Interim Phase 1 Part A Results for ALN-APP, the First Investigational RNAi Therapeutic in Development for Alzheimer's Disease

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ALN-APP is an investigational drug being studied for the treatment of AD and CAA. ALN-APP is not approved by any health authority, and the safety and efficacy of ALN-APP has not been established.

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

Disclosures for Sharon Cohen

All fees paid to Institution (no personal conflict of interest)	Entities
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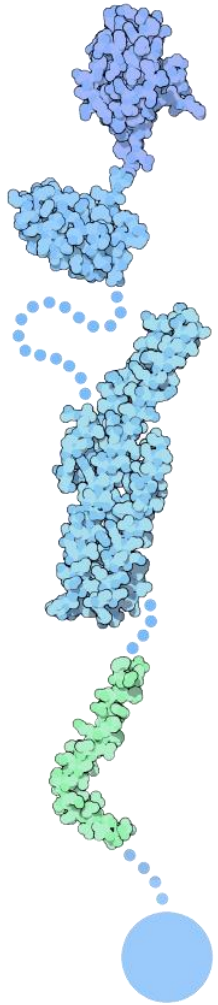
Introduction

Amyloid Precursor Protein (APP) is a Genetically Validated Target for Alzheimer's Disease (AD)

- APP is a membrane-associated protein, which is processed via serial cleavage to produce a variety of peptides, including amyloid beta (Aβ)[1]
  - Aβ deposits in the brain are a pathological hallmark of AD[1] and cerebral amyloid angiopathy (CAA)[2]

- Genetic alterations that modify APP expression and proteolysis cause early-onset Alzheimer's disease (EOAD)[3]
  - APP locus duplications and trisomy 21 (Down syndrome) result in quantitative increases in APP expression and lead to EOAD
  - Variants in *APP*, *presenilin 1* (*PSEN1*), and *presenilin 2* (*PSEN2*) alter APP proteolysis and can lead to autosomal-dominant Alzheimer's disease (ADAD)
  - *APP* A673T variants reduce Aβ production and lower Aβ levels, protecting against AD[4,5]



Aβ, amyloid beta; AD, Alzheimer's disease; ADAD, autosomal-dominant Alzheimer's disease; APP, amyloid precursor protein; CAA, cerebral amyloid angiopathy; EOAD, early-onset Alzheimer's disease; *PSEN1*, presenilin; *PSEN2*, presenilin 2.

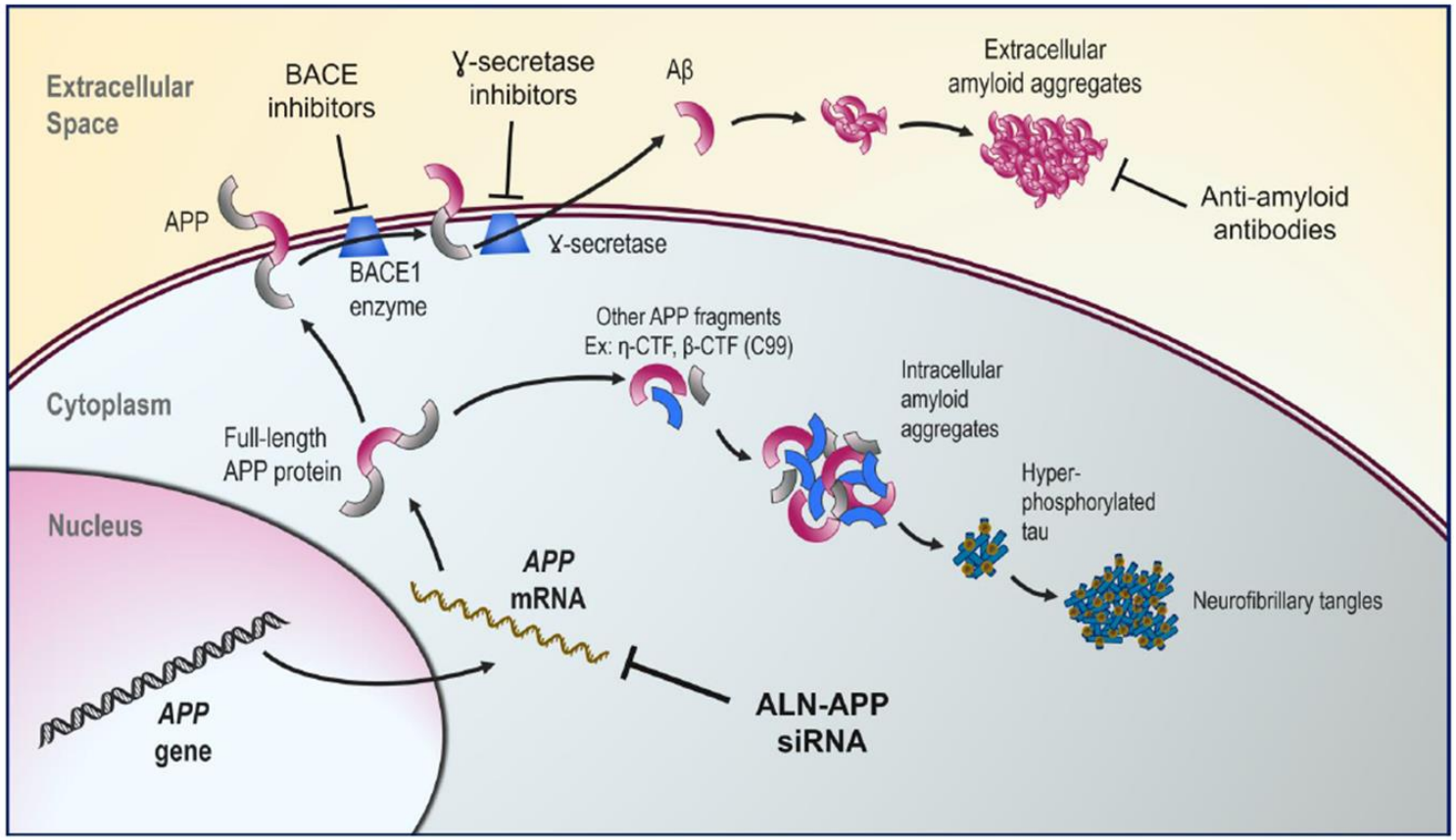
Image: APP Protein Structure courtesy of David S. Goodsell and the RCSB Protein Data Bank.

1. O'Brien RJ, Wong PC. Annu Rev Neurosci. 2011; 34: 185–204. 2. Biffi A, Greenberg SM. J Clin Neurol. 2011; 7: 1–9. 3. Tcw J, Goate AM. Cold Spring Harb Perspect Med. 2017; 7: a024539. 4. Jonsson T, Atwal JK, Steinberg S et al. Nature. 2012: 488; 96–99. 5. Martiskainen H, Herukka SK, Stančáková A et al. Ann Neurol. 2017: 8; 128–132.

ALN-APP, an Investigational RNAi Therapeutic for Patients with AD

Therapeutic Hypothesis

- ALN-APP is an intrathecally (IT) administered, investigational RNAi therapeutic in development for the treatment of AD and CAA
- siRNA is conjugated to 2′-O-hexadecyl (C16) to enhance cellular uptake in the CNS
  - Incorporated into the RISC that binds and cleaves *APP* mRNA
- ALN-APP reduces production of APP, which is the source of all downstream Aβ protein species, including Aβ40 and Aβ42
  - Reduces substrate for brain amyloid deposition and may enable natural clearance
  - Reduces intracellular Aβ and may reduce neuronal dysfunction



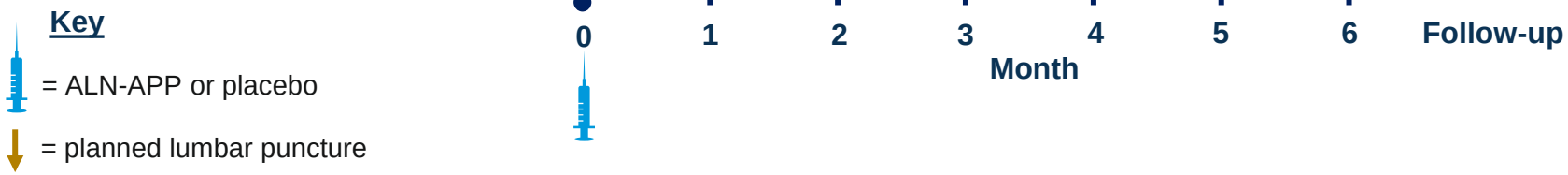
Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid precursor protein; BACE, beta-secretase; CAA, cerebral amyloid angiopathy; CNS, central nervous system; CTF, c-terminal fragment; IT, intrathecally; mRNA, messenger ribonucleic acid; RISC, ribonucleic acid-induced silencing complex; RNAi, RNA interference; siRNA, small interfering ribonucleic acid.

ALN-APP-001 Study Design

Part A, Randomized, Placebo-Controlled, Single-Ascending Dose Study

Patient Population

- Symptom onset <65 years (i.e., EOAD)
- Clinical diagnosis of MCI or mild dementia due to AD
- AD diagnosis confirmed by CSF biomarkers or Aβ-PET
- Clinical Dementia Rating® global score of 0.5 or 1.0
- Mini-Mental State Examination (MMSE) score >20



Primary Endpoint

- Safety and tolerability

Secondary Endpoints

- Change from baseline in CSF sAPPα and sAPPβ
- PK profile in CSF, plasma

- Additional cohorts are being studied in Part A
- Initiation of Part B, multi-dose open-label study imminent

Aβ, amyloid beta; AD, Alzheimer's disease; CSF, cerebrospinal fluid; EOAD, early-onset Alzheimer's disease; IT, intrathecally; MCI, mild cognitive impairment; PET, positron emission tomography; PK, pharmacokinetic; sAPP, soluble amyloid precursor protein.

Demographic and Baseline Disease Characteristics

Pooled Data for Cohorts 1–3[a]

Baseline Characteristics	All Patients (N=20)
Age, years, mean (range)	61.3 (53–73)
Male, n (%)	12 (60.0)
Race, n (%)	
White	15 (75.0)
Asian	3 (15.0)
Black/African American	1 (5.0)
CDR® global score, n (%)	
0.5	16 (80.0)
1.0	4 (20.0)
MMSE score, mean (SD)	23.6 (2.4)
BMI, kg/m^2, mean (SD)	25.9 (3.5)
Duration in study, months, mean (SD)	
Cohort 1 (ALN-APP 25mg or Placebo, n=6)	8.2 (2.0)
Cohort 2 (ALN-APP 75mg or Placebo, n=6)	7.1 (1.2)
Cohort 3 (ALN-APP 50mg or Placebo, n=8)	4.2 (0.6)

BMI, body mass index; CDR, clinical dementia rating; MMSE, Mini Mental State Examination; SD, standard deviation.

[a]Data shown as of June 29, 2023.

ALN-APP-001 Blinded Safety Summary

Pooled Adverse Event (AE) Summary for Cohorts 1–3[a]

n (%)	ALN-APP 25mg or PBO (N=6, PY=4.1)	ALN-APP 50mg or PBO (N=8, PY=2.8)	ALN-APP 75mg or PBO (N=6, PY=3.6)
At least one mild AE	5 (83.3)	6 (75.0)	4 (66.7)
At least one moderate AE	4 (66.7)	4 (50.0)	3 (50.0)
At least one serious AE	0	0	0
Death	0	0	0
At least one AE related to LP	4 (66.7)	6 (75.0)	2 (33.3)

- All AEs were mild or moderate in severity
- No deaths, SUSARs, or treatment or study discontinuations occurred
- One individual in the 50mg or PBO cohort had two mild AEs that were deemed drug-related by the investigator and included post-LP headache and post-LP nausea, both of which resolved on the same day

AE, adverse event; LP, lumbar puncture; PBO, placebo; PY, patient years; SUSAR, suspected unexpected serious adverse reaction.

[a]Data shown as of June 29, 2023.

ALN-APP-001 Blinded Safety Summary

Pooled Adverse Events (AEs) by Preferred Term for Cohorts 1–3[a]

n (%) of events occurring in ≥2 study patients	ALN-APP 25mg or PBO (N=6, PY=4.1)	ALN-APP 50mg or PBO (N=8, PY=2.8)	ALN-APP 75mg or PBO (N=6, PY=3.6)
At least one adverse event	6 (100.0)	7 (87.5)	5 (83.3)
Post lumbar puncture syndrome	3 (50.0)	5 (62.5)	0
Back pain	2 (33.3)	1 (12.5)	1 (16.7)
Presyncope	0	1 (12.5)	2 (33.3)
Syncope	2 (33.3)	0	1 (16.7)
Headache	0	1 (12.5)	1 (16.7)
Nasopharyngitis	0	0	2 (33.3)
Vomiting	2 (33.3)	0	0

- Many AEs reported to date have been deemed related to LP by the investigator
  - These included post LP syndrome (40% of patients), back pain (15%), vomiting (10%), injection site swelling (5%), neck pain (5%), presyncope (5%), procedural nausea (5%), puncture site pain, (5%) and syncope (5%)

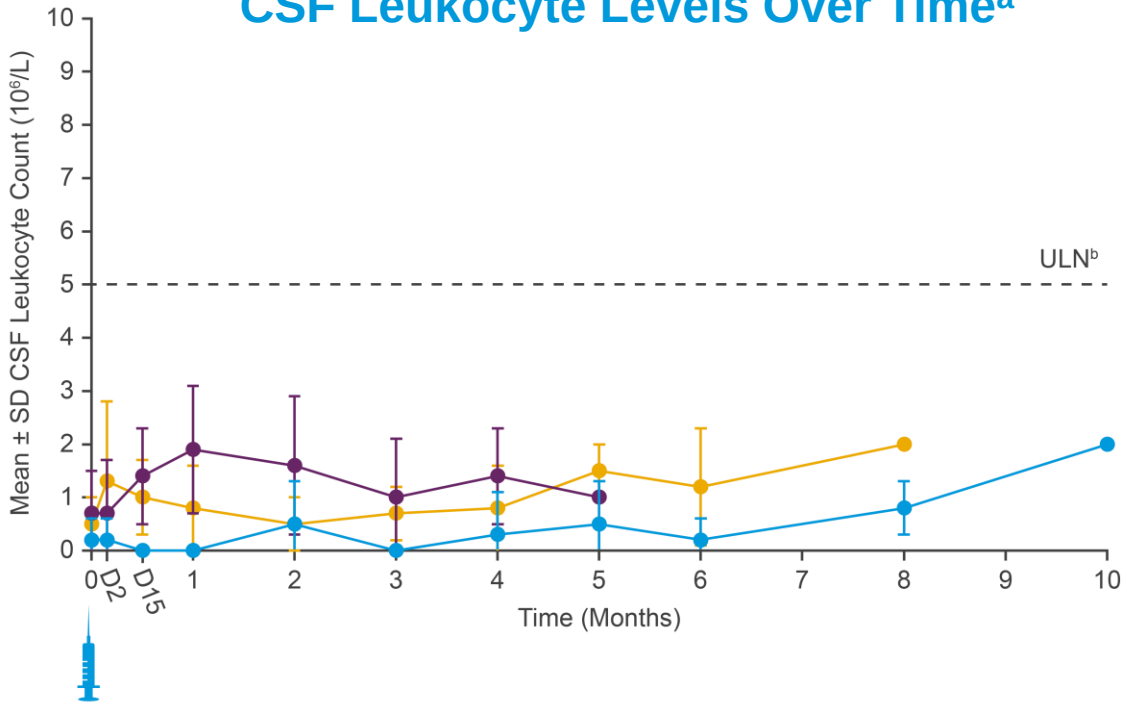
AE, adverse event; LP, lumbar puncture; PBO, placebo; PY, patient years.

[a]Data shown as of June 29, 2023.

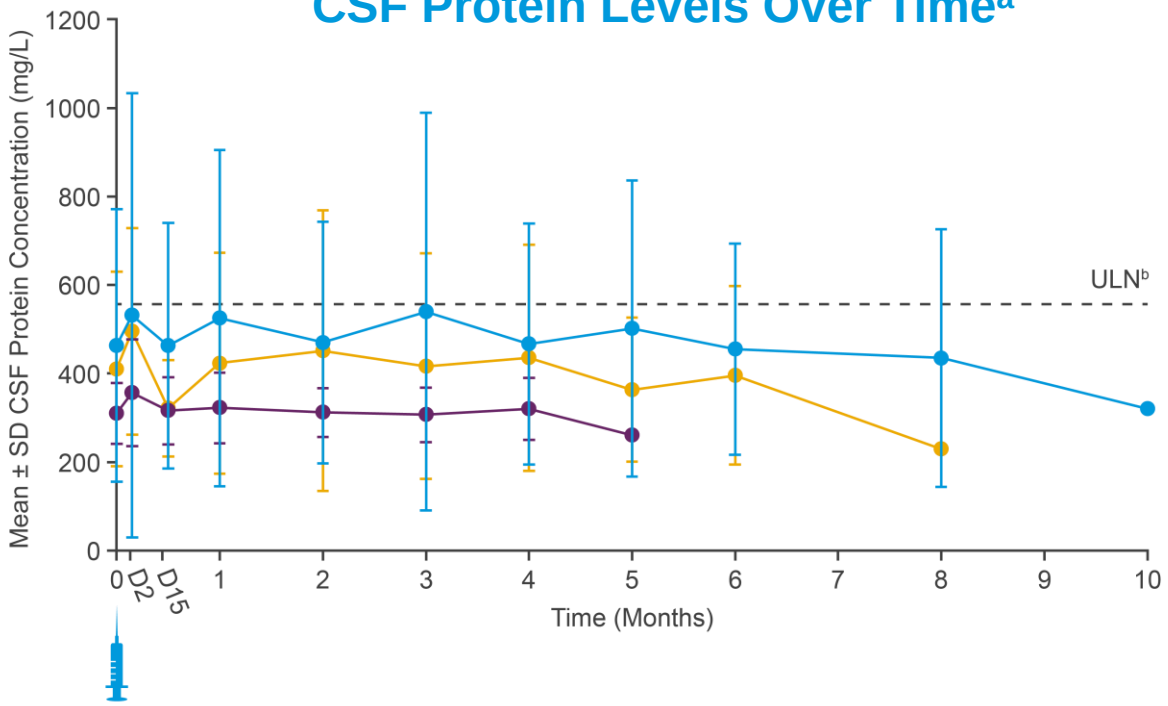
ALN-APP CSF Safety Labs

- CSF white blood cell levels for all patients remained within the reference range for healthy individuals
- No remarkable elevations from baseline were observed for CSF protein levels
- Routine lab assessments (hematology, serum chemistry, liver function, urinalysis, coagulation) as well as preliminary data for the exploratory biomarker neurofilament light chain (NfL) do not reveal significant abnormalities

CSF Leukocyte Levels Over Time[a]



CSF Protein Levels Over Time[a]



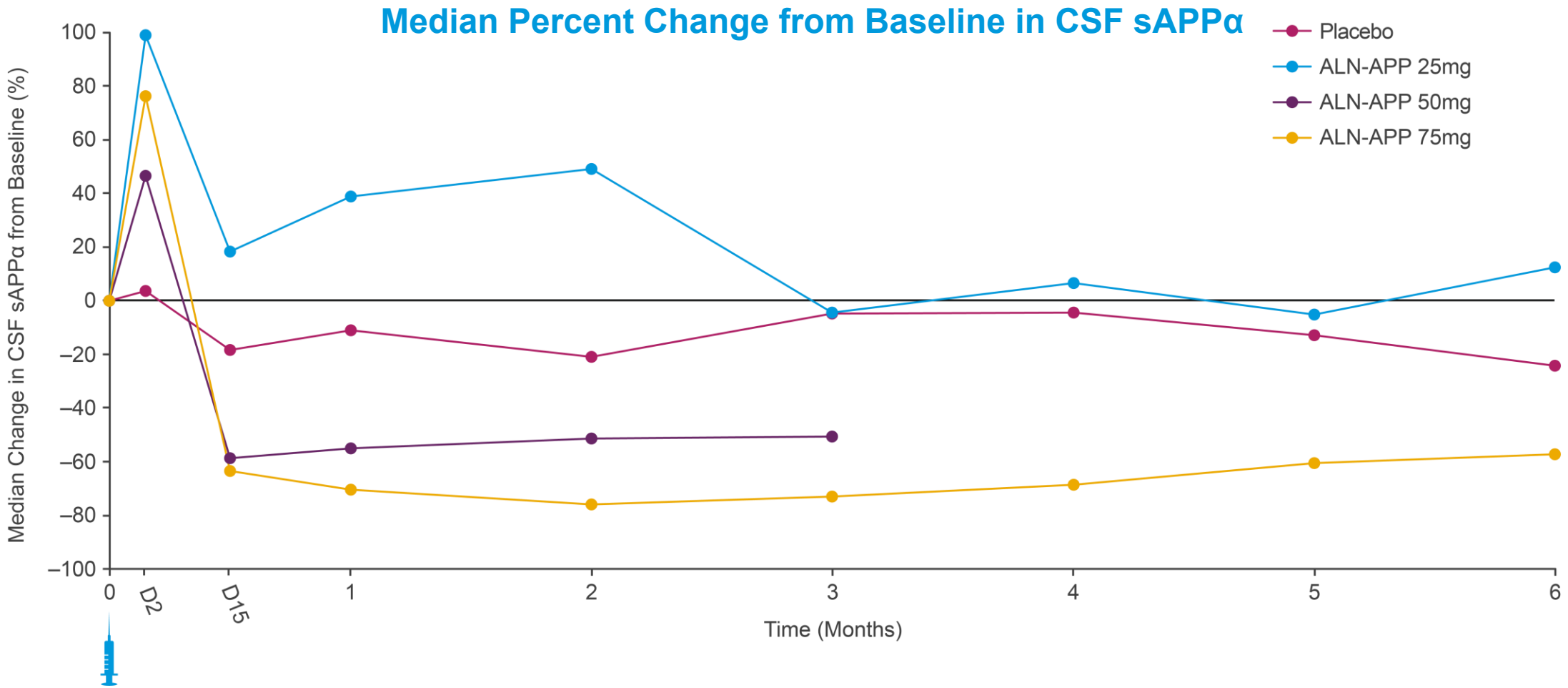
ALN-APP 25mg or Placebo
ALN-APP 50mg or Placebo
ALN-APP 75mg or Placebo

CSF, cerebrospinal fluid, D, day; NfL, neurofilament light chain; SD, standard deviation; ULN, upper limit of normal.

[a]Data shown as of June 29, 2023.[b]Reference lines based on average upper limit of normal for healthy individuals across the five central labs used for assessment: CSF leukocytes = 5 x 10^6/L.; CSF protein = 552 mg/L.

Rapid and Sustained Reductions in CSF sAPPα

- Peak mean (±SEM) reduction in sAPPα was 69% (±9.6) for 75 mg dose occurring at Month 2, with a maximum reduction of 84% observed
- Reduction in sAPPα was sustained, with a 56% (±7.5) mean reduction 6 months after a single 75mg dose

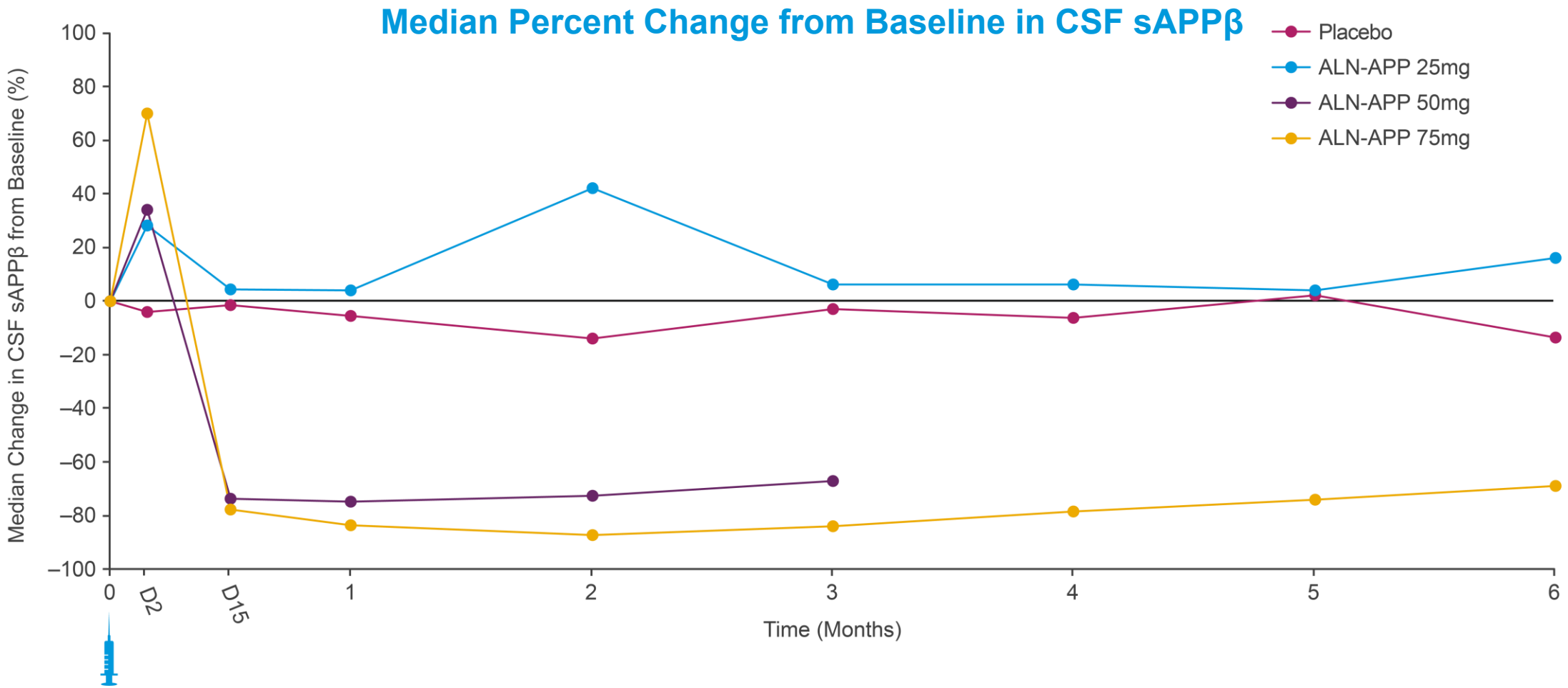


CSF, cerebrospinal fluid; D, Day; sAPP, soluble amyloid precursor protein; SEM, standard error of the mean.

[a]Data shown as of June 29, 2023.

Rapid and Sustained Reductions in CSF sAPPβ

- Peak mean (±SEM) reduction in sAPPβ was 82% (±6.3) for 75 mg dose occurring at Month 2, with a maximum reduction of 90% observed
- Reduction in sAPPβ was sustained, with a 65% (±9.2) mean reduction 6 months after a single 75mg dose



CSF, cerebrospinal fluid; D, Day; sAPP, soluble amyloid precursor protein; SEM, standard error of the mean.

[a]Data shown as of June 29, 2023.

Interim ALN-APP-001 Summary

- ALN-APP is an intrathecally administered, investigational RNAi therapeutic targeting APP, in development for the treatment of AD and CAA

- In this Phase 1 study in patients with EOAD, rapid and sustained reductions in sAPPα and sAPPβ were observed following a single dose of ALN-APP
  - Peak mean (±SEM) reduction in sAPPβ was 82% (±6.3) for 75 mg dose occurring at Month 2, with maximum reduction of 90% observed
  - >65% mean reduction in sAPPβ was sustained for 6 months following 75 mg dose

- ALN-APP was generally well tolerated, with all AEs mild or moderate in severity and the most common being related to LP

- These interim results support further evaluation of ALN-APP in patients with AD and CAA

AD, Alzheimer's disease; AE, adverse event; APP, amyloid precursor protein; CAA, cerebral amyloid angiopathy; EOAD, early-onset Alzheimer's disease; LP, lumbar puncture; RNAi, RNA interference; sAPP, soluble amyloid precursor protein; SEM, standard error of the mean.

Presented on behalf of the authors:

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