Amyloid-Related Imaging Abnormalities in a Phase 1 Study of Mivelsiran in Patients With Early-Onset Alzheimer's Disease

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Disclosures for Sharon Cohen, MD FRCPC

Conflict	Disclosures
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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.

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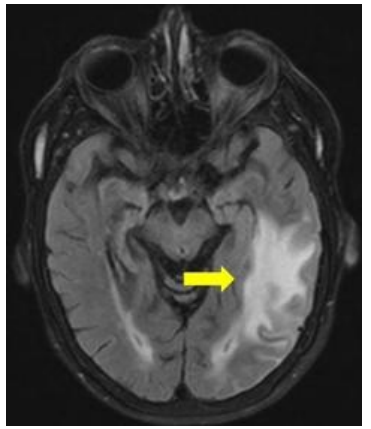
Background: Amyloid-Related Imaging Abnormalities (ARIA)

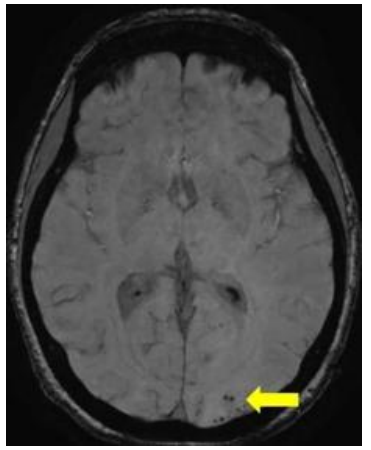
ARIA Have Been Observed in Clinical Trials in Alzheimer's Disease (AD)

- Can occur spontaneously in individuals with AD, manifesting as edema/effusion (ARIA-E) and/or microhemorrhages and hemosiderin deposits (ARIA-H)[1–3]
- Increased incidence of ARIA in patients treated with commercially available anti-amyloid monoclonal antibody (mAb) therapies complicates treatment and leads to restricted treatment eligibility[2–4]
  - In pivotal trials, ARIA-E rates were greater in mAb-treated (12.6–24.0%) versus placebo-treated patients (1.7–2.1%)[2,3]
  - Isolated ARIA-H occurred at similar rates in mAb-treated (8.9–12.7%) and placebo-treated patients (7.8–12.4%)[2,3]

ARIA-E[6a]



ARIA-H[6a]



Risk Factors

APOE4 carrier status
Increasing risk from heterozygous to homozygous[5,6]

Baseline hemorrhagic lesions
e.g. imaging evidence of cerebral amyloid angiopathy (CAA)[5,6]

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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. Cummings J *et al. J Prev Alzheimers Dis* 2023;10:362–77. 5. Zimmer JA *et al. JAMA Neurol* 2025;82:461–9. 6. Greenberg SM *et al. Stroke*. 2025;56:e30–e38.

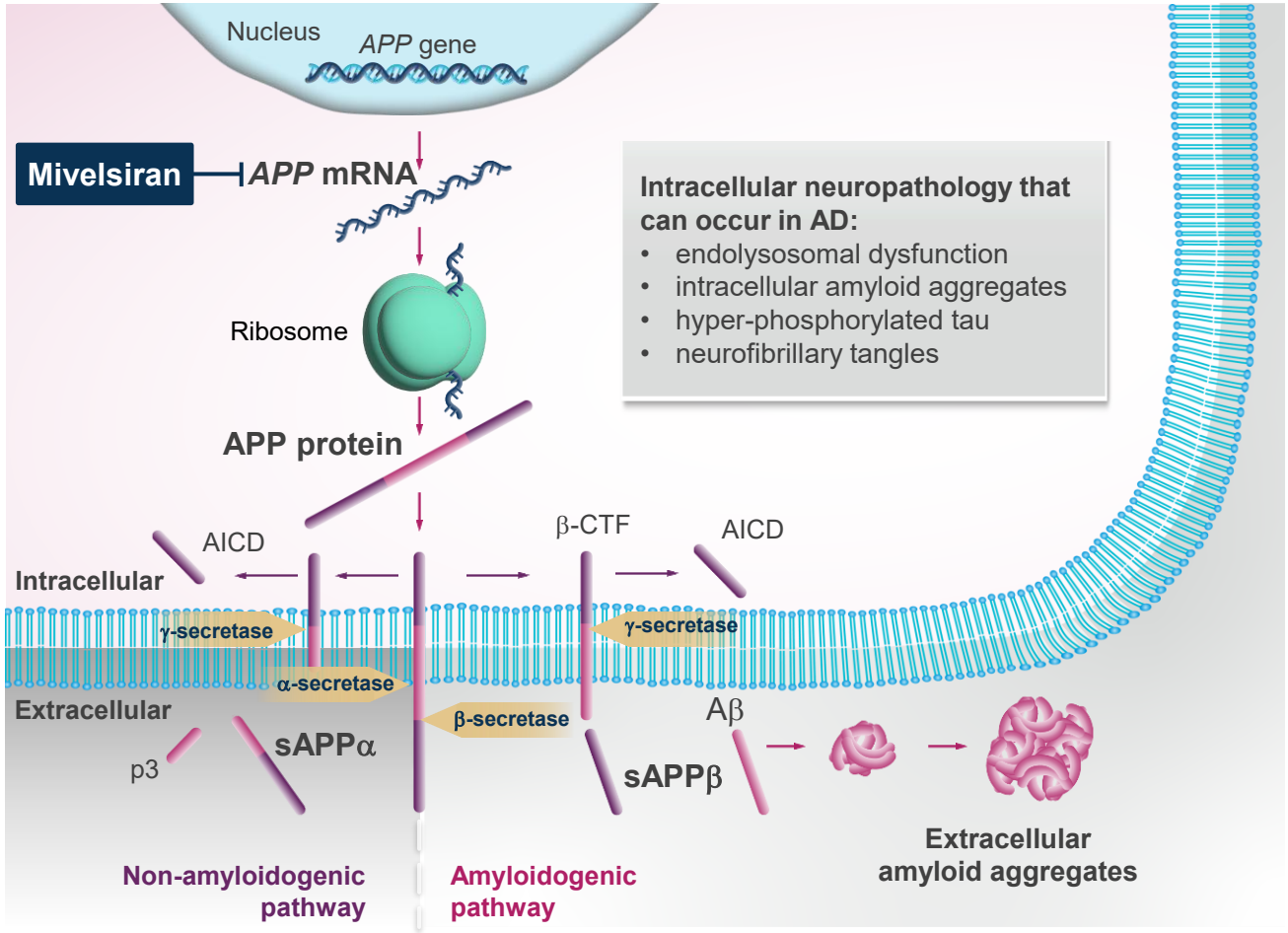
AD, Alzheimer's disease; *APOE4*, *apolipoprotein E ε4* allele; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities-edema/effusion; ARIA-H, amyloid-related imaging abnormalities-hemorrhage/hemosiderin; CAA, cerebral amyloid angiopathy; mAb, monoclonal antibody.

Mivelsiran Targets Amyloid-Beta Precursor Protein (APP)

- Mivelsiran is an investigational RNAi therapeutic for AD and CAA
- Targets *APP* mRNA to reduce production of APP and downstream amyloid-beta species (Aβ40 and Aβ42), thereby reducing intracellular and extracellular drivers of AD[1–3]
- Not hypothesized to increase ARIA risk
  - RNAi is not expected to interact directly with vascular amyloid or drive immuno-active Aβ clearance

Objective

- Describe rates of ARIA in patients with early-onset AD (EOAD) as part of an ongoing Phase 1 study of mivelsiran



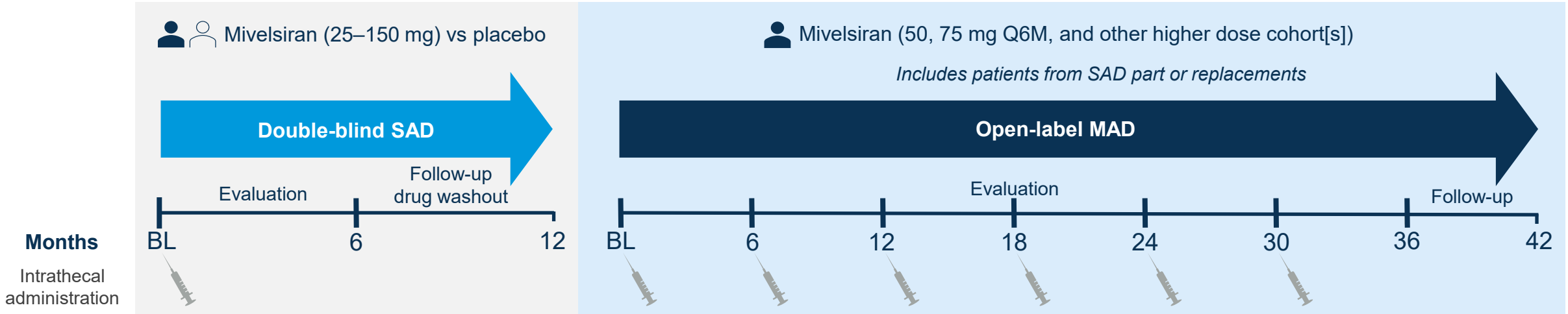
AD, Alzheimer's disease; AICD, amyloid-beta precursor protein intracellular domain; APP, amyloid-beta precursor protein; ARIA, amyloid-related imaging abnormalities; Aβ, amyloid-beta; CAA, cerebral amyloid angiopathy; EOAD, early-onset Alzheimer's disease; p3, p3 peptide; RNAi, RNA interference; sAPP, soluble amyloid-beta precursor protein; β-CTF; C-terminal fragment beta.

1. Brown KM *et al.* International Conference on Alzheimer's and Parkinson's Diseases (AD/PD). March 28–April 1, 2023, Gothenburg Sweden. 2. Taillie D *et al.* Alzheimer's Association International Conference, July 27–31, 2025, Toronto, ON, Canada. Poster. 3. Cohen S *et al. Alzheimers Dement* 2024;20(Suppl 6):e08421.

Methods: Mivelsiran Phase 1 Study in EOAD

Study Population

- Mild cognitive impairment or mild dementia due to EOAD confirmed by CSF biomarkers or Aβ PET, and symptom onset before the age of 65
- **No** exclusion for CAA, ARIA, or *APOE* genotype



ARIA Monitoring and Assessment

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

NCT05231785.

AD, Alzheimer's disease; APOE, apolipoprotein E; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities-edema/effusion; ARIA-H, amyloid-related imaging abnormalities-hemorrhage/hemosiderin; 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	Double-blind SAD		Open-label MAD[a]
	Placebo N=15	Mivelsiran N=38	Mivelsiran Q6M N=57
Age, years, mean (SD)	61.1 (4.9)	61.9 (5.4)	62.1 (6.0)
Male, n (%)	7 (46.7)	22 (57.9)	34 (59.6)
Race, n (%)			
White	13 (86.7)	34 (89.5)	49 (86.0)
Asian	2 (13.3)	2 (5.3)	5 (8.8)
Black/African American	0	1 (2.6)	1 (1.8)
Unknown/Other	0	1 (2.6)	2 (3.5)
CDR® global score, n (%)			
0.0	0	1 (2.6)	2 (3.5)
0.5	10 (66.7)	32 (84.2)	33 (57.9)
1.0	5 (33.3)	5 (13.2)	20 (35.1)
2.0	0	0	1 (1.8)
Missing	0	0	1 (1.8)
MMSE score, mean (SD)	24.1 (2.9)	25.4 (3.0)	23.7 (3.7)
Centiloid PET, CL, mean (SD)	106.41 (24.30)	101.09 (38.32)	97.03 (32.79)
***APOE4* genotype, n (%)**			
Carrier[b]	9 (60.0)	26 (68.4)	35 (61.4)
Homozygous	4 (26.7)	7 (18.4)	13 (22.8)
Missing genotype status	0	1 (2.6)	2 (3.5)
ARIA status, n (%)			
ARIA-H, present	1 (6.7)	2 (5.3)	6 (10.5)
ARIA-E, present	0	0	0
Missing ARIA status[c]	1 (6.7)	1 (2.6)	0

Unique patients: N=63
- Patients in both Part A and Part B: n=47
- Patients in Part A only: n=6
- Replacement patients in Part B: n=10

ARIA risk factors in study participants across treatment arms and study parts

- *APOE4* carrier: 63.5% (40/63) patients
  - *APOE4* homozygous: 22.2% (14/63) patients
- ARIA-H at study baseline: 9.5% (6/63) patients
  - Cerebral microhemorrhages: 9.5% (6/63) patients
  - Superficial siderosis: 1.6% (1/63) patients
  - Includes patients with moderate and severe ARIA-H

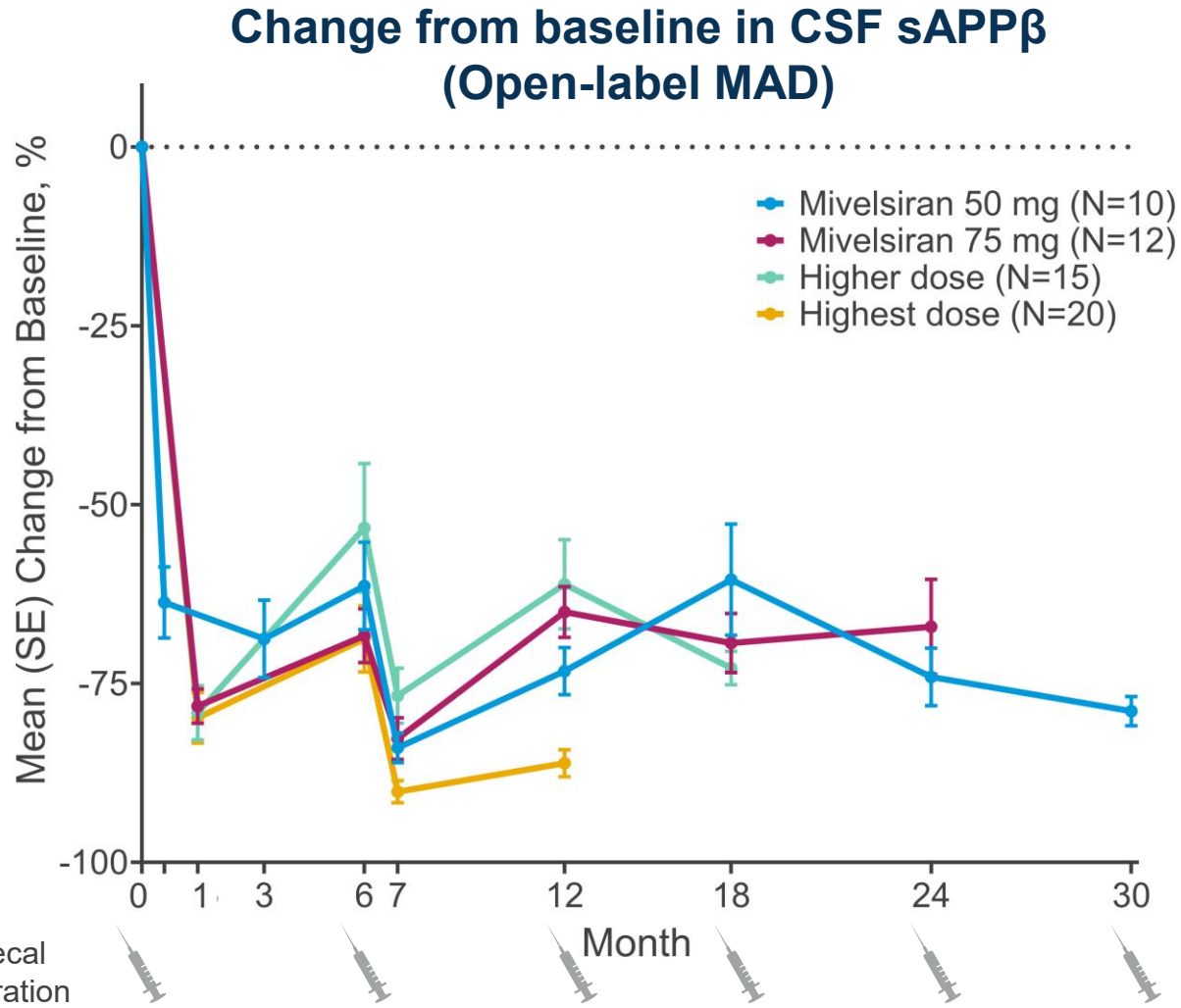
ARIA cases reported at baseline were detected prior to drug exposure

Data shown as of May 21, 2026, [a]MAD part includes patients from SAD part or their replacements. [b]At least one ε4 allele. [c]One patient receiving placebo and one patient receiving mivelsiran in the SAD study part had no MRI scan at baseline so were considered to be missing ARIA data at baseline. *APOE4*, *apolipoprotein E ε4* allele; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities-edema/effusion; ARIA-H, amyloid-related imaging abnormalities-hemorrhage/hemosiderin; 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.

Interim Results: Safety and Pharmacodynamic Changes

Mivelsiran was Well Tolerated with Robust and Durable Reductions in sAPPβ and Aβ42

- Single and multiple doses of mivelsiran were generally well tolerated across all dose levels with up to 30 months of treatment exposure
  - The most common AEs were procedural pain and procedural headache
  - No serious or severe AEs were deemed related to study drug
  - CSF safety labs showed no significant elevations of CSF total protein or white blood cells
- Robust and durable reductions in CSF sAPPβ and Aβ42 were observed across all MAD groups and sustained with dosing Q6M
- Mean maximum reductions in the highest dose group:
  - sAPPβ: 89.9%
  - Aβ42: 70.2%



Data shown as of May 21, 2026. Time points with an n<3 are not plotted.

AE, adverse event; APP, amyloid-beta precursor protein; Aβ, amyloid-beta; CSF, cerebrospinal fluid; MAD, multiple ascending dose; Q6M, once every 6 months; SAD, single ascending dose; SE, standard error; sAPP, soluble amyloid-beta precursor protein.

Interim 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	Double-blind SAD		Open-label MAD
	Placebo N=15	Mivelsiran N=38	Mivelsiran Q6M N=57
New/worsened, post-baseline ARIA-H, n (%)	1 (6.7)[b]	2 (5.3)	4 (7.0)[c]
Site investigator-reported ARIA-H AE, n (%)[d]	1 (6.7)	2 (5.3)[e]	3 (5.3)[e]

MRI Data

- No patients with ARIA-E
- Eight patients with ARIA-H
  - Two with stable ARIA-H from baseline, who were *APOE4/4* and *APOE3/4*
  - Six with new or worsened post-baseline ARIA-H, of whom three were *APOE4/4*

SAD

#1: Placebo[b] (microhemorrhage) – *Baseline ARIA missing, assumed new post baseline*
#2: Mivelsiran 75 mg (microhemorrhage)
#3: Mivelsiran 100 mg (microhemorrhage and superficial siderosis)

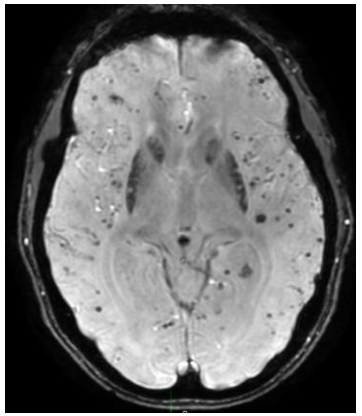
MAD[c]

#4: Mivelsiran 75 mg (superficial siderosis)
#5: Mivelsiran 75 mg (microhemorrhage)
#6: Mivelsiran higher dose (microhemorrhage)
#7: Mivelsiran higher dose (microhemorrhage and superficial siderosis)[c]

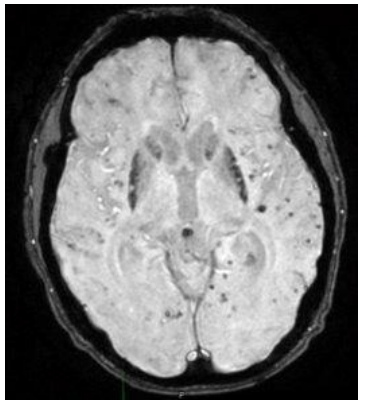
AE Data[d]

- No ARIA-E AEs reported. ARIA-H AEs reported in six patients, totaling eight events
- All ARIA-H AEs reported as mild in severity, and none were deemed related to treatment by the investigators
- No symptoms associated with ARIA-H AEs reported

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 is *APOE4* homozygous and received high doses of mivelsiran in the SAD and MAD parts.

Data shown as of May 21, 2026. [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 non-present at baseline. [c]One patient also had worsened ARIA-H in the SAD part of the study. [d]AEs are reported by principal investigators at their discretion and includes patients with stable ARIA from baseline. [e]One patient had baseline ARIA-H. AE, adverse event; *APOE4*, *apolipoprotein E ε4* allele; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities-edema/effusion; ARIA-H, amyloid-related imaging abnormalities-hemorrhage/hemosiderin; MAD, multiple ascending dose; MRI, magnetic resonance imaging; Q6M, once every 6 months; SAD, single ascending dose; SWI, susceptibility-weighted imaging.

Summary

Scan to view
Country restrictions apply

Interim Data from Phase 1 Study of the Novel Investigational RNAi Therapeutic Mivelsiran Show No Evidence of Increased Risk of ARIA in Patients with EOAD

- Rates of new/worsened ARIA-H were low in both mivelsiran (SAD, 5.3% [2/38]; MAD, 7.0% [4/57]) and placebo arms (SAD, 6.7%, [1/15]), consistent with isolated ARIA-H rates in placebo-treated patients in trials of anti-Aβ mAbs[1,2]
- No ARIA-E has been observed in Phase 1 to date
- Analysis included patients with ARIA risk factors of *APOE4* homozygosity (22.2% [14/63]) and baseline ARIA-H (9.5% [6/63])[3,4]
- All investigator-reported AEs of ARIA-H were mild in severity, and deemed not related to mivelsiran
- Low occurrence of ARIA, in a sample including patients with ARIA risk factors, supports use of mivelsiran in a broad range of patients with EOAD with potential to forgo complex safety monitoring
- Mivelsiran is also being investigated in patients with CAA in the ongoing Phase 2 cAPPricorn-1 study (NCT06393712) and in individuals with Down syndrome-associated AD in the Phase 2 APPlauDS trial

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in this study

AE, adverse event; AD, Alzheimer's disease; APOE4, *apolipoprotein E ε4* allele; ARIA, amyloid-related imaging abnormalities; ARIA-E, amyloid-related imaging abnormalities-edema/effusion; ARIA-H, amyloid-related imaging abnormalities-hemorrhage/hemosiderin; CAA, cerebral amyloid angiopathy; EOAD, early-onset Alzheimer's disease; mAb, monoclonal antibody; MAD, multiple ascending dose; RNAi, RNA interference; SAD, single ascending dose.

1. van Dyck CH *et al. N Engl J Med* 2023;388:9–21. 2. Sims JR *et al. JAMA* 2023;330:512–27. 3. Rabinovici GD *et al. J Prev Alzheimers Dis* 2025;12;12:100150. 4. Cummings J *et al. J Prev Alzheimers Dis* 2023;10:362–77.