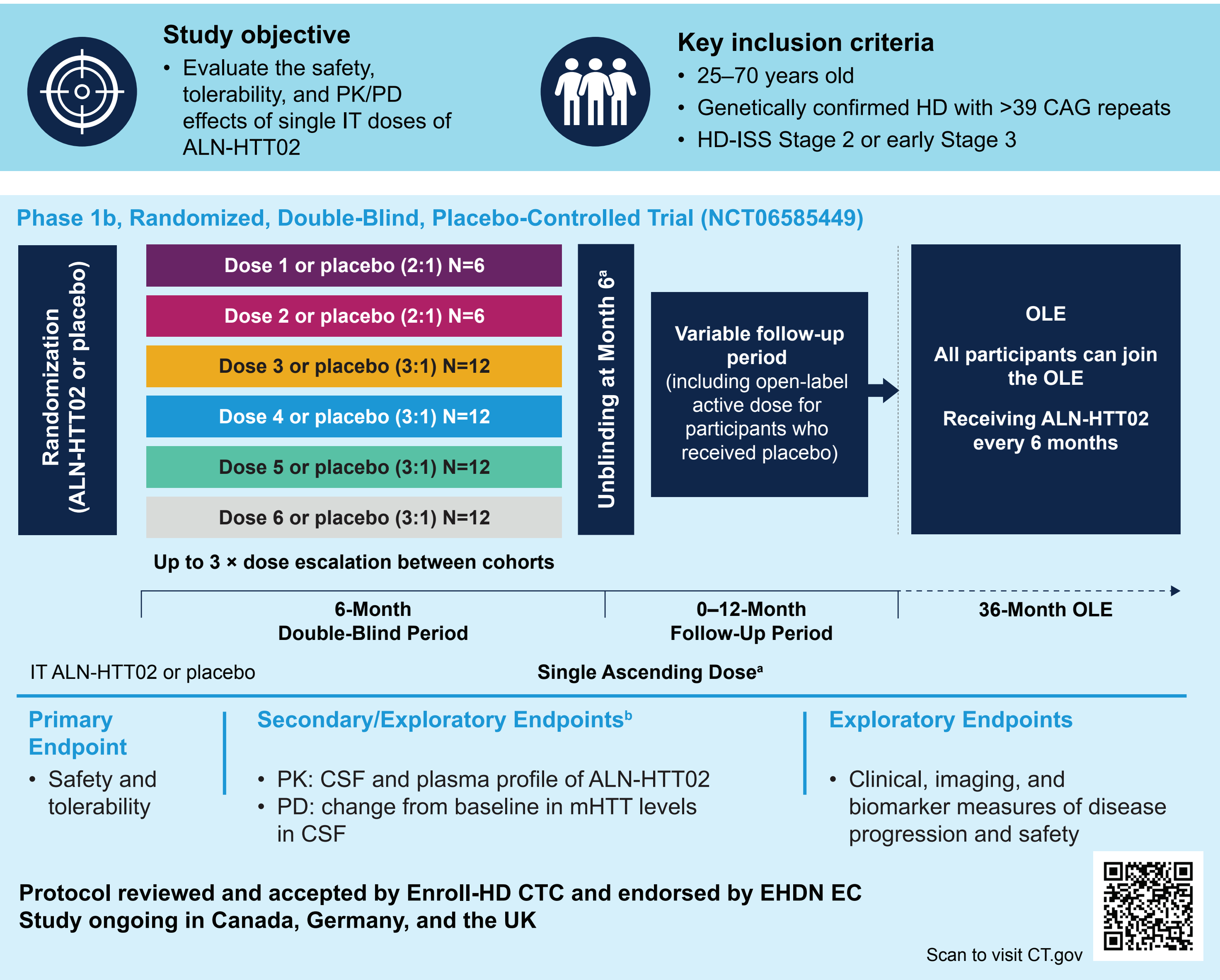
HTT1a Isoform: A Therapeutic Target in HD

- ALN-HTT02 is an intrathecally administered investigational RNAi therapeutic for HD that utilizes the C16-small interfering RNA (siRNA) delivery platform to target the CNS.
- Full-length mutant HTT and the shorter exon 1 splice isoform HTT1a both likely contribute to HD pathology.¹
- In mouse models of HD, HTT-lowering approaches that include HTT1a are more effective at preventing protein aggregation and transcriptional dysregulation versus those only targeting full-length-HTT.^{2,3}
- ALN-HTT02 targets a conserved sequence in exon 1 to lower all forms of HTT.

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Methods



^aThe decision to proceed to the next dosing cohort is determined by the Safety Review Committee. Each cohort is unblinded after all patients 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; EHDN EC, European Huntington’s Disease Network Executive Committee; HD, Huntington’s disease; HD-ISS, Huntington’s Disease Integrated Staging System; IT, intrathecal; mHTT, mutant huntingtin; OLE, open-label extension; PD, pharmacodynamic; PK, pharmacokinetic.

Results (Interim Data Available from Cohorts 1–5)

Table 1. Baseline Patient and Disease Characteristics

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 score, mean (SD)	12.2 (0.8)	12.0 (1.3)	12.5 (0.7)	11.8 (1.1)	12.2 (1.0)

Data for dose 6 cohort are not yet available.
BMI, body mass index; CAP100, CAG Age Product 100 score; HD-ISS, Huntington’s Disease Integrated Staging System; SD, standard deviation.

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ACKNOWLEDGMENTS

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

FUNDING

This study is funded by Alnylam Pharmaceuticals.

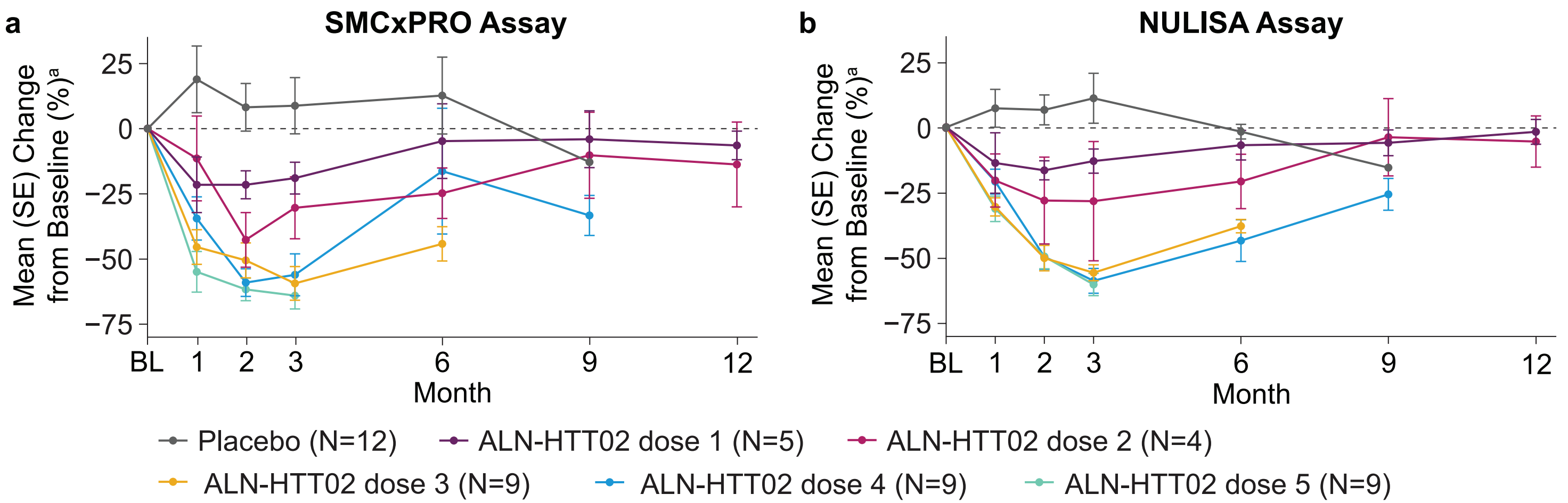
DISCLOSURES

ST, EJW, BL, and MG have received consultancy fees from Alnylam Pharmaceuticals. CS has received consultancy fees and travel grants from Alnylam Pharmaceuticals as well as speaker honoraria for activities with Alnylam Pharmaceuticals. AS, RG, SR, ML, and KS are employees and shareholders in Alnylam Pharmaceuticals.

Summary of Results

- Participant cohorts were well matched for demographics and disease characteristics (**Table 1**).
- Robust, dose-dependent mHTT-lowering was confirmed with two independent assays (**Figure 1**).
- Mean CSF mHTT reductions of up to 60–64% at month 3 and up to 80–83% individual max were observed using SMC and NULISA assays.
- The improved dynamic range of the NULISA assay helps quantify mHTT-lowering across all participants.
- ALN-HTT02 has shown a favorable safety profile to date (**Table 2**).
- No dose-dependent changes were observed in markers of neuroinflammation, neuroaxonal injury, or brain atrophy (**Figure 2**).

Figure 1. Change in CSF mHTT, Shown by (a) SMCxPRO and (b) NULISA Assays



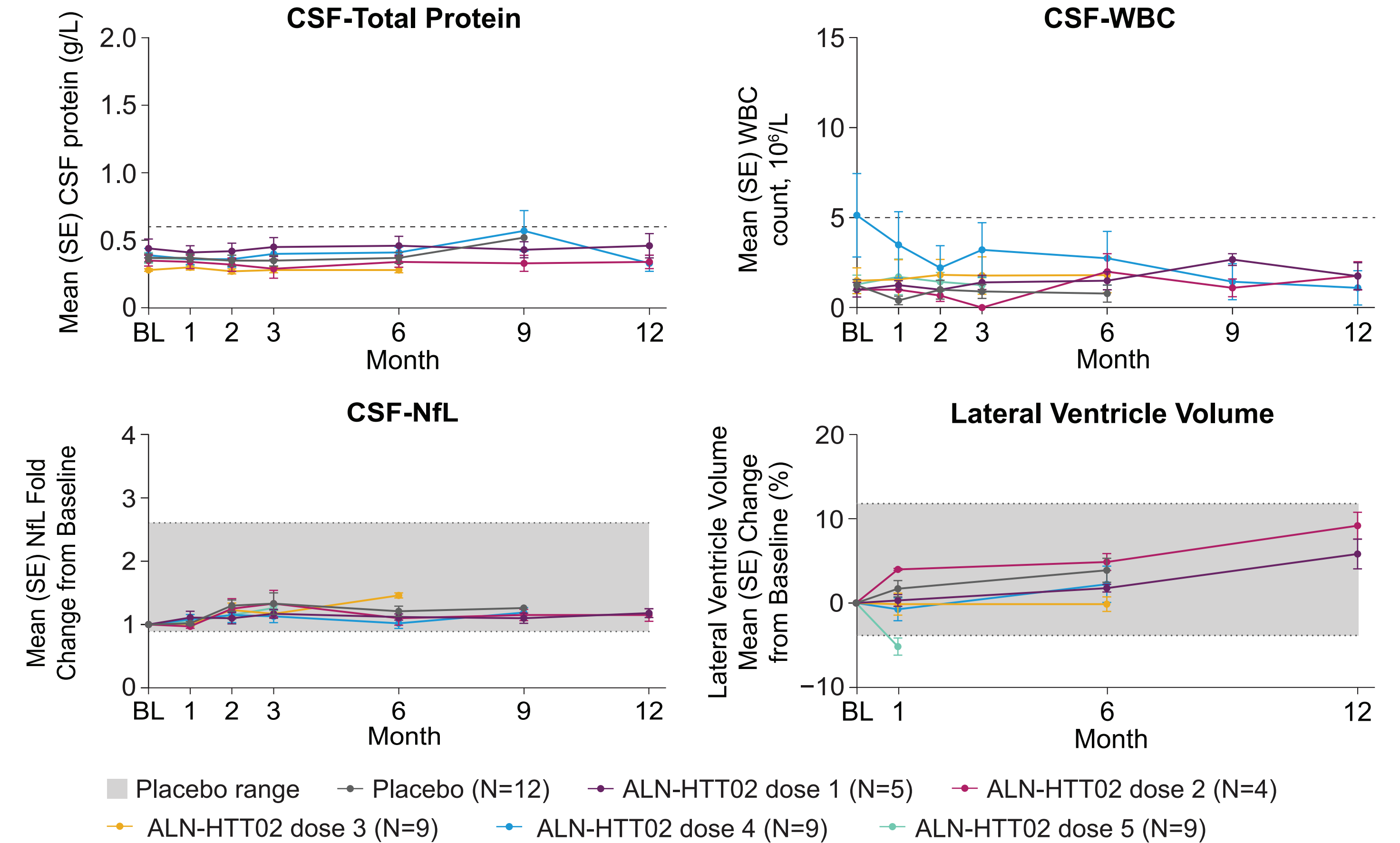
^aPost-baseline values reported as less than the LLoQ are set to LLoQ/2, which was the case for 16 and 0 participants, respectively, for the SMCxPRO and NULISA assays.
BL, baseline; CSF, cerebrospinal fluid; LLoQ, lower limit of quantification; mHTT, mutant huntingtin; NULISA, Nucleic acid Linked Immuno-Sandwich Assay; SE, standard error; SMC, single molecule counting immunoassay.

Table 2. Summary of AEs

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)
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 AECl, 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 participant experienced asthenia, assessed as mild, unrelated to study drug or lumbar puncture; the event was resolved. ^eOne participant experienced feeling of imbalance, assessed as mild, unrelated to study drug or lumbar puncture; the event was not resolved.
AE, adverse event; AECl, adverse event of clinical interest; SD, standard deviation.

Figure 2. CSF Biomarkers of Neuroinflammation and Neuroaxonal Injury, and Ventricular Volume



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 due to suspected site input error. Dashed lines on upper panels denote typical reference values. Shaded placebo range indicates maximum and minimum observed individual placebo values.
BL, baseline; CSF, cerebrospinal fluid; NfL, neurofilament light chain; SE, standard error; WBC, white blood cell.

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 advice and program support



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