Amyloid-Related Imaging Abnormalities in an Ongoing Phase 1 Study of Mivelsiran, an Investigational RNA Interference Therapeutic Targeting Amyloid Precursor Protein, in Patients with Alzheimer's Disease

Neal S Parikh[1], Sharon Cohen[2], Sandeep Chaudhari[1], Lynn Farrugia[1], Andrew H Ahn, Julia Shirvan[1], Steven M Greenberg[3]

[1]Alnylam Pharmaceuticals, Inc., Cambridge, MA, USA; [2]Toronto Memory Program, Toronto, ON, Canada; [3]Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA

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Disclosure

Speaker: Neal S Parikh, MD, MS

Conflict	Disclosure
Employee	Alnylam Pharmaceuticals
Shareholder	Alnylam Pharmaceuticals

Mivelsiran:

Mivelsiran is an investigational drug being studied for the treatment of cerebral amyloid angiopathy and Alzheimer's disease. Mivelsiran is not approved by any regulatory authority, and the safety and efficacy of mivelsiran have not been established.

Funding:

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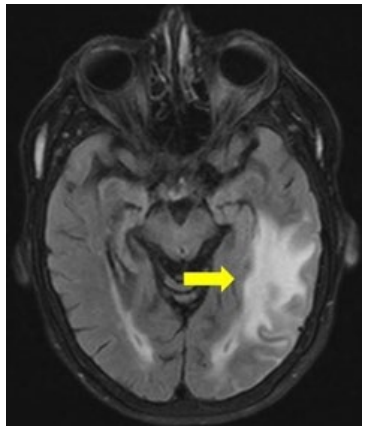
Background: Amyloid-Related Imaging Abnormalities (ARIA)

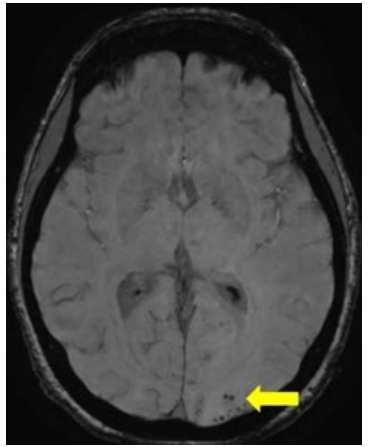
ARIA have been observed in previous clinical trials in Alzheimer's disease (AD)

- ARIA can occur in individuals with AD, manifesting as edema/effusion (ARIA-E) and hemorrhage (ARIA-H)[1]
- ARIA incidence is increased in patients treated with commercially available anti-amyloid monoclonal antibody (mAb) therapies[2,3]
  - In pivotal trials, ARIA-E rates were 12.6–24.0% with mAb compared with 1.7–2.1% with placebo[2,3]
  - Isolated ARIA-H occurred at similar rates in placebo-treated (7.8–12.4%) and mAb-treated patients (8.9–12.7%)[2,3]
- Risk factors include APOE4 carrier status and greater burden of baseline hemorrhagic lesions, for example, imaging evidence of cerebral amyloid angiopathy (CAA)[1-5]

ARIA-E[6a]



ARIA-H[6a]



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1. Jeong SY *et al. Neurology* 2025;104:e213483. 2. van Dyck CH *et al.* N Engl J Med 2023;388:9–21. 3. Sims JR *et al. JAMA* 2023;330:512–27. 4. Zimmer JA et al. JAMA Neurol. 2025;82:461–9. 5. Greenberg SM et al. Stroke. 2025;56:e30–e38. 6. Paczynski M *et al. JAMA Neurol* 2025;82:655–65.

AD, Alzheimer's disease; *APOE4*, apolipoprotein E ε4 allele; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemorrhage; Aβ, amyloid-beta; CAA, cerebral amyloid angiopathy; mAb, monoclonal antibody.

Objective

To evaluate rates of ARIA in an ongoing Phase 1 study of mivelsiran in early-onset AD (EOAD)

Mivelsiran
- **Targets amyloid-beta precursor protein (APP) mRNA to reduce the production of APP and downstream Aβ species[1,6,7]**
- **Not hypothesized to increase ARIA risk due to its mechanism of action**

Mivelsiran:
C16-conjugated siRNA targeting **APP mRNA[1,2]**

Image credit: Alnylam Pharmaceuticals. Figure adapted from information in Friedrich & Aigner, and Niemietz et al.

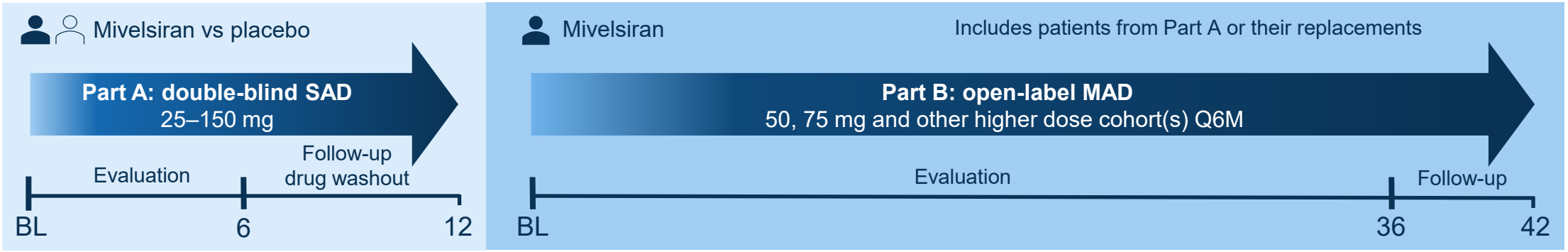
1. Brown KM *et al*. Presented at AD/PD congress. March 28–April 1, 2023, Gothenburg Sweden. 2. Brown KM *et al. Nature Biotechnology*. 2022;40(10):1500–8. 3. Niemietz C *et al. Molecules* 2015;20(10):17944–75. 4. An G. *J Clin Pharmacol* 2024;64(1):45–57. 5. Aagaard L, Rossi JJ. *Adv Drug Deliv Rev* 2007;59(2-3):75–86. 6. Taillie D *et al.* Alzheimer's Association International Conference, July 27–31, 2025, Toronto, ON, Canada. Poster. 7. Cohen S *et al.* Alzheimers Dement 2024;20(Suppl 6):e08421. Aβ, amyloid-beta; Aβ40, Aβ peptide length 40 amino acids; Aβ42, Aβ peptide length 42 amino acids; APP, Aβ precursor protein; ARIA, amyloid-related imaging abnormalities; CNS, central nervous system; EOAD, early-onset Alzheimer's disease; mRNA, messenger RNA; RISC, RNA-induced silencing complex; siRNA, small interfering RNA.

Methods: Trial Design and ARIA Measurement

ARIA were assessed in an ongoing Phase 1 study of mivelsiran in EOAD

Study Population

- Mild dementia or MCI due to AD confirmed by CSF biomarkers or Aβ PET, and disease onset before the age of 65
- **No** exclusion for CAA, ARIA, or *APOE* genotype at baseline



ARIA Measurement

- Brain MRI included T2, FLAIR, SWI, and T2*GRE sequences:
  - Baseline and Months 1, 3, 6 (SAD, MAD), 9, 12, 18, 24, and 36 (MAD)
- Blinded radiologists evaluated MRIs for ARIA-E and ARIA-H; ARIA-H reported if identified on either SWI or T2*GRE
- Descriptive statistics were used to summarize ARIA rates, including rates of reported ARIA adverse events
  - In patients with missing baseline ARIA data, it was assumed that ARIA were absent at baseline

NCT05231785.

AD, Alzheimer's disease; *APOE*, apolipoprotein E; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemorrhage; Aβ, amyloid-beta; BL, baseline; CAA, cerebral amyloid angiopathy; CSF, cerebrospinal fluid; EOAD, early-onset Alzheimer's disease; FLAIR, fluid-attenuated inversion recovery; MAD, multiple ascending dose; MCI, mild cognitive impairment; MRI, magnetic resonance imaging; PET, positron emission tomography; Q6M, once every 6 months; SAD, single ascending dose; SWI, susceptibility-weighted imaging; T2*GRE, T2-star gradient echo.

Baseline Characteristics

Ongoing phase 1 study in EOAD includes participants with ARIA risk factors

Baseline characteristic	Part A: double-blind SAD		Part B: open-label MAD[a]
	Placebo N=15	Mivelsiran N=38	Mivelsiran Q6M N=51
Age, years, mean (SD)	61.1 (4.9)	61.9 (5.4)	62.1 (6.1)
Male, n (%)	7 (46.7)	22 (57.9)	30 (58.8)
Race, n (%)			
White	13 (86.7)	34 (89.5)	44 (86.3)
Asian	2 (13.3)	2 (5.3)	4 (7.8)
Black/African American	0	1 (2.6)	1 (2.0)
Unknown/Other	0	1 (2.6)	2 (3.9)
CDR® global score, n (%)			
0.0	0	1 (2.6)	1 (2.0)
0.5	10 (66.7)	32 (84.2)	28 (54.9)
1.0	5 (33.3)	5 (13.2)	19 (37.3)
2.0	0	0	1 (2.0)
Missing	0	0	2 (3.9)
MMSE score, mean (SD)	24.1 (2.9)	25.4 (3.0)	23.0 (3.0)
***APOE4* carrier,[b] n (%)**	9 (60.0)	26 (68.4)	29 (56.9)
***APOE4* homozygous, n (%)**	4 (26.7)	7 (18.4)	10 (19.6)
ARIA status, n (%)[c]	**n=12**	**n=34**	**n=45**
ARIA-H, present	1 (8.3)	2 (5.9)	3 (6.6)
ARIA-E, present	0	0	0
ARIA status missing	3	4	6

ARIA risk factors in study participants

- 20% of patients (11/54) were homozygous for *APOE4*
- Approximately 6% of patients (3/53) with ARIA-H at study baseline[c,d]

Data shown as of September 18, 2025, in patients with EOAD.
[a]Part B includes patients from Part A or their replacements. [b]At least one ε4 allele. [c]Seven patients were missing baseline MRI sequences required for ARIA adjudication before September 1, 2022. [d]3 of 53 unique patients across SAD/MAD
APOE4, apolipoprotein E ε4 allele; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemorrhage; CDR, Clinical Dementia Rating; EOAD, early-onset Alzheimer's disease; MAD, multiple ascending dose; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; Q6M, once every 6 months; SAD, single ascending dose; SD, standard deviation.

Results: ARIA Rates in Phase 1 Study

No ARIA-E and low rates of ARIA-H observed

ARIA Rates by Treatment Group[a]

ARIA Measure	Part A: double-blind SAD		Part B: open-label MAD
	Placebo N=15	Mivelsiran N=38	Mivelsiran Q6M N=51
New, post-baseline ARIA-H, n (%)	1 (6.7)[b]	1 (2.6)	2 (3.9)
Site investigator-reported ARIA-H AE, n (%)[c]	1 (6.7)	2 (5.3)[d]	1 (2.0)

- No patients with ARIA-E
- In total, seven patients with ARIA-H
  - Three patients with stable ARIA-H, present at baseline
  - Four patients with new post-baseline ARIA-H (including two who are homozygous for *APOE4*)[b]

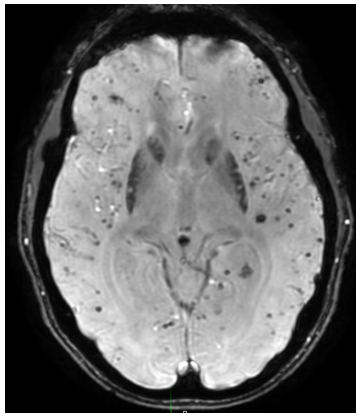
SAD	**#1: Placebo[b] (microhemorrhage)** – *Baseline ARIA missing, assumed new post baseline* **#2: Mivelsiran 75 mg (microhemorrhage)**
MAD	**#3: Mivelsiran 75 mg (superficial siderosis)** **#4: Mivelsiran 75 mg (microhemorrhage)**

- No post-baseline ARIA developed in dose cohorts above 75 mg to date

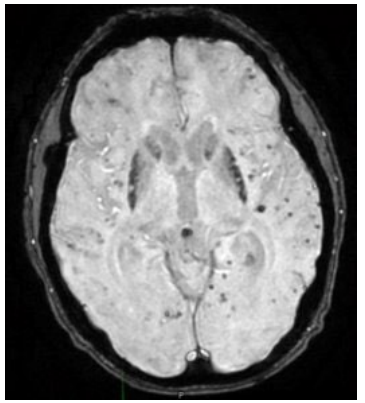
ARIA as Reported AEs[c]

- No ARIA-E AEs observed. ARIA-H AEs reported in four patients, totaling six events
- All ARIA-H AEs reported as mild or moderate in severity, and asymptomatic, and none were deemed related to treatment by investigators

SAD Baseline Brain MRI (SWI)



MAD Month 3 Brain MRI (SWI)



Images show no new post-baseline ARIA-H observed in a patient with baseline ARIA-H who received high doses of mivelsiran in SAD and MAD parts

Data shown as of September 18, 2025. [a]Incidence was calculated by dividing the number of new cases of ARIA that developed post baseline by the total population. [b]Patient was missing baseline MRI sequences required for ARIA adjudication; for patients with missing baseline data, ARIA were assumed to be zero at baseline. [c]AEs are reported by principal investigators at their discretion. [d]Of the two patients with investigator-reported ARIA AEs, one had baseline ARIA-H.
AE, adverse event; *APOE4*, apolipoprotein E ε4 allele; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemorrhage; MAD, multiple ascending dose; MRI, magnetic resonance imaging; Q6M, once every 6 months; SAD, single ascending dose; SWI, susceptibility-weighted imaging.

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Summary

Phase 1 interim data of mivelsiran in EOAD show no evidence of increased risk of ARIA

- Interim Phase 1 analysis included patients with ARIA risk factors, such as *APOE4* homozygosity (~20%) and baseline ARIA-H (~6%)
- Patients with EOAD who received mivelsiran had low rates of ARIA-H (comparable to placebo) and no ARIA-E
  - No ARIA-E has been observed in Phase 1 to date
  - Rates of ARIA-H were low in both active (~5%) and placebo arms (~7%), consistent with isolated ARIA-H rates in placebo-treated patients in trials of anti-Aβ mAb[1,2]
- All ARIA-H events reported as AEs were asymptomatic, mild or moderate in severity, and deemed not related to mivelsiran by investigators
- Mivelsiran is a novel investigational RNAi therapeutic being studied for CAA in the ongoing Phase 2 cAPPricorn-1 study (NCT06393712)

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

AE, adverse event; *APOE4*, apolipoprotein E ε4 allele; ARIA, amyloid-related imaging abnormalities; ARIA-E, ARIA-edema/effusion; ARIA-H, ARIA-hemorrhage; Aβ, amyloid-beta; CAA, cerebral amyloid angiopathy; EOAD, early-onset Alzheimer's disease; mAb, monoclonal antibody; RNAi, RNA interference.

1. van Dyck CH *et al. N Engl J Med* 2023;388:9–21. 2. Sims *JR et al. JAMA.* 2023;330;(6):512-527.