ALN-5288, an Investigational RNA Interference Therapeutic Targeting *MAPT* in Phase 1 Development for Alzheimer's Disease

Kevin Sloan[1]; Matthew Whittaker[1]; Jeffrey Kurz[1]; Shelley Patrick[1]; Jon Farley[1]; Rosalind Chuang[1]; Julia Shirvan[1]; Joe Dybowski[1]; Kirk Brown[1]; on behalf of the ALN-5288 program team

[1]Alnylam Pharmaceuticals, Cambridge, MA, USA

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Takeaways

- The hexadecyl (C16)-small interfering RNA (siRNA) platform offers a new approach for microtubule-associated protein tau (*MAPT*)-lowering in the central nervous system (CNS).
- Tau-lowering may represent a potential therapeutic strategy for Alzheimer's disease (AD) and other tauopathies.
- ALN-5288 is an investigational therapeutic designed to durably lower *MAPT*.
- *MAPT*-lowering in the CNS in nonhuman primates (NHPs) after intrathecal (IT) dosing with ALN-5288 led to deep and sustained lowering of tau protein and an encouraging safety and tolerability profile following broad distribution across the brain.
- Phase 1b, randomized, placebo-controlled study of ALN-5288 is ongoing in patients with AD (NCT07214727).

Background

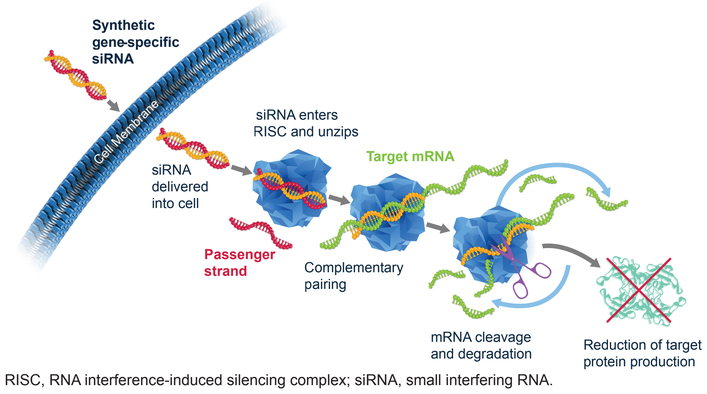
- AD is a progressive, life-limiting neurodegenerative disorder associated with a decline in cognitive function.[1]
- *MAPT* mRNA encodes the protein tau, which forms toxic aggregates in AD and other tauopathies.[1]
- Tau reduction represents a potential strategy to slow or prevent progression of AD.
- We describe nonclinical data for ALN-5288 in NHPs, and introduce the design of an ongoing Phase 1 clinical study of ALN-5288 in patients with AD.

MAPT-Lowering Strategies May be Effective in Alzheimer's Disease and Other Tauopathies

- Tau accumulation as neurofibrillary tangles as well as amyloid plaques are hallmarks of AD and are associated with the severity and progression of patient cognitive decline.[1]
- Patients with genetic predispositions to AD and significant amyloid accumulation, but low tau burden, show delayed cognitive impairment, highlighting tau as a potential therapeutic target.[2,3]
- Clinical studies in AD using monoclonal antibodies and O-GlcNAcase inhibitors to clear or stabilize extracellular tau, respectively, have reported limited efficacy in reducing tau accumulation or clinical decline.[4–6]
- Genetic targeting approaches using tau-lowering siRNAs and antisense oligonucleotides (ASOs) to modulate both intracellular and extracellular tau have been reported to facilitate clearance of existing tau deposits in preclinical and clinical studies, suggesting potential for pre- and post-symptomatic treatment applications.[7–9]

ALN-5288 Targets *MAPT* mRNA to Reduce Tau Protein

Overview of the RNA Interference Mechanism of Action to Reduce Target Protein Production

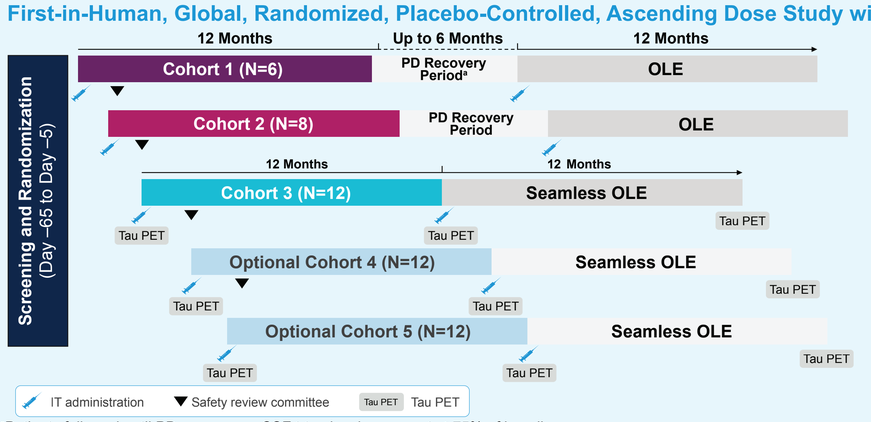


RISC, RNA interference-induced silencing complex; siRNA, small interfering RNA.

- RNA interference (RNAi) is a natural biological process that regulates gene expression.[10]
- Synthetic siRNAs are designed to specifically degrade mRNA encoding a disease-associated protein.[10]
- Catalytic mechanism enables a single siRNA molecule to target multiple *MAPT* mRNA transcripts.[10,11]
- RNAi therapeutics are a unique class of genetic medicine that is distinct from ASOs.[10]
- Approved RNAi therapeutics have demonstrated potent and durable efficacy, supporting infrequent dosing regimens, with acceptable safety profiles.[12,13]
- ALN-5288 is an intrathecally administered, C16-conjugated RNAi therapeutic developed to lower tau protein expression in the CNS by targeting *MAPT* mRNA.

Phase 1b Study of ALN-5288 in Patients with Alzheimer's Disease (NCT07214727)

First-in-Human, Global, Randomized, Placebo-Controlled, Ascending Dose Study with Open-Label Extension



[a]Patients followed until PD recovery or CSF t-tau levels recover to ≥75% of baseline.
AD, Alzheimer's disease; AE, adverse event; AUC, area under the curve; CDR, Clinical Dementia Rating scale; C_{max}, maximum observed concentration; CSF, cerebrospinal fluid; f_e, fraction of dose excreted unchanged into urine; IT, intrathecal; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; OLE, open-label extension; PD, pharmacodynamic; PET, positron emission tomography; PK, pharmacokinetic; Q4, fourth quarter of the year; t-tau, total tau.

Objective

- Evaluate the safety, tolerability, PD, and PK of IT administered ALN-5288 in patients with AD

Study Population

- Aged 40–80 years
- CSF- or PET-confirmed AD
- MCI or dementia due to probable AD
  - Confirmed by CDR Global score 0.5–1.0 and CDR Memory Box score ≥0.5
- MMSE score of 20–30

Primary Endpoint

- Incidence and severity of AEs

Secondary Endpoints

- PD: Change from baseline in total tau protein CSF concentration
- PK: Plasma and CSF concentration of ALN-5288
- PK: AUC, C_{max} and f_e of ALN-5288 in plasma, urine, and CSF

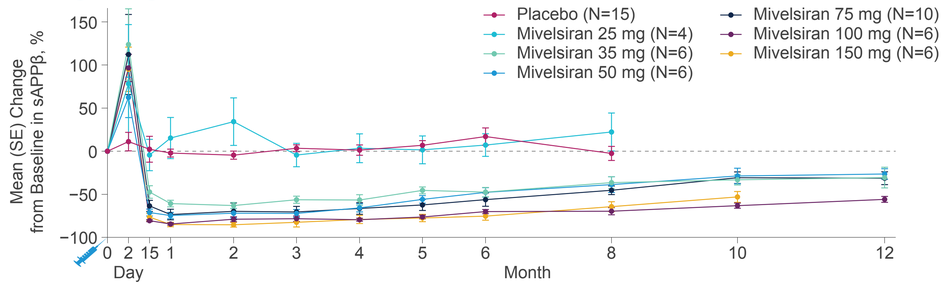
Enrollment

- Study initiating in Canada, Netherlands, Spain and UK; initial participants received study drug Q4 2025
- Interested investigators and referring physicians may contact clinicaltrials@alnylam.com

Scan to visit ClinicalTrials.gov

Successful Human Translation of the C16-siRNA Platform in the CNS[14]

Durability of C16-siRNA Platform Highlighted by Change in sAPPβ Over 12 Months Following a Single Dose of Mivelsiran

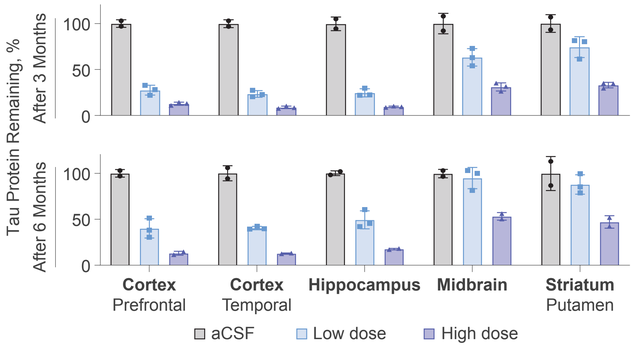


sAPP, soluble amyloid-beta precursor protein; SE, standard error. Data previously presented at AAIC.[14]

- Mivelsiran is a C16-conjugated siRNA designed to treat patients with AD by targeting *amyloid-beta precursor protein* (*APP*) mRNA to reduce APP protein production.
- In a Phase 1 study, single mivelsiran doses led to robust and sustained lowering of soluble APPβ in the CSF through Month 12 versus placebo.
- The majority of adverse events were mild or moderate and nonserious.
- CSF safety biomarkers, routine laboratory assessments, and exploratory neurofilament light data showed no abnormalities of concern.
- Tau-targeting with ALN-5288 represents an alternative strategy for potential treatment of patients with AD using the C16-siRNA platform.

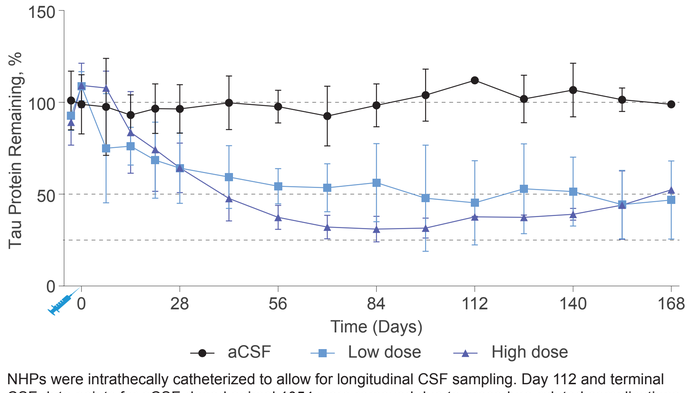
ALN-5288 Demonstrates Broad Distribution, Durable Tau-Lowering, and a Favorable Safety Profile in NHPs[15]

Change in Brain Tau Protein at 3- and 6-Months Following a Single IT Dose of ALN-5288



Brain tissue sectioned into 4 mm coronal slabs, dissected to isolate subregions, and flash frozen for PK/PD analyses. Tau protein in tissue analyzed by SIMOA method.
aCSF, artificial cerebrospinal fluid; IT, intrathecal; PK/PD, pharmacokinetic/pharmacodynamic; SIMOA, Single Molecular Array.

Change in Tau Protein in CSF Over 6-Months Following a Single IT Dose of ALN-5288



NHPs were intrathecally catheterized to allow for longitudinal CSF sampling. Day 112 and terminal CSF data points for aCSF-dosed animal 1054 were removed due to procedure-related complications in collection and subsequent sample contamination.
aCSF, artificial cerebrospinal fluid; CSF, cerebrospinal fluid; IT, intrathecal; NHP, nonhuman primate.

- Treatment of NHPs with a single IT dose of ALN-5288 led to dose-dependent reductions of tau protein up to 90% in AD-relevant brain regions (cortex, hippocampus).
- Durable tau-lowering was observed in CSF over 6 months.
- Following multiple IT doses of ALN-5288, no in-life neurological abnormalities, adverse changes in CSF parameters, or adverse microscopic findings were reported through 6 months, including after >90% reduction of tau protein in the cortex.

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