Baseline Characteristics in cAPPricorn-1, a Phase 2 Study in Cerebral Amyloid Angiopathy

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Disclosure for Neal S Parikh, MD

Conflict	Disclosure
Employee and 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 health authority, and the safety and efficacy of mivelsiran have not been established.

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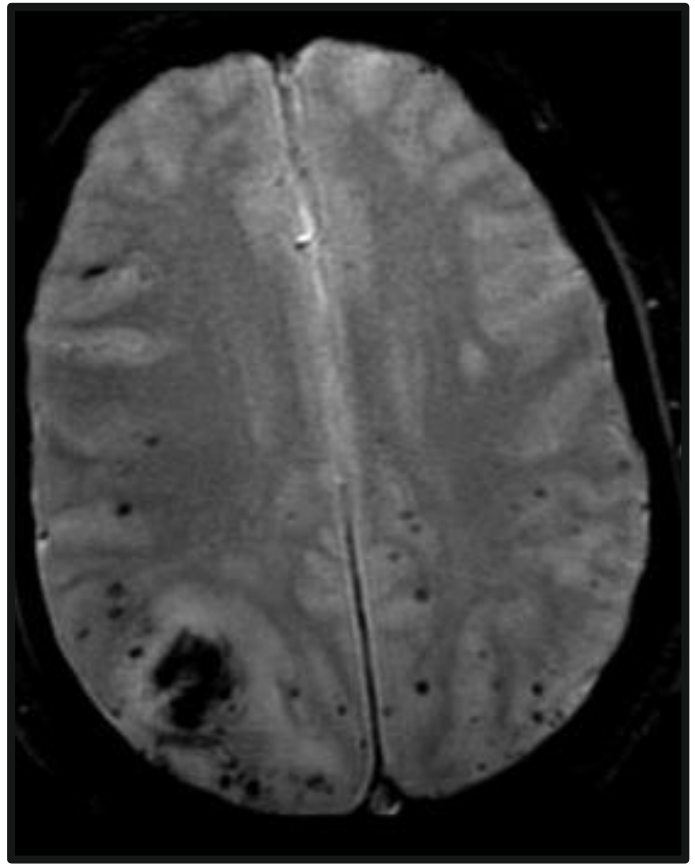
Pursuing Therapeutic Progress for Individuals with CAA

- Cerebral amyloid angiopathy (CAA) can be sporadic or hereditary[1]
- Individuals with CAA can present with intracerebral hemorrhage (ICH), convexity subarachnoid hemorrhage (cSAH), cognitive impairment, dementia, and transient focal neurological episodes[1,2]
- Imaging manifestations include hemorrhagic and nonhemorrhagic findings[2]
- CAA is characterized by the accumulation of amyloid precursor protein (APP) cleavage products, predominantly amyloid-beta 1-40 (Aβ40), in the cerebrovasculature[1,2]
- Mivelsiran is an investigational RNAi therapeutic that targets APP, the precursor to all Aβ peptides[3]
- Alnylam has initiated a Phase 2 study of mivelsiran, a first-in-class approach for treating individuals with CAA[4]

Lobar Hemorrhagic Lesions in an Individual Diagnosed with CAA[5,a]



T2-weighted MRI image

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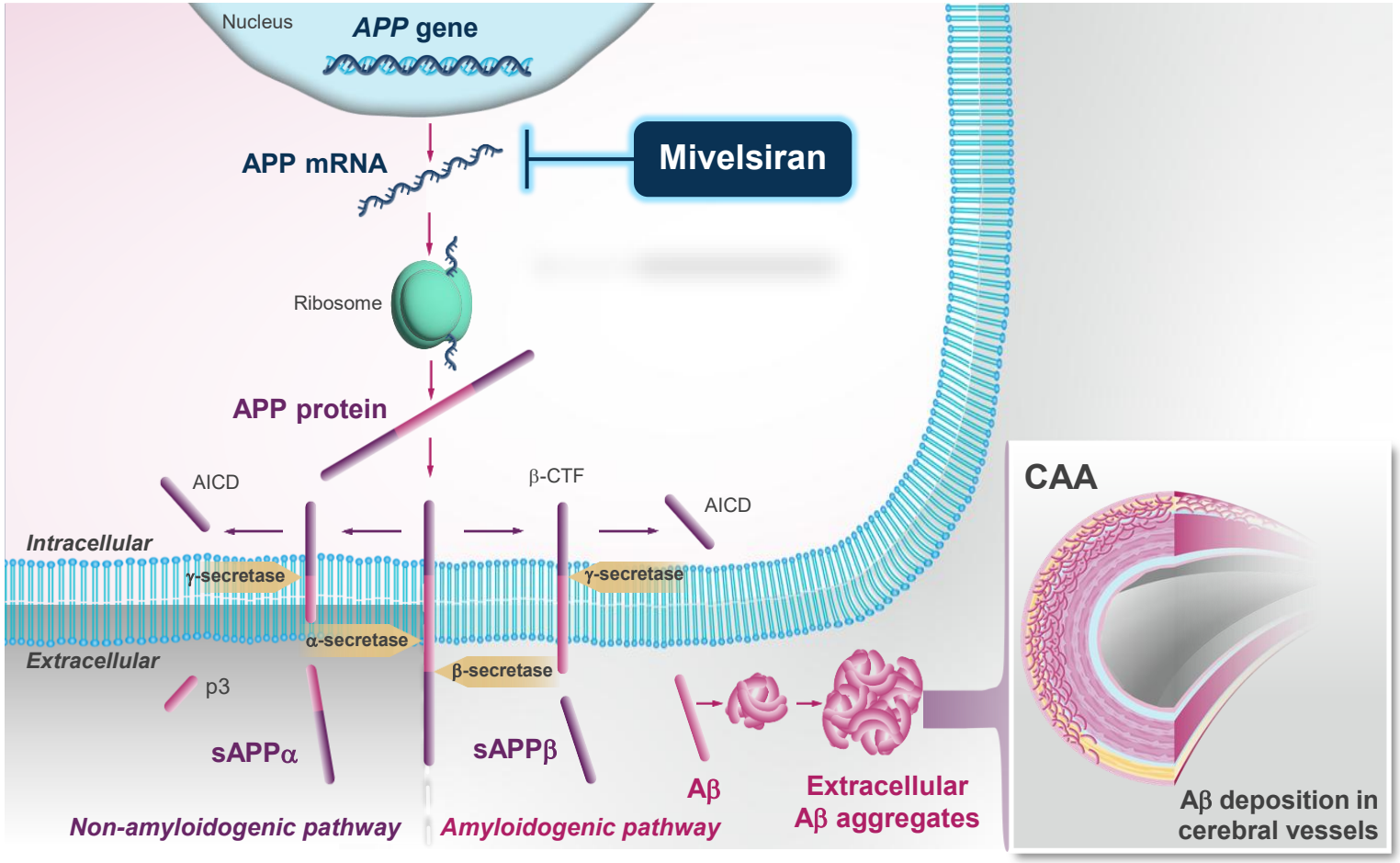
Aβ, amyloid-beta; APP, amyloid precursor protein; CAA, cerebral amyloid angiopathy; cSAH, convexity subarachnoid hemorrhage; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; RNAi, RNA interference

1. Banerjee G *et al. J Neurol Neurosurg Psychiatry* 2017;88:982–94. 2. Greenberg SM *et al. Nat Rev Neurol* 2020;16:30–42. 3. Pfundstein G *et al. Front Cell Dev Biol* 2022;10:969547. 4. ClinicalTrials.gov: NCT06393712. 5. Vilela P, Wiesmann M. In: Hodler J *et al.*, editors. *Diseases of the Brain, Head and Neck, Spine 2020–2023:* Springer, 2020

Mivelsiran Is a Novel, Investigational RNAi Therapeutic Designed to Target APP and Thereby Reduce Aβ Production

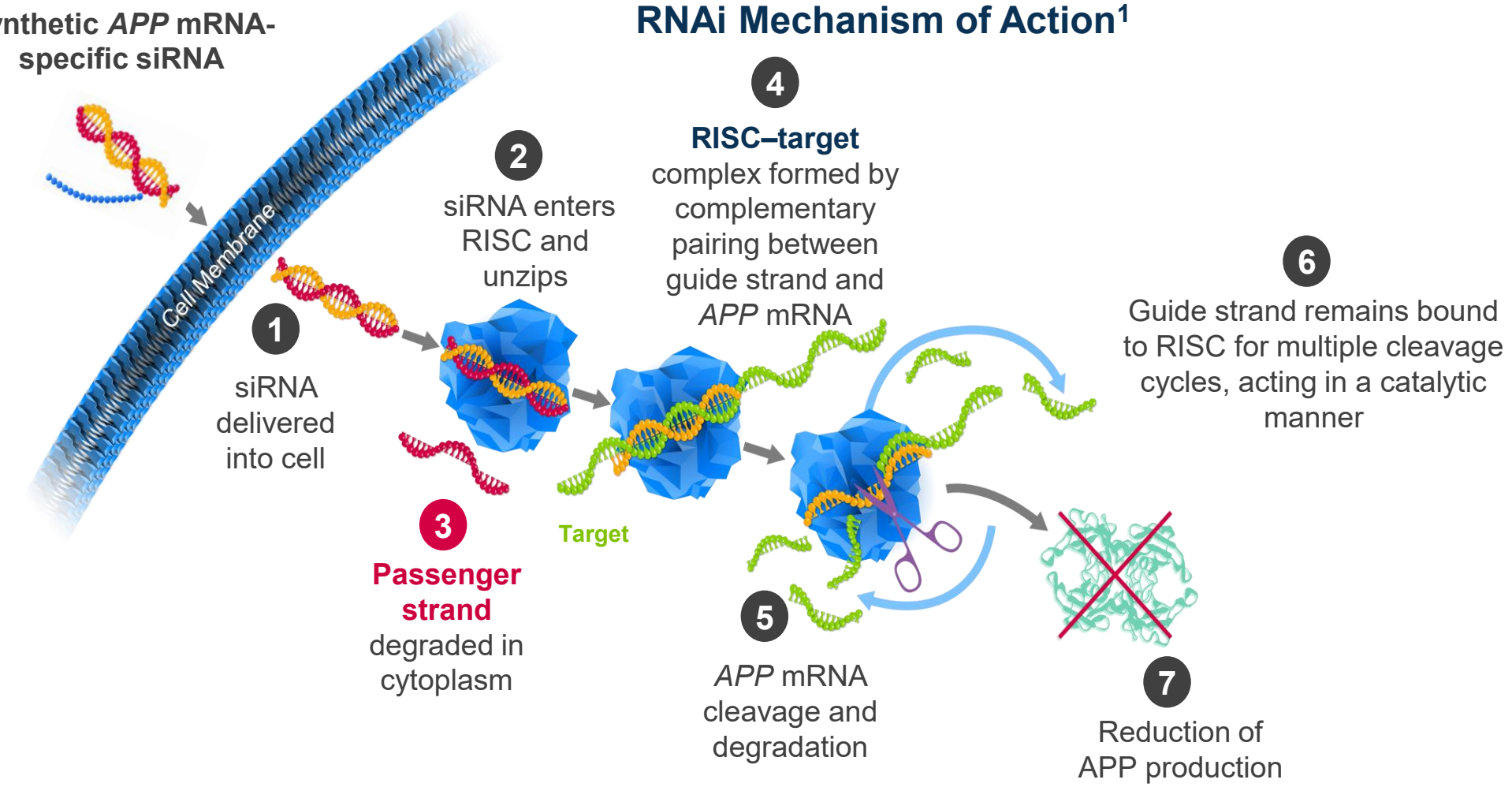
- Reducing Aβ by lowering APP expression reduces the substrate for new amyloid deposition[1,2]
- Decreasing vascular Aβ deposition in CAA may preserve vascular reactivity and integrity, and reduce the risk of hemorrhage and ischemia[3–5]
- Mivelsiran is also in development for the treatment of early-onset Alzheimer's disease[6] and Down syndrome-associated Alzheimer's disease[7]



Aβ, amyloid-beta; AICD, APP intracellular domain; APP, amyloid precursor protein; β-CTF, C-terminal fragment beta; CAA, cerebral amyloid angiopathy; mRNA, messenger RNA; p3, p3 peptide; RNAi, RNA interference; sAPP, soluble APP; siRNA, small interfering RNA. 1. Cohen S *et al. Alzheimer's Association International Conference (AAIC)*, July 16–20, 2023, Amsterdam, Netherlands. 2. Zhang Y *et al. Signal Transduct Target Ther* 2023;8:248. 3. Biffi A, Greenberg SM. *J Clin Neurol* 2011;7:1-9. 4. Smith EE *et al. Stroke*. 2009;40:2601–6. 5. Hartz AMS *et al. Stroke* 2011;43:514–23. 6. ClinicalTrials.gov: NCT05231785. 7. ClinicalTrials.gov: NCT07636811.

RNA Interference Therapeutics Harness an Endogenous Process to Lower Protein Production

Conjugation to a C16 lipid chain facilitates cellular uptake and enables CNS delivery[2]



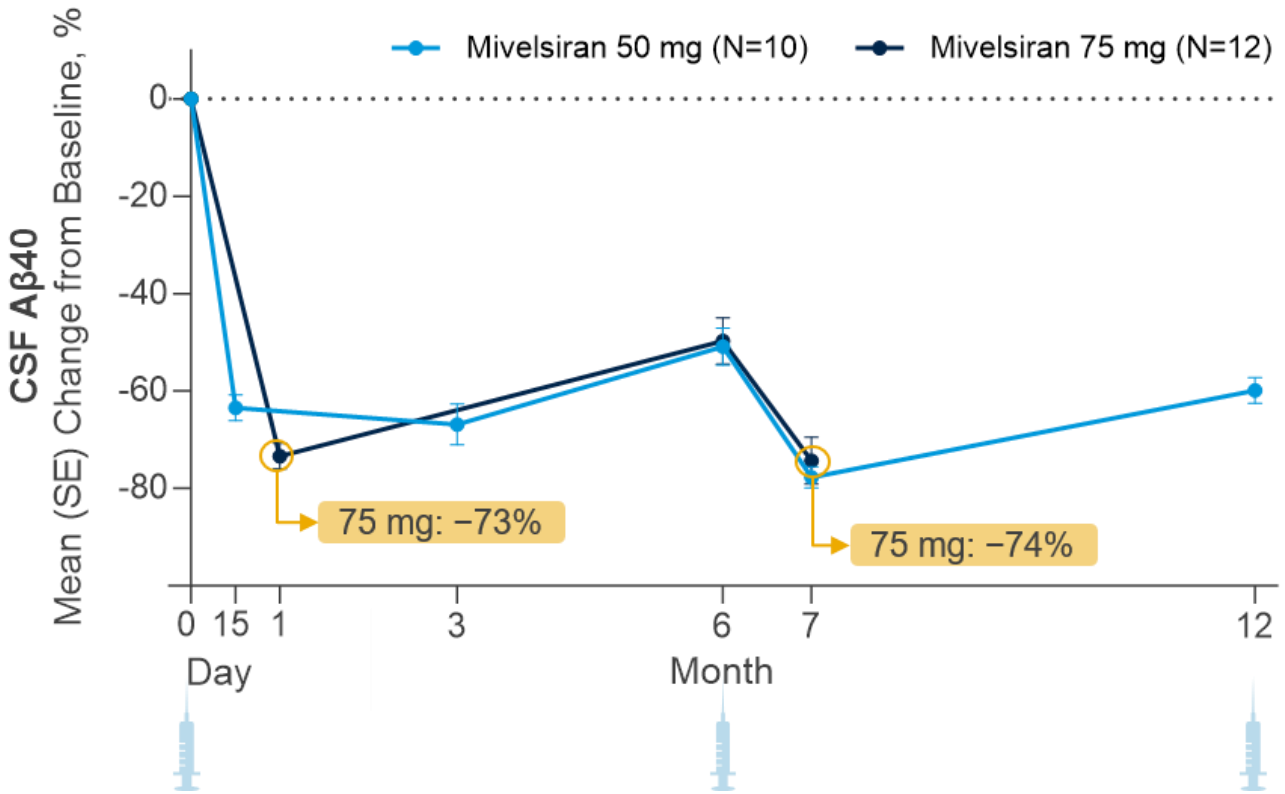
APP, amyloid precursor protein; C16, 2'-O-hexadecyl; CNS, central nervous system; RISC, RNA-induced silencing complex; RNAi, RNA interference; siRNA, small interfering RNA.

Image credit: Alnylam Pharmaceuticals. Figure adapted from data published in Jadhav V *et al. Nat Biotechnol* 2024;42:394–405.

1. Jadhav V *et al. Nat Biotechnol* 2024;42:394–405. 2. Brown KM *et al. Nat Biotechnol* 2022;40:1500–8.

Mivelsiran Was Associated with Marked Reduction in Aβ40 in a Phase 1 Trial in Early-Onset Alzheimer's Disease

- Deep, sustained reductions in CSF Aβ40 were observed following both a single dose (data not shown) and multiple doses of mivelsiran[1]



Data shown as of May 15, 2025. Time points with n<3 are not plotted.

Aβ, amyloid-beta; Aβ40, Aβ peptide length 40 amino acids; CSF, cerebrospinal fluid; SE, standard error.

1. Cohen S *et al. Alzheimer's Association International Conference (AAIC)*, July 27–31, 2025, Toronto, Canada. ClinicalTrials.gov: NCT05231785.

cAPPricorn-1: A Phase 2, Double-Blind, Placebo-Controlled Study of Mivelsiran in Individuals with CAA

cAPPricorn-1

Study Population

Sporadic CAA Cohort

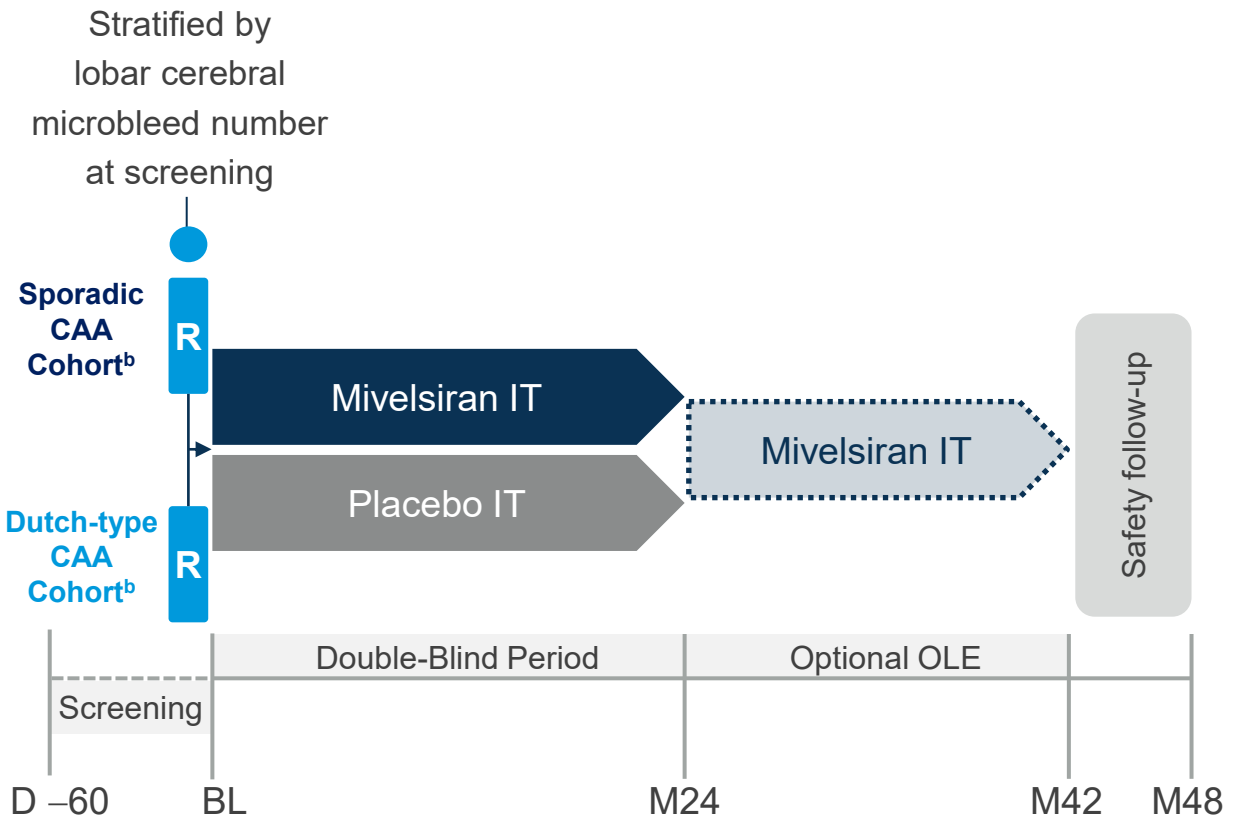
- Age ≥50 years
- Probable CAA or probable CAA with pathology[a]
- >50% with prior CAA-related hemorrhagic stroke, e.g., ICH

Dutch-type CAA Cohort

- Age ≥30 years
- Documented E693Q *APP* variant

Key Exclusions (both cohorts)

- Moderate or severe stage AD or severe CI
- Previous ICH with onset <90 days prior to randomization
- History of CAAri or ABRA



Endpoints

Primary Endpoint

- Annualized rate of new lobar cerebral microbleeds[c]

Selected Secondary Endpoints

- Global rank endpoint
- Hemorrhagic disease progression
- Vascular reactivity
- PD: CSF sAPPα and sAPPβ

Selected Exploratory Endpoint

- Nonhemorrhagic disease progression

Safety

- Frequency of adverse events

ClinicalTrials.gov: NCT06393712

[a]As adjudicated by adapted Boston Criteria version 2.0; [b]Sporadic and Dutch-type CAA cohorts will be analyzed separately. [c]Based on blinded, centrally adjudicated analysis of magnetic resonance imaging

ABRA, amyloid-beta-related angiitis; AD, Alzheimer's disease; APP, amyloid precursor protein; BL, baseline; CAA, cerebral amyloid angiopathy; CAAri, cerebral amyloid angiopathy-related inflammation; CI, cognitive impairment; cSAH, convexity subarachnoid hemorrhage; CSF, cerebrospinal fluid; D, day; ICH, intracerebral hemorrhage; IT, intrathecal; M, month; OLE, open-label extension; PD, pharmacodynamic; R, randomization; sAPP, soluble amyloid precursor protein

Participant Recruitment

sCAA Cohort

- Participants were enrolled at 44 sites across 6 countries

- Enrollment took place between:
  - May 17, 2024 (first participant screened)
  - March 16, 2026 (last participant enrolled)

Screened
N=318

Screen failures: n=148
Reasons for screen failure[a]
- Did not meet eligibility criteria: n=143
  - Did not meet Boston Criteria 2.0: n=51
  - Did not meet additional imaging criteria: n=26
  - CDR Global Score ≥2.0 or MMSE score <20: n=16
  - Use of investigational drug: n=7
  - Use of prohibited medication: n=6
- Physician decision: n=1
- Withdrawal by participant: n=5
- Other or missing: n=5

Randomized
n=170

Received treatment
n=168

[a]Participants may have had more than one reason for screen failure

CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; sCAA, sporadic cerebral amyloid angiopathy

Baseline Demographics and Comorbidities

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Characteristic	sCAA (n=168)
Age at informed consent, years, mean (SD)	71.8 (6.3)
Sex, male, n (%)	107 (63.7)
Race, n (%)[a]	
Asian	1 (0.6)
Black or African American	3 (1.8)
White	160 (95.2)
Ethnicity, n (%)[a]	
Hispanic or Latino	2 (1.2)
Not Hispanic or Latino	162 (96.4)
Comorbidities, n (%)	
Hypertension	111 (66.1)
Hyperlipidemia/dyslipidemia	96 (57.1)
Coronary artery disease[b]	19 (11.3)
Atrial fibrillation/atrial flutter	14 (8.3)
Diabetes	11 (6.5)
Receiving acetylsalicylic acid, n (%)	25 (14.9)
Systolic/diastolic blood pressure, mmHg, mean (SD)	127.7 (13.4) / 73.7 (7.9)

[a]Missing, not reported, or other n=4 (2.4%). [b]Defined as medical history of coronary artery disease, myocardial infarction, percutaneous coronary intervention, or coronary artery bypass grafting

sCAA, sporadic cerebral amyloid angiopathy; SD, standard deviation

Baseline Characteristics (1/2)

Clinical Presentation and Cognitive Parameters

cAPPricorn-1

Clinical Presentation/Cognitive Parameter	sCAA (n=168)
Prior History of CAA-related clinically symptomatic hemorrhagic stroke,[a] n (%) Primary, non-traumatic ICH, n (%)[b] Acute cSAH, n (%)[b]	93 (55.4) 84 (50.0) 28 (16.7)
Transient focal neurological episodes,[c] n (%)	48 (28.6)
Cognitive impairment or dementia,[c] n (%)	123 (73.2)
CDR Global Score, n (%) 0 0.5 1	n=167 39 (23.4) 111 (66.5) 17 (10.2)
MMSE score, median (IQR)	28.0 (25.5–29.0)

[a]This represents participants with symptomatic lobar ICH and symptomatic acute convexity subarachnoid hemorrhage. [b]Some participants had both primary, non-traumatic ICH and acute cSAH. [c]Acute transient focal neurological episodes and cognitive impairment/dementia are not mutually exclusive

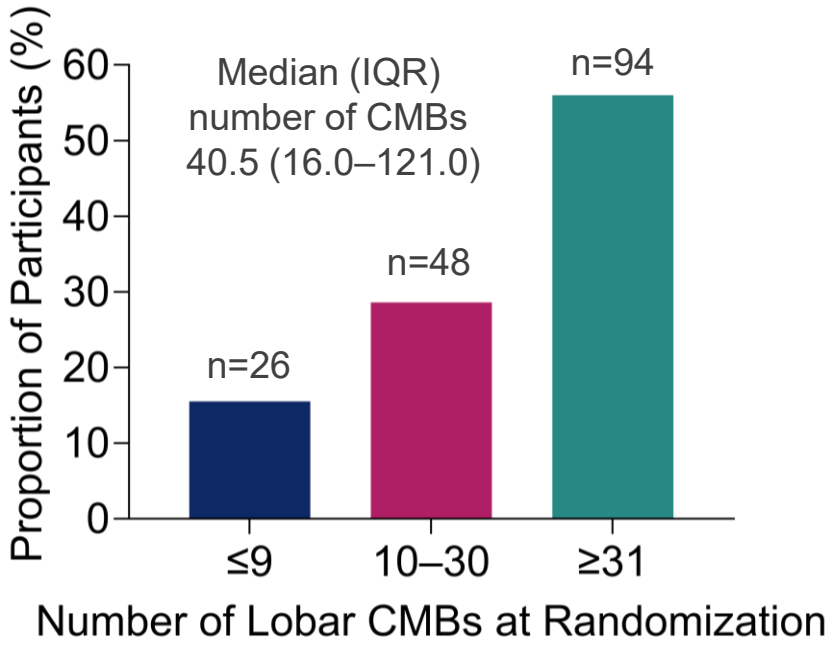
CAA, cerebral amyloid angiopathy; CDR, Clinical Dementia Rating; cSAH, convexity subarachnoid hemorrhage; ICH, intracerebral hemorrhage; IQR, interquartile range; MMSE, Mini-Mental State Examination; sCAA, sporadic cerebral amyloid angiopathy; SD, standard deviation.

Baseline Characteristics (2/2)

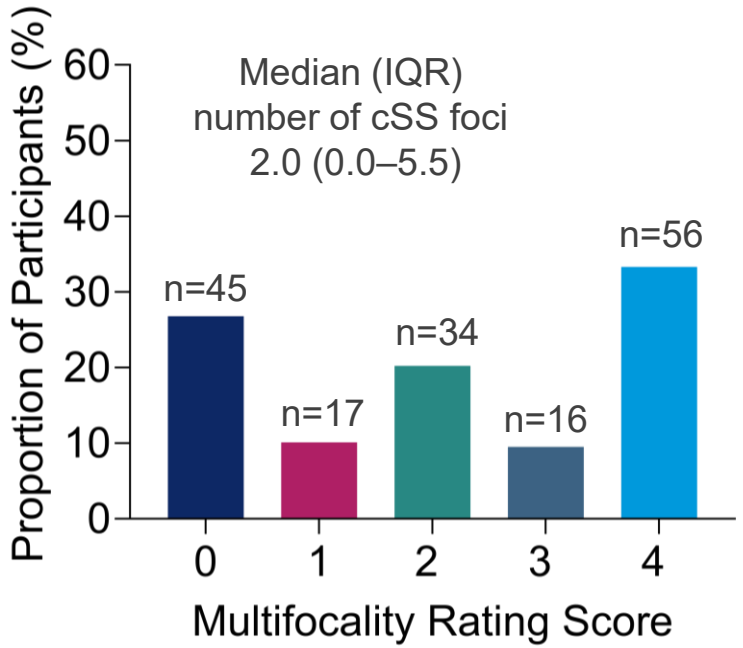
Imaging Parameters (N=168)

cAPPricorn-1

Lobar CMBs[a]



cSS Multifocality Rating Scale[a]



Hemorrhagic lesions were confirmed by blinded, centrally read T2–weighted susceptibility–weighted imaging*

[a]From baseline Day1 efficacy/safety imaging data

CAA, cerebral amyloid angiopathy; CMB, cerebral microbleed; cSS, cortical superficial siderosis; ICH, intracerebral hemorrhage; IQR, interquartile range; sCAA, sporadic cerebral amyloid angiopathy

Scan to view
Country restrictions apply

Summary

- Enrollment of the sCAA cohort in cAPPricorn-1 is complete
  - Enrolled participants included those with prior CAA-related hemorrhagic stroke, cognitive impairment and/or TFNEs, and had a high burden of hemorrhagic imaging features at baseline
  - The enrolled population reflects the broad spectrum of CAA-related clinical presentations
- The Dutch-type CAA cohort has recently completed enrollment; baseline characteristics for this cohort will be summarized in a future presentation
- Initial results from this study are expected in 2028

CAA, cerebral amyloid angiopathy; sCAA, sporadic cerebral amyloid angiopathy; TFNE, transient focal neurological episode

Thank you to the participants, their families, investigators, study staff, collaborators, and the Global Steering Committee for their support and participation in the ongoing cAPPricorn-1 study