Phase 1 Safety, Tolerability, and Pharmacological Results of ALN-APP, the First Investigational RNA Interference Therapeutic in Development for Early-Onset Alzheimer's Disease

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Disclosures

Disclosures for Catherine Mummery

Activity	Entities
Advisory board/consultancy	Alector, Biogen, Ionis, Lilly, Prevail, Roche
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Speaker for sponsored events – honoraria	Biogen, Eisai, Ionis, Lilly, PeerView, Roche

ALN-APP

ALN-APP is an investigational drug being studied for the treatment of Alzheimer's disease and cerebral amyloid angiopathy. ALN-APP is not approved by any health authority, and the safety and efficacy of ALN-APP has not been established.

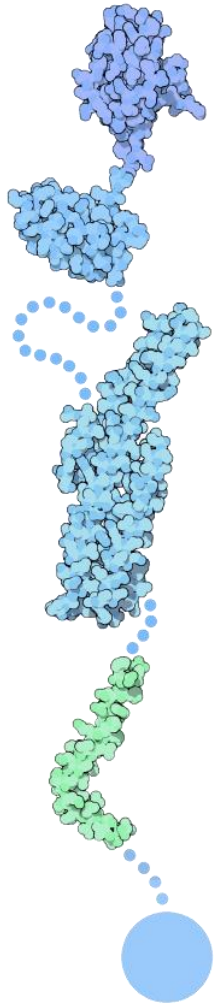
The ALN-APP clinical program is being conducted as a partnership between Alnylam Pharmaceuticals and Regeneron Pharmaceuticals, Inc.

MRI, magnetic resonance imaging.

Introduction

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

- APP is a membrane-associated protein, which is processed via serial cleavage to produce a variety of peptides, including Aβ[1]
  - Aβ deposits in the brain are a pathological hallmark of both Alzheimer's disease[1] and cerebral amyloid angiopathy[2]
- Genetic alterations that modify APP expression and proteolysis cause early-onset Alzheimer's disease[3]
  - APP locus duplications and trisomy 21 (Down syndrome) result in quantitative increases in APP expression and lead to early-onset Alzheimer's disease
  - Variants in *APP*, *presenilin 1*, and *presenilin 2* alter APP proteolysis and can lead to autosomal-dominant Alzheimer's disease
  - *APP* A673T variants reduce Aβ production and lower Aβ levels, protecting against Alzheimer's disease[4,5]



Aβ, amyloid beta; APP, amyloid precursor protein.

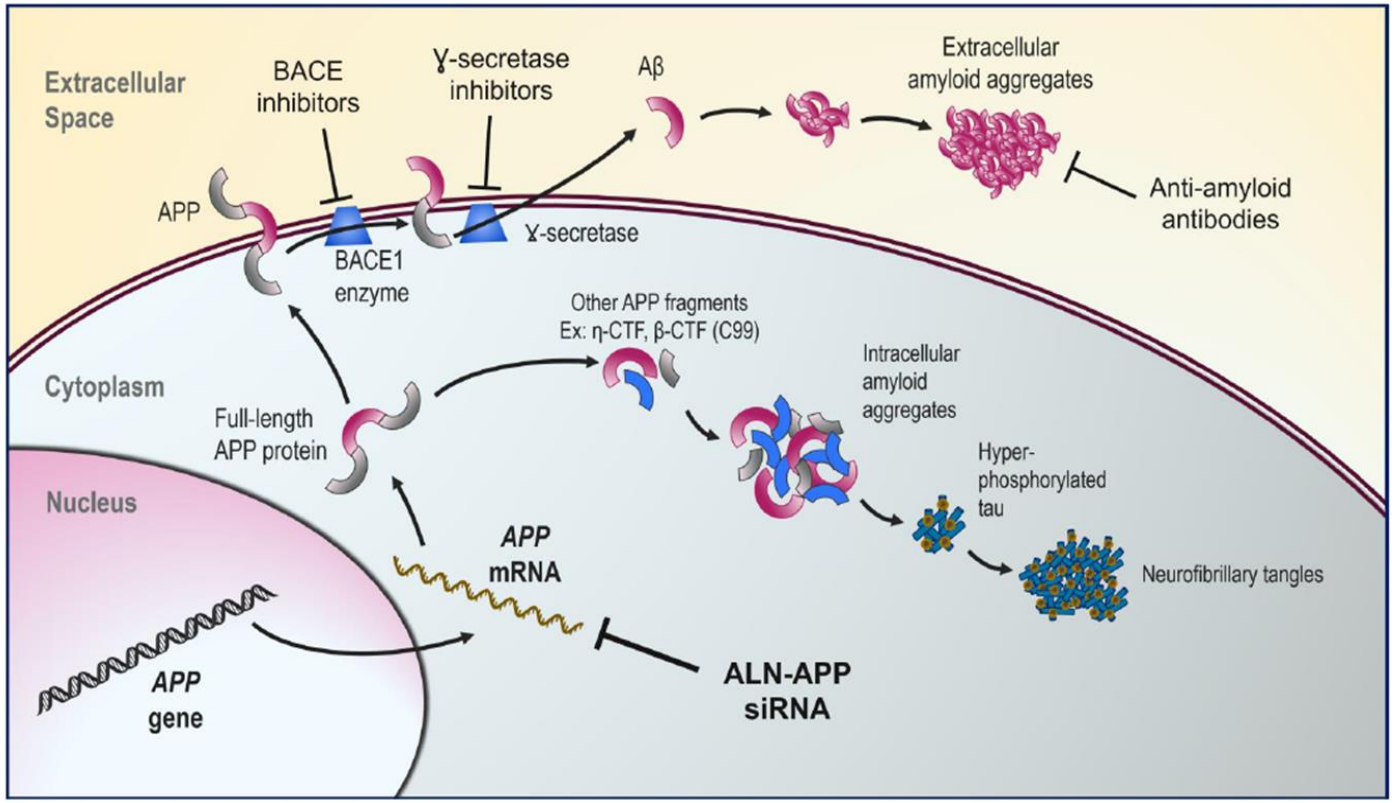
Image: APP Protein Structure courtesy of David S. Goodsell and the RCSB Protein Data Bank.

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 *et al. Nature* 2012;488:96–99. 5. Martiskainen H *et al. Ann Neurol.* 2017;8:128–132.

ALN-APP Therapeutic Hypothesis

An Investigational RNA Interference Therapeutic for Patients with Alzheimer's Disease

- ALN-APP is an intrathecally administered, investigational RNA interference therapeutic in development for treatment of patients with Alzheimer's disease or cerebral amyloid angiopathy
- siRNA 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, the source of all downstream Aβ protein species, including Aβ42 and Aβ40
  - Reduces substrate for brain amyloid deposition and may enable natural clearance
  - Reduces intracellular Aβ and may reduce neuronal dysfunction



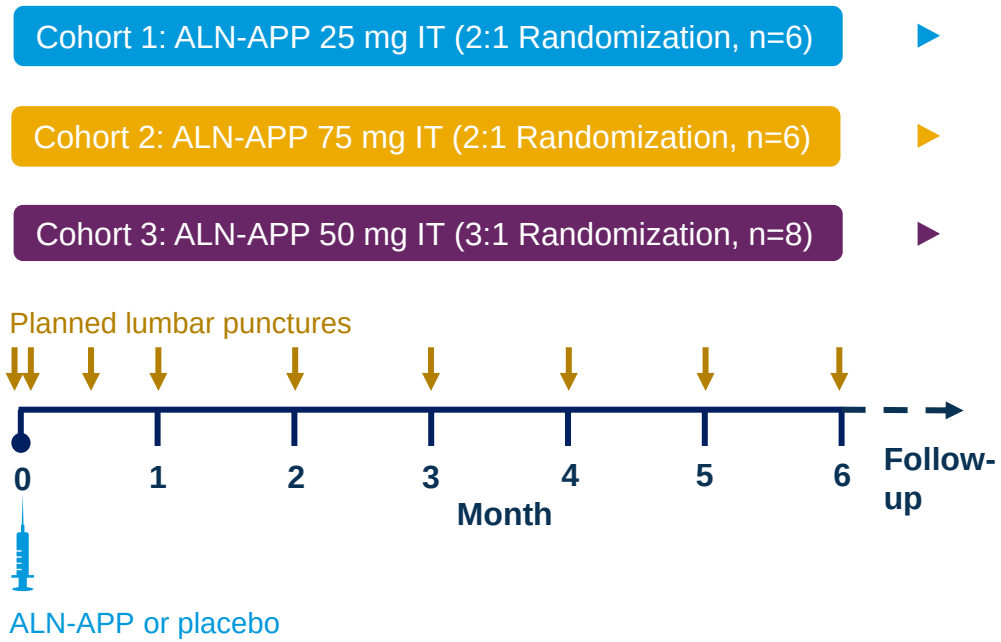
Aβ, amyloid beta; APP, amyloid precursor protein; BACE, beta-secretase; CNS, central nervous system; CTF, c-terminal fragment; mRNA, messenger ribonucleic acid; RISC, ribonucleic acid-induced silencing complex; siRNA, small interfering ribonucleic acid.

ALN-APP-001 Study Design

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

Patient Population

- Symptom onset <65 years (i.e., early-onset Alzheimer's disease)
- Clinical diagnosis of MCI or mild dementia due to Alzheimer's disease
- Alzheimer's disease diagnosis confirmed by CSF biomarkers or Aβ-PET
- Clinical Dementia Rating® global score of 0.5 or 1.0
- MMSE score >20



Primary Endpoint

- Safety and tolerability

Secondary Endpoints

- Change from baseline in PD effects of ALN-APP
  - CSF sAPPα and sAPPβ
- PK profile in CSF and plasma

Exploratory Endpoints

- Change from baseline in biomarkers of disease activity
  - CSF Aβ42 and Aβ40

- Additional cohorts are being studied in Part A; the Part B multi-dose, open-label study has been initiated

Here, we present longer term safety and pharmacodynamic data of ALN-APP than previously reported plus novel data describing disease-related biomarkers

As of September 20, 2023. Cohorts 1, 2, and 3 have a mean time from randomization of 14.8, 9.9, and 6.6 months, respectively.

Aβ, amyloid beta; Aβ40, amyloid beta peptide length 40 amino acids; Aβ42, amyloid beta peptide length 42 amino acids; CSF, cerebrospinal fluid; IT, intrathecally; MCI, mild cognitive impairment; MMSE, Mini Mental State Examination; PD, pharmacodynamic; PET, positron emission tomography; PK, pharmacokinetic; sAPP, soluble amyloid precursor protein.

Demographic and Baseline Disease Characteristics

Pooled Data for Cohorts 1–3

Baseline Characteristics	All Patients (N=20)
Age, years, mean (range)	61.3 (53–73)
Male, n (%)	12 (60.0)
Race, n (%)	
White	16 (80.0)
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)

Time from Randomization, Months, Mean (SD) Data cut used for safety analyses	All Patients (N=20)
Cohort 1 (ALN-APP 25 mg or Placebo, n=6)	14.8 (1.7)
Cohort 2 (ALN-APP 75 mg or Placebo, n=6)	9.9 (1.2)
Cohort 3 (ALN-APP 50 mg or Placebo, n=8)	6.6 (1.3)

Data shown as of September 20, 2023.

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

ALN-APP-001 Blinded Safety Summary

Pooled AE Summary for Cohorts 1–3

Patients with events, n (%)	ALN-APP 25 mg or PBO (N=6, PY=7.4)	ALN-APP 50 mg or PBO (N=8, PY=4.4)	ALN-APP 75 mg or PBO (N=6, PY=4.9)
At least one AE	6 (100.0)	7 (87.5)	6 (100.0)
Related to study drug	0	1 (12.5)	0
At least one moderate AE	4 (66.7)	5 (62.5)	4 (66.7)
Related to study drug	0	0	0
At least one severe AE	0	0	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 or SUSARs occurred
- One individual in the 50 mg or placebo cohort had two mild AEs (post-LP headache and post-LP nausea) that were each deemed both drug-related and procedure-related by the investigator; both events resolved on the same day

Data shown as of September 20, 2023. Cohorts 1, 2, and 3 have a mean time from randomization of 14.8, 9.9, and 6.6 months, respectively.

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

ALN-APP-001 Blinded Safety Summary

Pooled AEs by Preferred Term for Cohorts 1–3

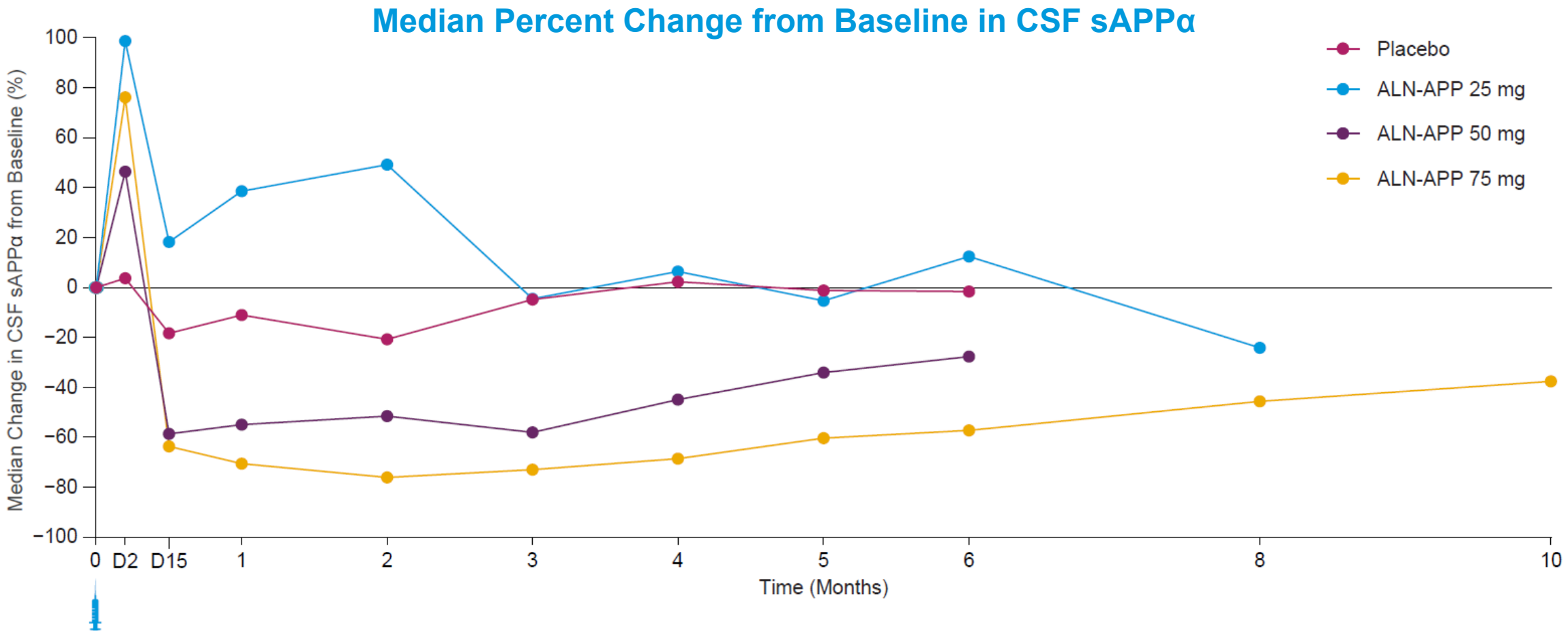
Patients with events, n (%)[a]	ALN-APP 25 mg or PBO (N=6, PY=7.4)	ALN-APP 50 mg or PBO (N=8, PY=4.4)	ALN-APP 75 mg or PBO (N=6, PY=4.9)
At least one adverse event	6 (100.0)	7 (87.5)	6 (100.0)
Procedural headache	3 (50.0)	5 (62.5)	0
Procedural pain	1 (16.7)	2 (25.0)	0
Back pain	2 (33.3)	0	1 (16.7)
Presyncope	0	1 (12.5)	2 (33.3)
Syncope	2 (33.3)	0	1 (16.7)
Headache	0	3 (37.5)	1 (16.7)
Nasopharyngitis	0	0	2 (33.3)
Vomiting	2 (33.3)	0	0

- To date, 60% of patients have experienced AEs that were deemed related to LP by the investigator
  - These AEs included procedural headache (40% of patients), headache (15%), back pain (10%), vomiting (10%), procedural pain (10%), dizziness (5%), injection site swelling (5%), neck pain (5%), presyncope (5%), procedural nausea (5%), puncture site pain (5%), and syncope (5%)

Data shown as of September 20, 2023. Cohorts 1, 2, and 3 have a mean time from randomization of 14.8, 9.9, and 6.6 months, respectively. [a]Only events that occurred in 2 or more patients in the total population are reported.
AE, adverse event; LP, lumbar puncture; PBO, placebo; PY, patient years.

Rapid and Durable Reductions in CSF sAPPα

- Peak mean (±SEM) reduction in sAPPα was 69% (±9.6) for the 75 mg dose occurring at Month 2, with a maximum individual reduction of 84% observed
- Reduction in sAPPα was sustained, with a 31% (±7.6) mean reduction at Month 6 after a single 50 mg dose, and a 56% (±7.5) and a 33% (±6.1) mean reduction at Months 6 and 10, respectively, after a single 75 mg dose

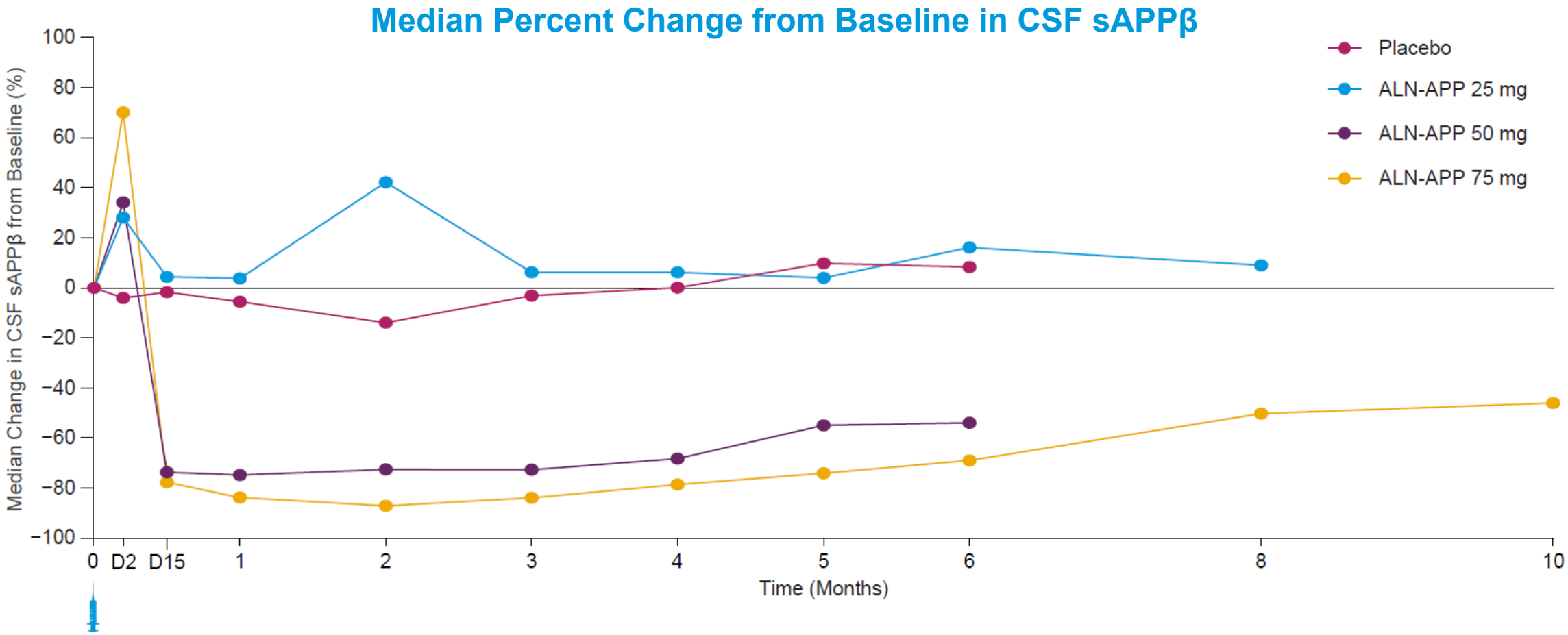


Data shown as of Oct 6, 2023. Timepoints with an n of ≤2 are not plotted.

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

Rapid and Durable Reductions in CSF sAPPβ

- Peak mean (±SEM) reduction in sAPPβ was 82% (±6.3) for the 75 mg dose occurring at Month 2, with a maximum individual reduction of 90% observed
- Reduction in sAPPβ was sustained, with a 48% (±5.5) mean reduction at Month 6 after a single 50 mg dose, and a 65% (±9.2) and a 39% (±11.5) mean reduction at Months 6 and 10, respectively, after a single 75 mg dose



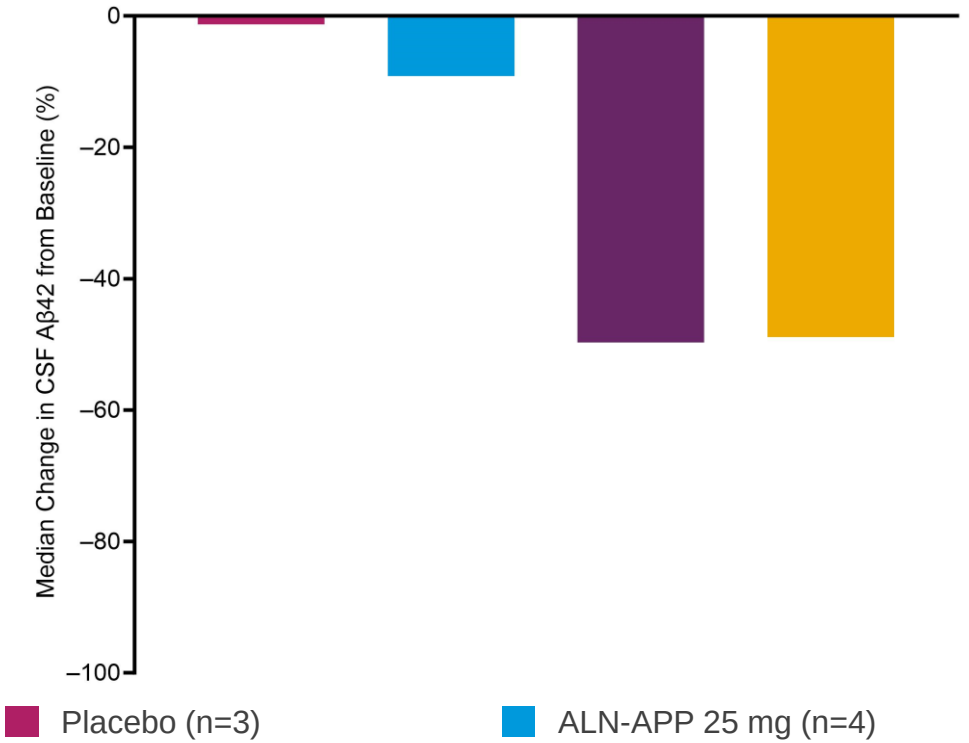
Data shown as of Oct 6, 2023. Timepoints with an n of ≤2 are not plotted.

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

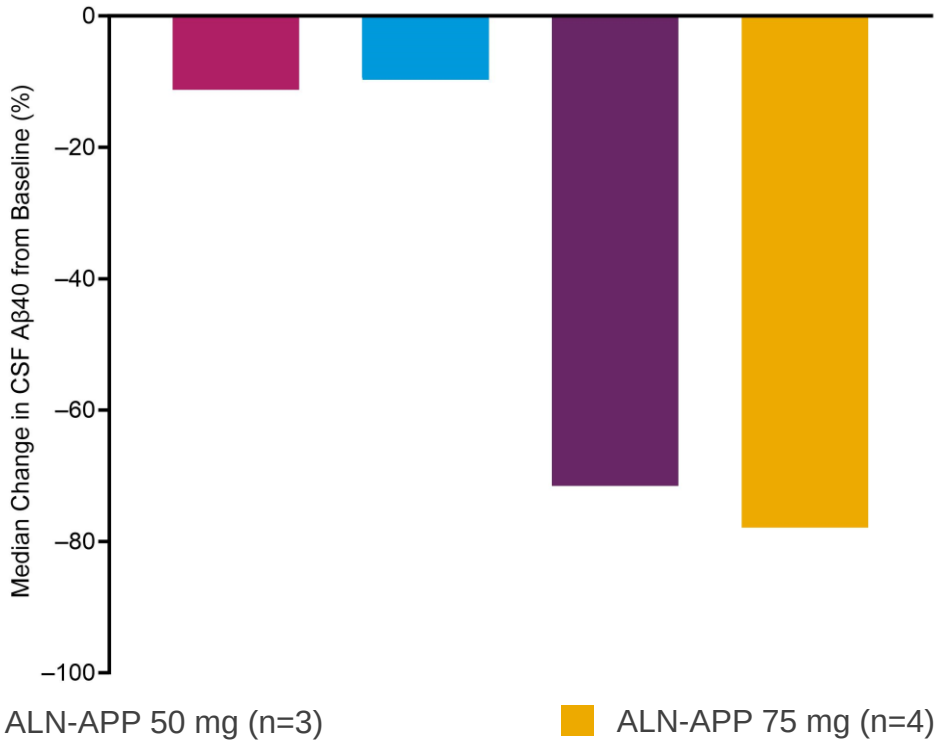
Marked Reductions in CSF Aβ42 and Aβ40 at Month 2

- At Month 2, reductions in CSF Aβ42 and Aβ40 were achieved after a single dose of ALN-APP
  - Mean (±SEM) reduction in CSF Aβ42 was 51.9% (±6.8) in the 50 mg, and 48.9% (±7.7) in the 75 mg cohort
  - Mean (±SEM) reduction in CSF Aβ40 was 69.8% (±7.0) in the 50 mg, and 70.6% (±9.3) in the 75 mg cohort

Median Percent Change from Baseline in CSF Aβ42



Median Percent Change from Baseline in CSF Aβ40



Placebo (n=3) | ALN-APP 25 mg (n=4) | ALN-APP 50 mg (n=3) | ALN-APP 75 mg (n=4)

- CSF safety biomarkers, routine lab assessments, and preliminary data for the exploratory biomarker neurofilament light chain all continued to show no significant abnormalities

Data shown as of August 17, 2023.

Data are not shown for later timepoints owing to the limited number of patients with data from Month 3.

Aβ40, amyloid beta peptide length 40 amino acids; Aβ42, amyloid beta peptide length 42 amino acids; CSF, cerebrospinal fluid; SEM, standard error of the mean.

Interim ALN-APP-001 Part A Summary

- In this Phase 1 study in patients with early-onset Alzheimer's disease, treatment with single-dose ALN-APP, with follow up from 6.6 to 14.8 months, was generally well tolerated
  - All AEs continued to be mild or moderate in severity, with the most common being related to LP
- Rapid, robust, and durable reductions in sAPPα and sAPPβ were observed
  - Reductions in sAPPα and sAPPβ were sustained at 6 months after a 50 mg dose and at 10 months after a 75 mg dose
- Marked reductions at 2 months were observed in CSF Aβ42 and Aβ40, the soluble forms of peptides that are the primary components of amyloid deposits in Alzheimer's disease and cerebral amyloid angiopathy
- These interim results support further evaluation of ALN-APP in patients with Alzheimer's disease and patients with cerebral amyloid angiopathy
  - The Part B multi-dose, open-label study is ongoing

Aβ40, amyloid beta peptide length 40 amino acids; Aβ42, amyloid beta peptide length 42 amino acids; AE, adverse event; APP, amyloid precursor protein; CSF, cerebrospinal fluid; LP, lumbar puncture; RNAi, RNA interference; sAPP, soluble amyloid precursor protein.

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