Design and Rationale of cAPPricorn-1, a Phase 2 Study of Mivelsiran in Patients with Cerebral Amyloid Angiopathy

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Disclosures

Presenter: Jin-Moo Lee, MD, PhD

Conflict	Disclosure
Research Support	NIH R01NS120481, R37NS110699, UFNS125512, RF1NS139970, R01NS120481, RF1AG079503
Unpaid Advisory Committee Member	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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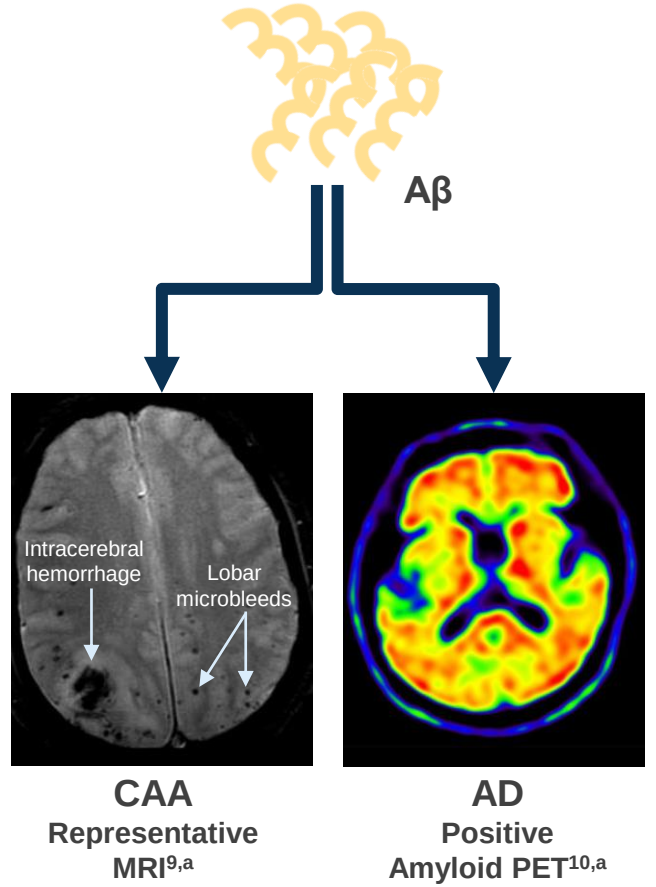
CAA and AD are Distinct but Related Diseases Linked by Aβ

In CAA, Progressive Aβ Accumulation Leads to Vascular Disease, Debilitating Strokes, and Cognitive Decline

- Cerebral amyloid angiopathy (CAA) is characterized by progressive deposition of Aβ in cerebral blood vessels[1]
- Manifestations include intracerebral hemorrhage, lobar microbleeds, and cortical superficial siderosis[1]
- CAA is often comorbid with Alzheimer's disease (AD), but also independently contributes to cognitive decline[2]
- Although CAA is most often sporadic, aggressive hereditary forms exist (e.g., Dutch-type)[1,3,4]
- There are no disease-modifying therapies for CAA[5]
  - Patients with a high number of lesions suggestive of CAA were excluded from AD clinical trials of antibody-based therapies targeting Aβ due to increased risk of intracerebral hemorrhage[6–8]



[a]Available through Creative Commons Attribution License, image labels added.

Aβ, amyloid beta; AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy; MRI, magnetic resonance imaging; PET, positron emission tomography.

1. Kozberg MG *et al. Int J Stroke* 2021;16:356–69. 2. Boyle PA *et al. Neurology* 2015;85:1930–6. 3. Chatterjee P *et al. J Alzheimers Dis* 2021;79:895–903. 4. Biffi A, Greenberg SM *J Clin Neurol* 2011;7:1–9. 5. Cozza M *et al. J Neurol Sci* 2023;454:120866. 6. Cummings J *et al. J Prev Alz Dis* 2023;3:362–77. 7. van Dyck CH *et al. N Engl J Med* 2023;388:Suppl. 8. Mintun *MA et al. N Engl J Med* 2021;384:Suppl. 9. Vilela P, Wiesmann M. Nontraumatic Intracranial Hemorrhage. In: Hodler J *et al.,* editors. Diseases of the Brain, Head and Neck, Spine 2020–23. electronic: IDKD Springer Series. Springer; 2020. 10. Chang Y *et al. Front Neurosci* 2020;14:745.

Aβ Precursor Protein (APP) is the Source of Aβ

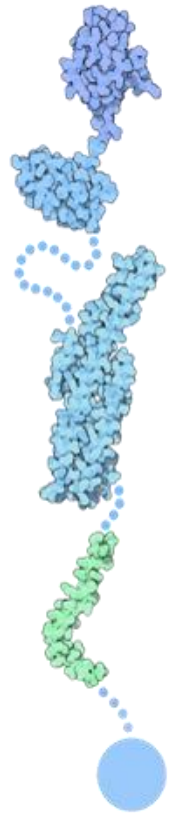
Aβ is Derived from APP and is Deposited in Vessels

- APP is a transmembrane protein that is cleaved to produce a variety of peptides, including Aβ[1]
- Vascular amyloid deposits are largely composed of Aβ40, and parenchymal plaques are mostly comprised of Aβ42[2,3]

APP is a Genetically Validated Target for CAA

- APP variants are associated with hereditary CAA[2]
  - Dutch-type, Iowa-type, and Italian-type variants cause early, aggressive forms of CAA with varying degrees of cognitive impairment and ICH[3]
- Having more than two copies of the *APP* gene can also result in early-onset CAA[3,4]
  - CAA pathology is seen in patients with trisomy 21, where the chromosome carrying *APP* is present in three copies[5,6]
  - No disease characteristics are seen in people with partial trisomy 21 who do not have increased *APP* copies[7]

APP Structure[8,a]



Lowering APP expression may reduce Aβ accumulation and downstream clinical consequences of CAA[9]

[a]Available through Creative Commons Attribution License.

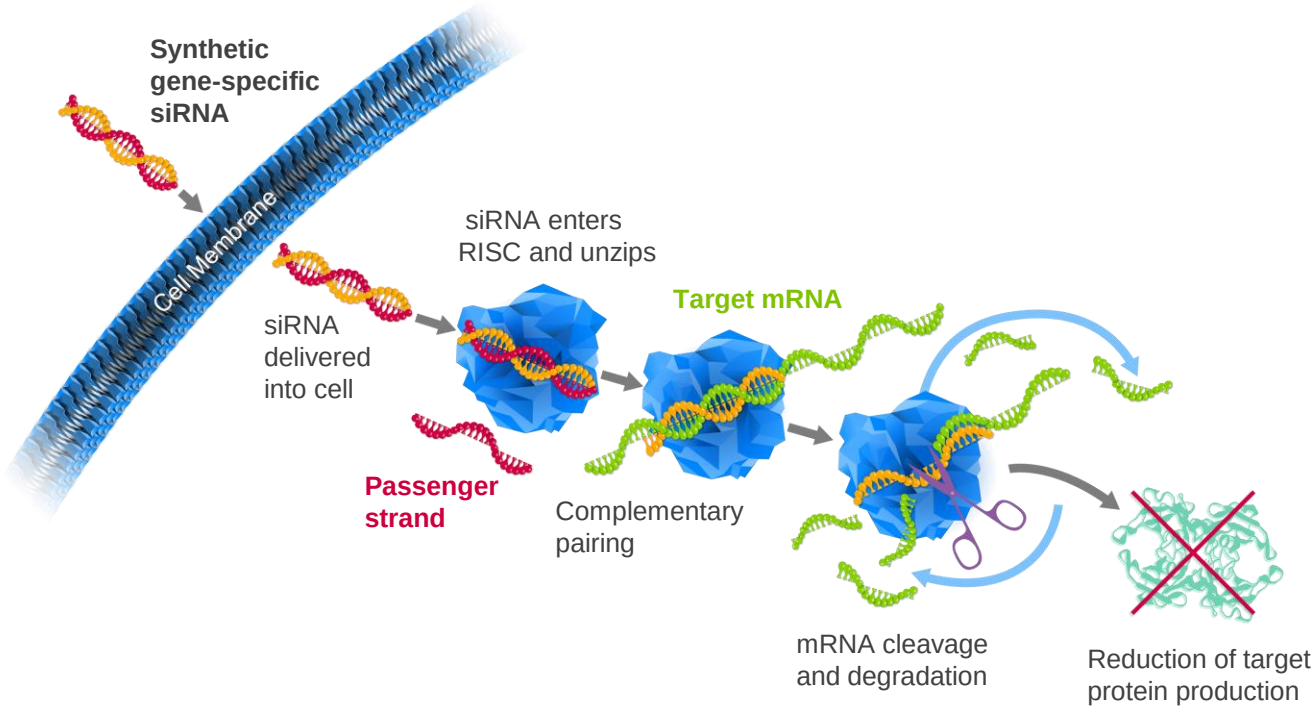
Aβ, amyloid beta; Aβ40, Aβ peptide length 40 amino acids; Aβ42, Aβ peptide length 42 amino acids; APP, Aβ precursor protein; CAA, cerebral amyloid angiopathy; ICH, intracerebral hemorrhage.

1. O'Brien RJ, Wong PC *Annu Rev Neurosci* 2011;34:185–204. 2. Greenberg SM *et al. Nat Rev Neurol* 2020;16:30–42. 3. Biffi A, Greenberg SM *J Clin Neurol* 2011;7:1–9. 4. Grangeon L *et al. Neurol Genet* 2021;7:e609. 5. Cabrejo L *et al. Brain* 2006;129:2966–76. 6. Head E *et al. Acta Neuropathol Commun* 2017;5:93. 7. Doran E *et al. J Alzheimers Dis* 2017;56:459–70. 8. Goodsell DS and the Protein Data Bank [online] 2006. Available from: https://pdb101.rcsb.org/motm/79 (Accessed October 15, 2024). 9. Sirisi S *et al. Alzheimers Res Ther* 2024;16:144.

RNA Interference Harnesses an Endogenous Process to Lower Expression of Disease-Associated Proteins Such as APP

- RNA interference (RNAi) is a natural process that regulates gene expression[1]
- Synthetic small interfering RNAs (siRNAs) are designed to specifically degrade mRNA encoding a disease-associated protein[2,3]
- RNAi works catalytically, repeatedly reducing target protein expression while leaving DNA intact[2,3]

RNAi Mechanism of Action[3,a]



[a]Image created by Alnylam Pharmaceuticals from data published in Jadhav *et al.* 2024[3]

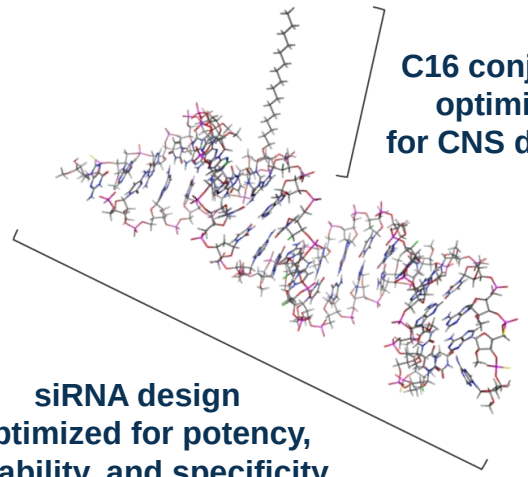
Aβ, amyloid beta; APP, Aβ precursor protein; mRNA, messenger RNA; RISC, RNA-induced silencing complex; RNAi, RNA interference; siRNA, small interfering RNA.

1. Niemietz C *et al. Molecules* 2015;20:17944–75. 2. Ranasinghe R *et al. Br J Pharmacol* 2023;180:2697–720. 3. Jadhav V *et al. Nature Biotechnol* 2024;42:394–405.

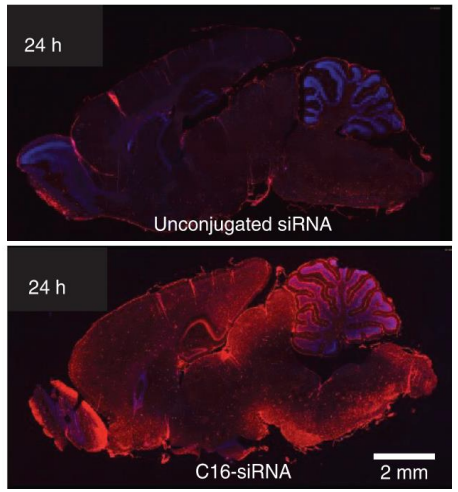
Intrathecal Delivery of C16-Conjugated siRNA Enables CNS Targeting in Preclinical Models, Supporting Clinical Development

- In preclinical models, intrathecally administered C16-conjugated siRNA enabled distribution throughout the CNS and durable target engagement in the deep brain,[1] supporting development of an investigational RNAi therapeutic

C16-Conjugated siRNA

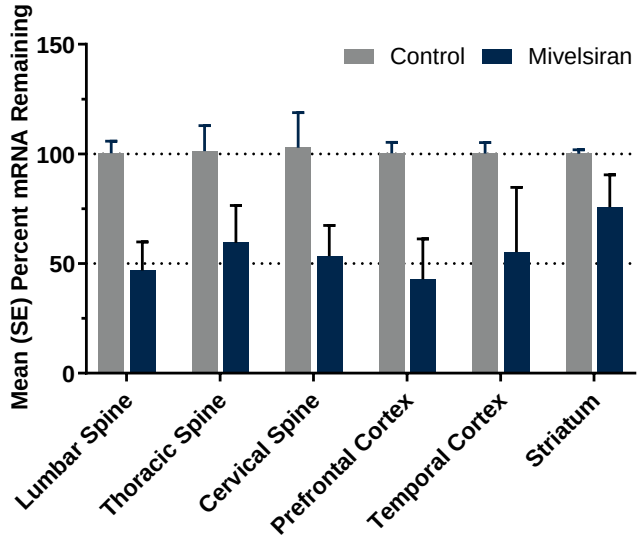


Biodistribution with Unconjugated versus C16-Conjugated siRNA[1]



24-hour after a single IT dose in rats
Red color denotes anti-siRNA antibody

APP mRNA Expression Lowered Throughout Spine and Brain[2]



3 months after a single IT dose in NHPs

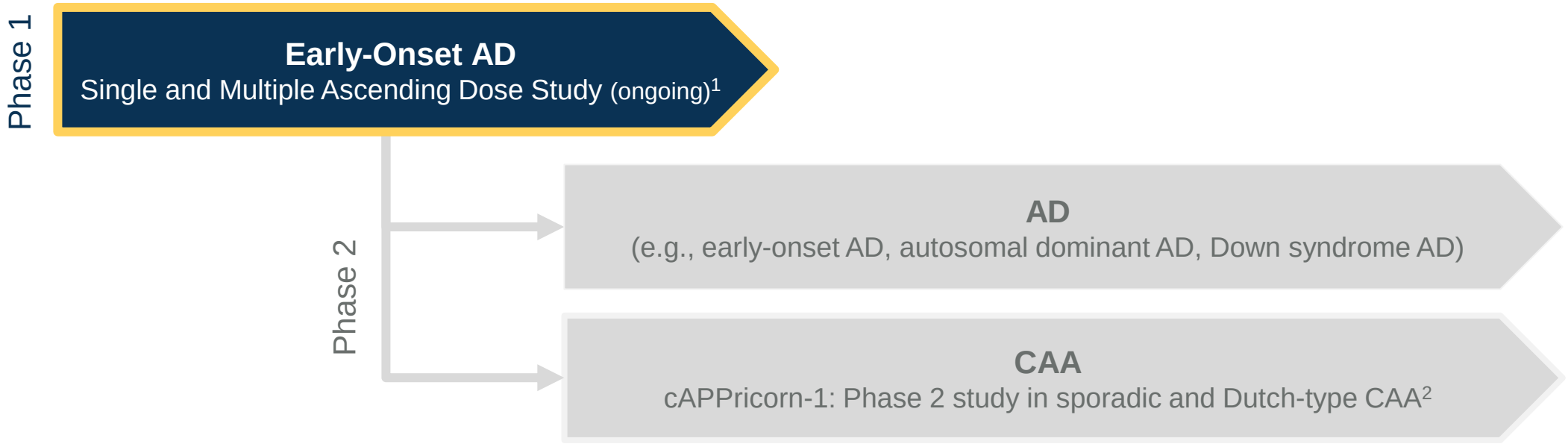
Mivelsiran is the first C16-conjugated siRNA to enter Phase 1 and Phase 2 development

Aβ, amyloid beta; APP, Aβ precursor protein; C16, 2'-O-hexadecyl; CNS, central nervous system; h, hour; IT, intrathecal; mRNA, messenger RNA; NHP, non-human primate; SE, standard error; siRNA, small interfering RNA.

1. Brown KM *et al. Nat Biotechnol* 2022;40:1500–08. 2. Kurz J *et al.* Oral presentation presented at the Alzheimer's & Parkinson's Diseases Conference (ADPD), March 28–April 1, 2023, Gothenburg, Sweden.

Mivelsiran is an Investigational RNAi Therapeutic Designed to Reduce APP Production in the CNS

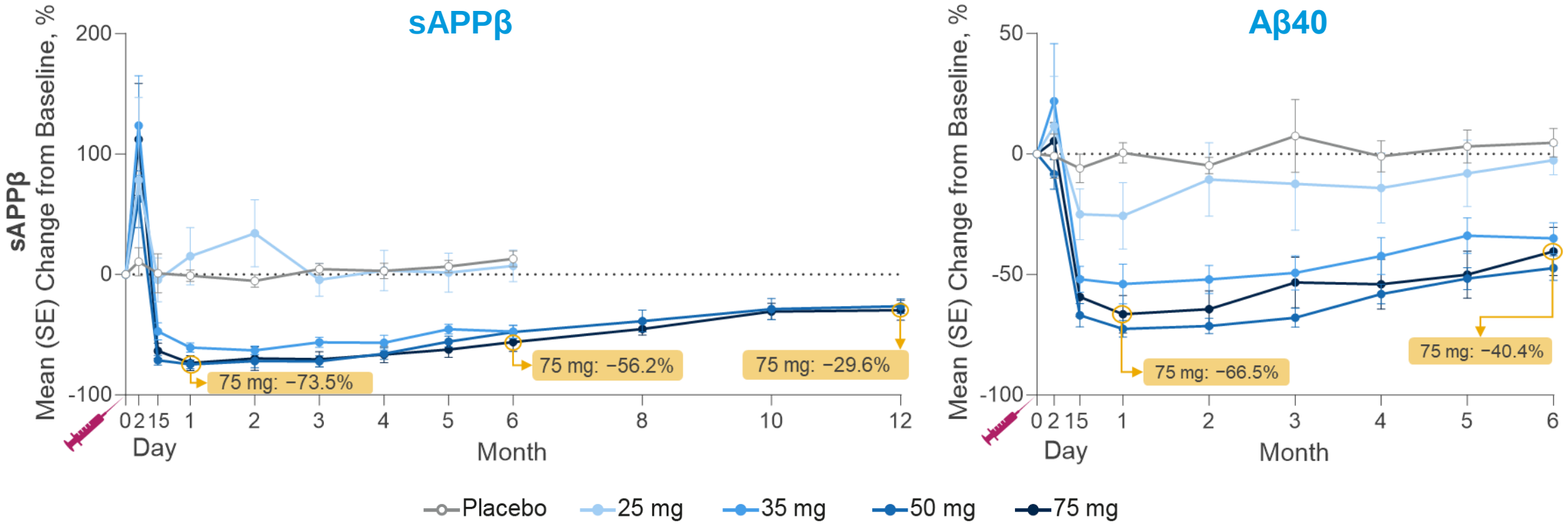
Mivelsiran is Being Evaluated in AD and in CAA



Aβ, amyloid beta; AD, Alzheimer's disease; APP, Aβ precursor protein; CAA, cerebral amyloid angiopathy; CNS, central nervous system; RNAi, RNA interference.

1. ClinicalTrials.gov. NCT05231785. Available from: https://clinicaltrials.gov/study/NCT05231785 (Accessed Oct 15, 2024). 2. ClinicalTrials.gov. NCT06393712. Available from: https://clinicaltrials.gov/study/NCT06393712 (Accessed Oct 15, 2024).

Single Doses of Mivelsiran Reduced CSF sAPPβ and Aβ40 in a Phase 1 Study of Patients With Early-Onset AD[a,1]



Mivelsiran has shown robust and durable reductions of amyloidogenic proteins in early-onset AD, supporting its further evaluation in CAA[1,2]

NCT05231785. Data shown as of August 2, 2024. [a]Similar reductions were observed for CSF sAPPα and Aβ42 levels.[1]
Aβ, amyloid beta; Aβ40, Aβ peptide length 40 amino acids; AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy; CSF, cerebrospinal fluid; sAPP, soluble Aβ precursor protein; SE, standard error.
1. Deering R *et al*. Oral Presentation at the International Cerebral Amyloid Angiopathy (ICAA) Conference, October 15–17, 2024, Munich, Germany. 2. Kozberg MG *et al. Int J Stroke* 2021;16:356–69.

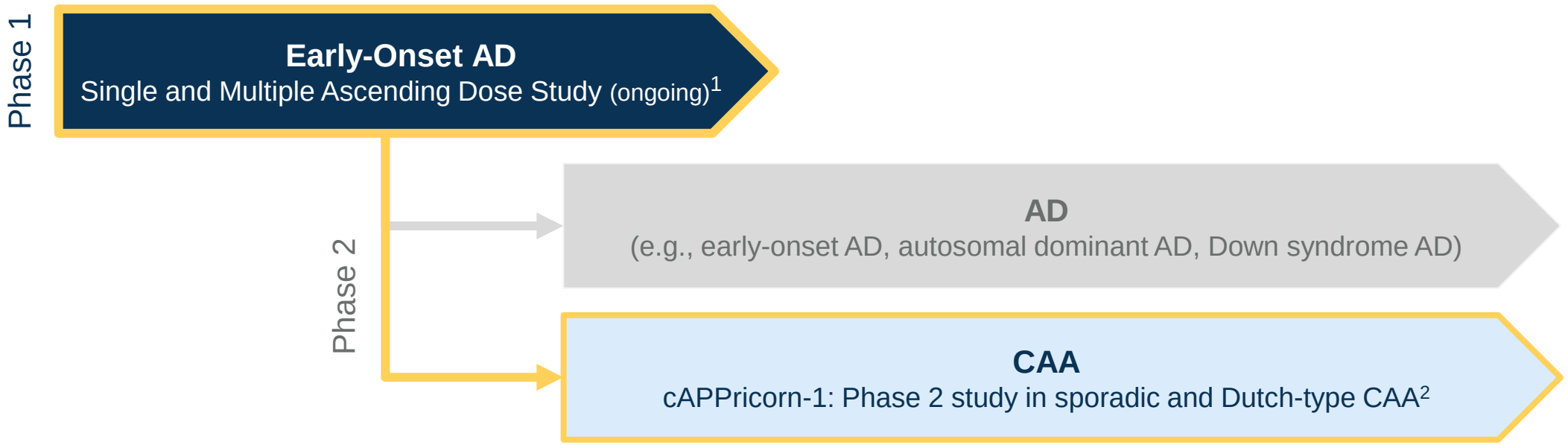
Phase 1 Safety Profile in Patients with Early-Onset AD Supports Continued Development of Mivelsiran[1]

Patients with events	Mivelsiran 25 mg or placebo (N=6, PY=6.9)	Mivelsiran 35 mg or placebo (N=8, PY=4.8)	Mivelsiran 50 mg or placebo (N=8, PY=7.6)	Mivelsiran 75 mg or placebo (N=14, PY=13.5)
Time from randomization, months, mean (SD)	13.89 (1.46)	7.27 (0.79)	11.45 (3.66)	11.60 (2.86)
At least one AE, n (%)	6 (100.0)	8 (100.0)	7 (87.5)	14 (100.0)
Related to study drug	0	0	1 (12.5)	2 (14.3)
Related to LP	4 (66.7)	7 (87.5)	6 (75.0)	7 (50.0)
At least one moderate AE, n (%)	4 (66.7)	4 (50.0)	5 (62.5)	10 (71.4)
At least one severe AE, n (%)	0	0	0	1 (7.1)[a]
At least one serious AE, n (%)	0	0	0	1 (7.1)[a]
Deaths, n (%)	0	0	0	1 (7.1)[a]

- Most adverse events were mild or moderate in severity and nonserious
- AEs deemed related to study drug were reported in three patients; all events resolved
  - Post-LP headache (n=3), post-LP nausea (n=1), post-LP vomiting (n=1), post-LP neck pain (n=1), vomiting due to LP (n=1), and lymphocytopenia (n=1)
- One serious and severe AE of acute pancreatitis deemed unrelated to the study drug was fatal

NCT05231785. Data shown as of April 18, 2024. [a]One AE of acute pancreatitis.
AD, Alzheimer's disease; AE, adverse event; LP, lumbar puncture; PY, patient-years; SD, standard deviation.
1. Deering R *et al*. Oral Presentation at the International Cerebral Amyloid Angiopathy (ICAA) Conference, October 15–17, 2024, Munich, Germany.

Mivelsiran Phase 1 and Phase 2 Development Overview



AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy.

1. ClinicalTrials.gov. NCT05231785. Available from: https://clinicaltrials.gov/study/NCT05231785 (Accessed Oct 15, 2024). 2. ClinicalTrials.gov. NCT06393712. Available from: https://clinicaltrials.gov/study/NCT06393712 (Accessed Oct 15, 2024).

cAPPricorn-1 is a Phase 2 Study Evaluating Mivelsiran in Patients with Sporadic or Hereditary CAA

cAPPricorn-1

Sporadic CAA

Rationale:
- High prevalence, later onset
- Significant unmet need to reduce risk of hemorrhagic progression associated with CAA

Key Inclusion Criteria
- ✓ Age ≥50 years
- ✓ Probable CAA diagnosis (Boston criteria v2.0 with adaptations)

Dutch-type CAA

Rationale:
- Rapidly progressive, genetically defined
- Earlier onset with fewer comorbidities
- Presymptomatic patients
- Well-characterized natural history

Key Inclusion Criteria
- ✓ Age ≥30 years
- ✓ Known E693Q *APP* gene variant

Key Inclusion Criteria (All Patients)
- ✓ Able to complete MRI
- ✓ BMI ≥18 and ≤34 kg/m^2
- ✓ Able to tolerate lumbar puncture
- ✓ Supportive psychosocial circumstances

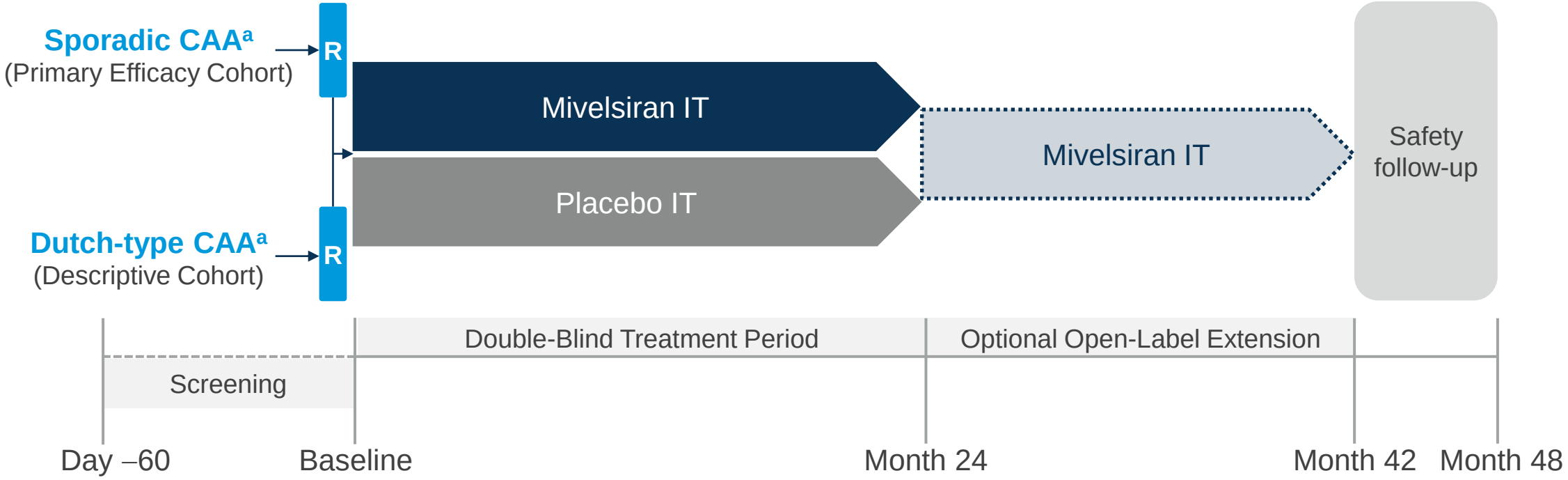
Key Exclusion Criteria
- Moderate or severe Alzheimer's disease (CDR global score 2.0 or 3.0) or severe cognitive impairment (MMSE <22)
- History of previous ICH with onset <90 days prior to randomization
- Any treatment with amyloid-targeting antibody

NCT06393712.

Aβ, amyloid beta; APP, Aβ precursor protein; BMI, body mass index; CAA, cerebral amyloid angiopathy; CDR, clinical dementia rating; ICH, intracerebral hemorrhage; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging.

cAPPricorn-1 Study Design

Phase 2 Multiple-Dose Study Evaluating Efficacy, Safety, and Pharmacodynamics



NCT06393712. [a]Sporadic and Dutch-type CAA cohorts will be analyzed separately.
CAA, cerebral amyloid angiopathy; IT, intrathecal; R, randomization.

cAPPricorn-1 will Evaluate Complementary Hemorrhagic and Non-Hemorrhagic Outcome Measures

Efficacy will be Assessed up to 24 Months and Safety up to 48 Months

Measure	Description
Hemorrhagic disease progression	**Annualized rate of new lobar cerebral microbleeds on MRI**
	Novel global rank endpoint integrating clinical and imaging findings
	Change in the total CAA small vessel disease score on MRI
	Incidence of new cerebral hemorrhagic lesions
Vascular physiology	Change in cerebrovascular vasoreactivity on BOLD-fMRI
Non-hemorrhagic disease progression	Incidence of white matter hyperintensities on MRI
Pharmacodynamics	Change in CSF sAPPα concentration
	Change in CSF sAPPβ concentration
Safety	Frequency of adverse events

Primary Endpoint[a]

Secondary Endpoints

NCT06393712. Changes in outcomes are measured from baseline. Imaging endpoints will be determined by blinded, centrally adjudicated MRI. [a]The primary endpoint will be formally analyzed in the sporadic CAA cohort only.
Aβ, amyloid beta; BOLD-fMRI, blood-oxygenation-level-dependent functional MRI; CAA, cerebral amyloid angiopathy; CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; OLE, open-label extension; sAPP, soluble Aβ precursor protein.

cAPPricorn-1 Overall Study Design

A Phase 2 Multiple-Dose Study Evaluating Efficacy, Safety, and Pharmacodynamics of Mivelsiran in Patients with CAA

Study Population (N~200)

Sporadic CAA Cohort

- Age ≥50 years
- Probable CAA (Boston v2.0 with adaptations)

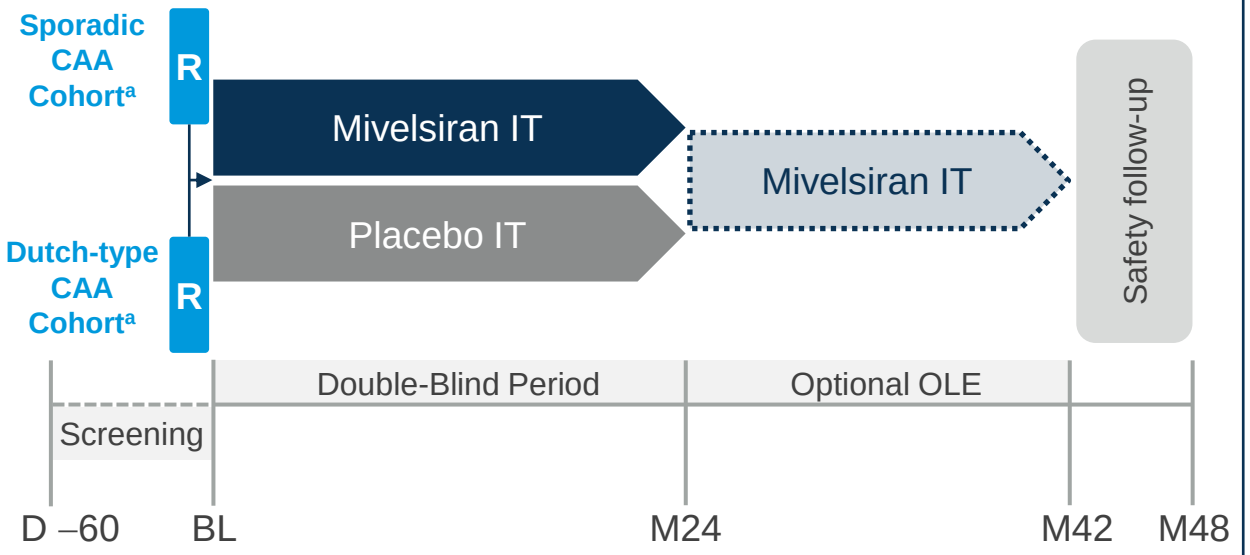
Dutch-type CAA Cohort

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

Key Exclusion (both cohorts)

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

Other protocol-defined inclusion and exclusion criteria apply



Outcome Measures[a]

Primary endpoint

Annualized rate of new lobar cerebral microbleeds

Select secondary endpoints

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

Safety

- Frequency of adverse events

NCT06393712. [a]Sporadic and Dutch-type CAA cohorts will be analyzed separately.
Aβ, amyloid beta; AD, Alzheimer's disease; APP, Aβ precursor protein; BL, baseline; CAA, cerebral amyloid angiopathy; CI, cognitive impairment; CSF, cerebrospinal fluid; D, day; ICH, intracerebral hemorrhage; IT, intrathecal; M, month; OLE, open-label extension; PD, pharmacodynamics; R, randomization; sAPP, soluble APP.

Summary

For US HCPs Only
Scan to View Congress Material Presented

For non-US HCPs, please contact MedInfo@alnylam.com

- CAA is characterized by cerebrovascular deposition of Aβ and is commonly comorbid with AD[1,2]
  - CAA increases the risk of hemorrhagic strokes and independently contributes to progressive cognitive decline[1,2]
- No disease-modifying therapies exist for CAA,[3] and Aβ-targeting antibody therapies for AD may increase risk of ICH in CAA[4]
- Mivelsiran is an investigational RNAi therapeutic designed to reduce APP production, thereby reducing downstream Aβ accumulation and potentially slowing CAA progression
- Interim Phase 1 results in early-onset AD demonstrate an encouraging safety profile and robust, durable reductions in APP CSF biomarkers[5,6]
- The Phase 2 cAPPricorn-1 study is assessing the efficacy, safety, and pharmacodynamics of mivelsiran in patients with CAA[7]
  - The study has initiated in select memory clinic and stroke care settings in Canada, Switzerland, the USA, and the UK, with additional sites planned pending regulatory and ethical reviews

Interested investigators and referring physicians may visit ClinicalTrials.gov NCT06393712

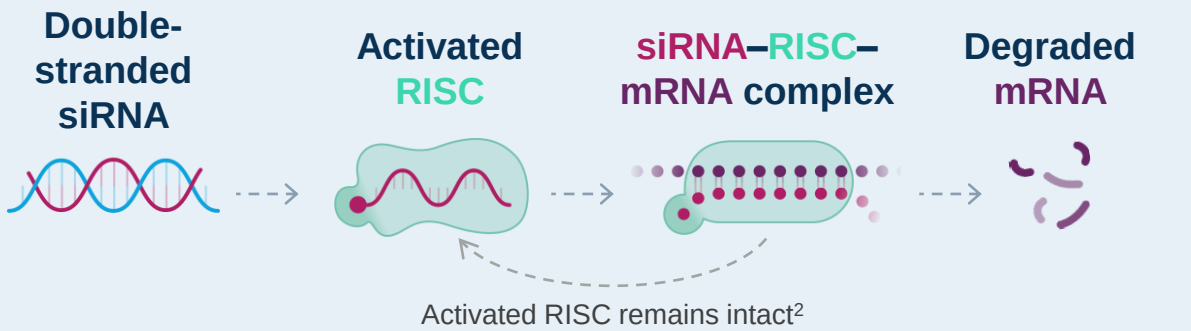
If you are seeking additional scientific information related to Alnylam therapeutics, US HCPs may visit the Alnylam US Medical Affairs website at RNAiScience.com. Non-US HCPs should contact medinfo@alnylam.com.
Aβ, amyloid beta; AD, Alzheimer's disease; APP, Aβ precursor protein; CAA, cerebral amyloid angiopathy; CSF, cerebrospinal fluid; HCP, healthcare professional; ICH, intracerebral hemorrhage; RNAi, RNA interference.
1. Kozberg MG *et al. Int J Stroke* 2021;16:356–69. 2. Boyle PA *et al. Neurology* 2015;85:1930–6. 3. Cozza M *et al. J Neurol Sci* 2023;454:120866. 4. Greenberg S *et al. Nat Rev Neurol* 2020;16:30–42. 5 ClinicalTrials.gov. NCT05231785. Available from: https://clinicaltrials.gov/study/NCT05231785 (Accessed Oct 15, 2024). 6. Deering R *et al*. Oral Presentation at the International Cerebral Amyloid Angiopathy (ICAA) Conference, October 15–17, 2024, Munich, Germany.
7. ClinicalTrials.gov. NCT06393712. Available from: https://clinicaltrials.gov/study/NCT06393712 (Accessed Oct 15, 2024).

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

Back Up

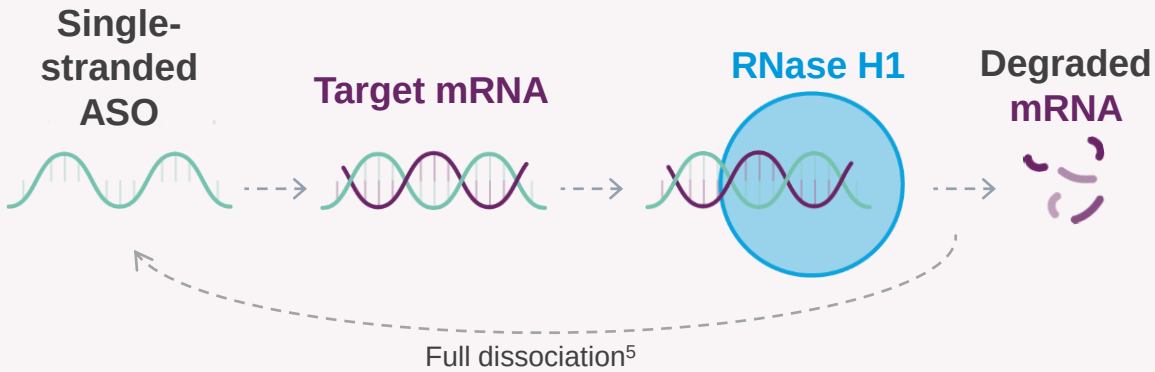
RNAi and ASO Therapeutics are Distinct Classes of Medicine[1]

RNAi



Acts in the cytoplasm[3,4]

ASO



Predominantly acts in the nucleus, partially in the cytoplasm[3,4]

	RNAi	ASO
Nature of Interaction	siRNA guide strand remains bound to RISC and further processes target mRNA[4]	Active complex fully dissociates after cleavage;[3,5] recruiting RNase H1 is rate-limiting[2,6]
Location of Action	Cytoplasm[3,4]	Nucleus and cytoplasm[3,4]
Non-specific Interactions	Double-stranded: low protein binding with plasma or cell surface proteins[7]	Single-stranded: high affinity for plasma and cell surface proteins[7]
Immuno-genicity	Lower potential for activating the immune system with modern modifications[3,8]	Historical risk of dose-limiting immunogenic responses; lower potential for immune system activation with modern modifications[2]
Dosing Interval	Monthly to biannual dosing[9]	Weekly, monthly dosing[10]

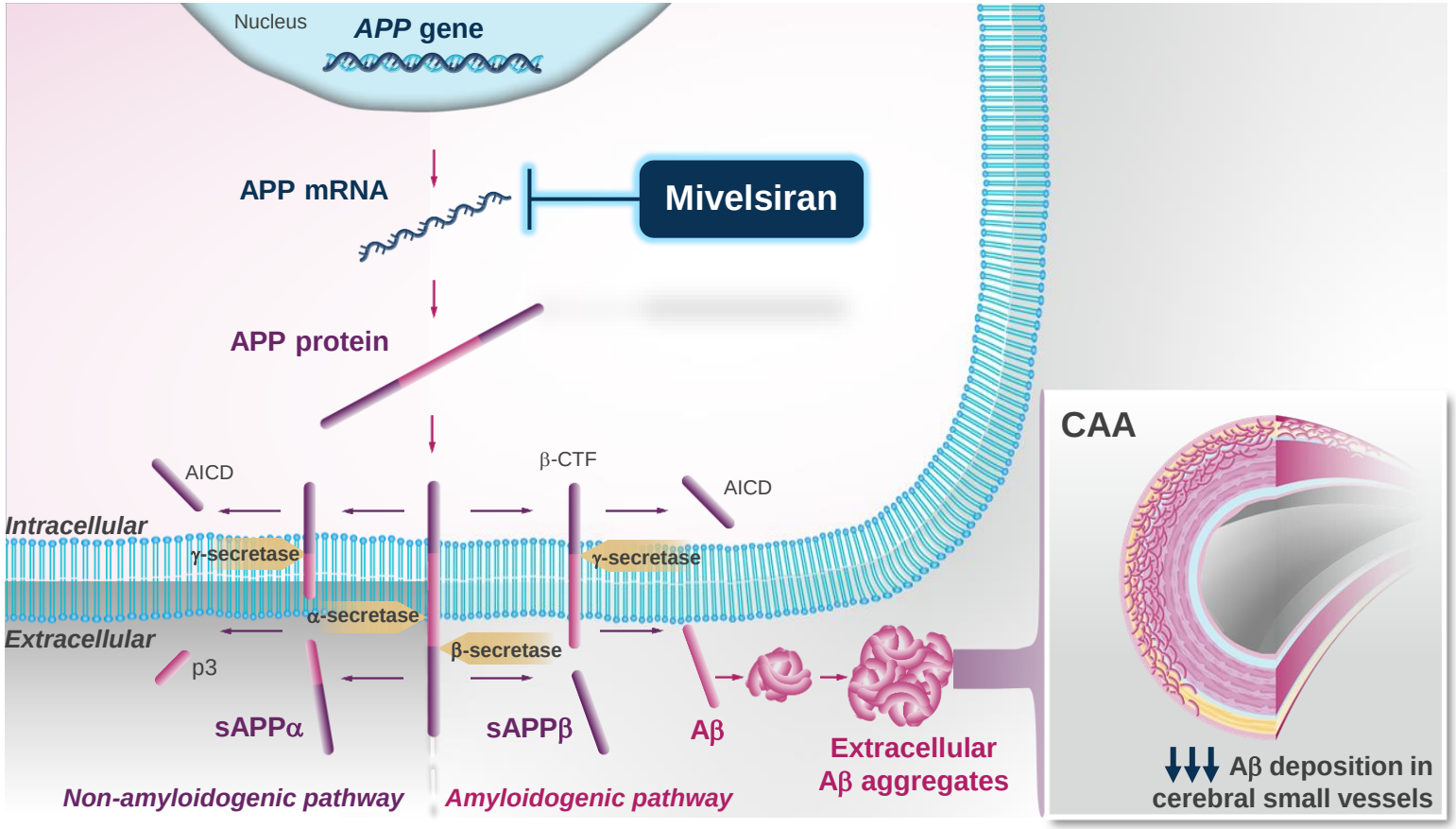
ASO, antisense oligonucleotide; mRNA, messenger RNA; RISC, RNA-induced silencing complex; RNAi, RNA interference; RNase, ribonuclease; siRNA, small interfering RNA.

1. Damase TR *et al. Front Bioeng Biotechnol* 2021;9:628137. 2. Gareri C *et al. J Clin Med* 2022;11:3884. 3. Chery J *Postdoc J* 2016;4:35–50. 4. MacLeod AR, Crooke ST. *J Clin Pharmacol* 2017:57(Suppl 10):S43–S59. 5. DeVos SL, Miller TM. *Neurotherapeutics* 2013;10:486–97. 6. Vickers AT, Crooke ST *Nucl Acids Res* 2015;43:8955–63. 7. Gardin A *et al. J Hepatol* 2022;76:1392–409. 8. Debacker AJ *et al. Mol Ther* 2020;28:1759–71. 9. Jadhav V *et al. Nature Biotechnol* 2024;42:394–405. 10. Collotta D *et al. Front Pharmacol* 2023;14:1304342.

Mivelsiran is an Investigational RNAi Therapeutic Designed to Reduce APP Production in the CNS

- Intrathecally administered C16-conjugated siRNA enables cellular uptake in the CNS[1]
- Reducing production of APP is expected to lower Aβ peptide levels[2]
- Accordingly, mivelsiran may:
  - Reduce intracellular (in AD)[3] and extracellular (in AD and CAA)[3,4] drivers of disease pathology
  - Enable natural clearance of Aβ aggregates
  - Avoid direct interaction with vascular amyloid or immuno-active Aβ clearance, reducing risk of ARIA
  - Stabilize or improve clinical manifestations of AD and CAA

Therapeutic Hypothesis of Mivelsiran in CAA



Aβ, amyloid beta; AD, Alzheimer's disease; AICD, APP intracellular domain; APP, Aβ precursor protein; ARIA, amyloid-related imaging abnormalities; β-CTF, C-terminal fragment beta; C16, 2'-O-hexadecyl; CAA, cerebral amyloid angiopathy; CNS, central nervous system; mRNA, messenger RNA; p3, p3 peptide; RNAi, RNA interference; sAPP, soluble APP; siRNA, small interfering RNA.

1. Brown KM *et al. Nat Biotechnol* 2022;40:1500–8. 2. Deering R *et al*. Oral Presentation at the International Cerebral Amyloid Angiopathy (ICAA) Conference, October 15–17, 2024, Munich, Germany. 3. Hampel H *et al. Mol Psychiatry* 2021;26:5481–503. 4. Biffi A, Greenberg SM *J Clin Neurol* 2011;7:1–9.

A Phase 1 Study Evaluating Safety and Efficacy of Single Ascending Doses of Mivelsiran in Early-Onset AD[1]

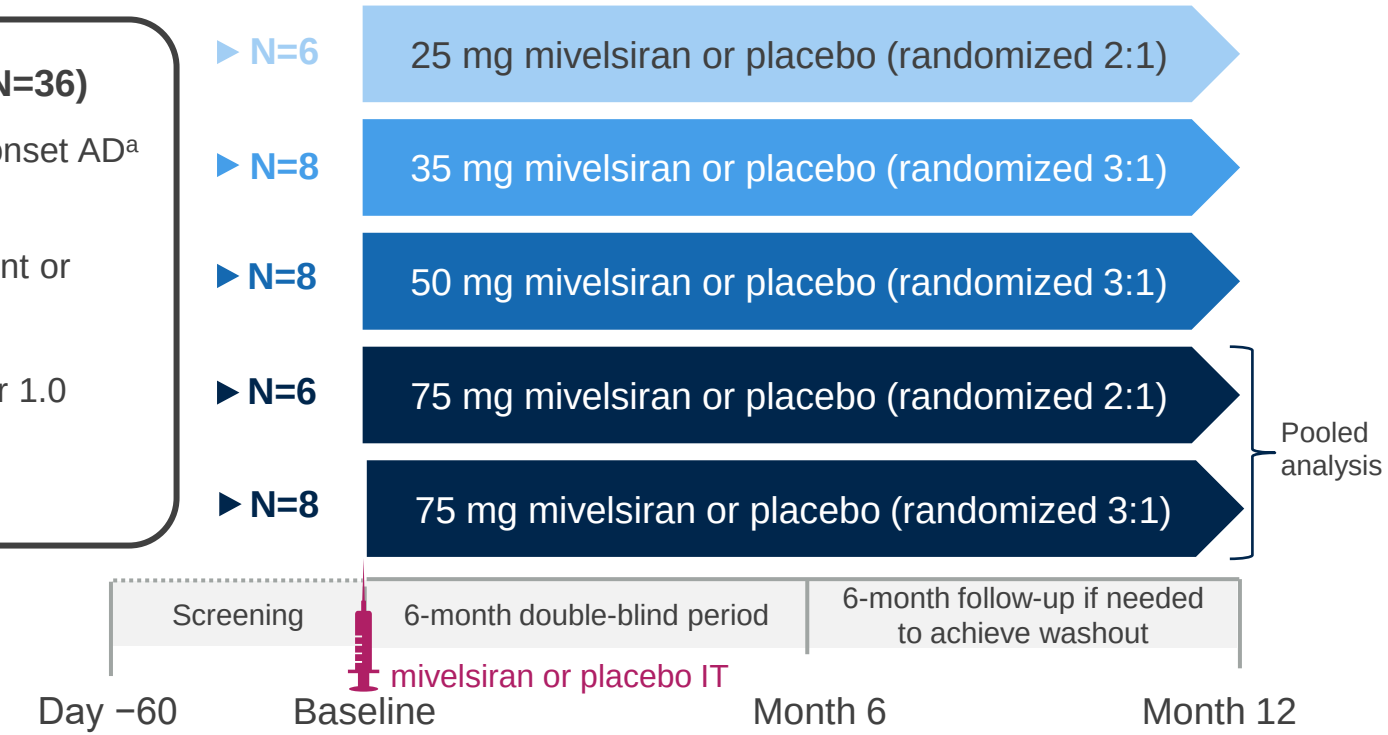
An Ongoing, Double-Blind, Placebo-Controlled Study

Study Population (N=36)

Adult patients with early-onset AD[a]

Key Inclusion Criteria

- Mild cognitive impairment or mild dementia
- MMSE score >20
- CDR global score 0.5 or 1.0
- AD confirmed via CSF biomarkers or Aβ-PET



Primary Endpoint

- Safety and tolerability (frequency of AEs)

Key Secondary Endpoints

- PK: mivelsiran CSF and plasma profiles
- PD: change from baseline in CSF levels of sAPPα and sAPPβ

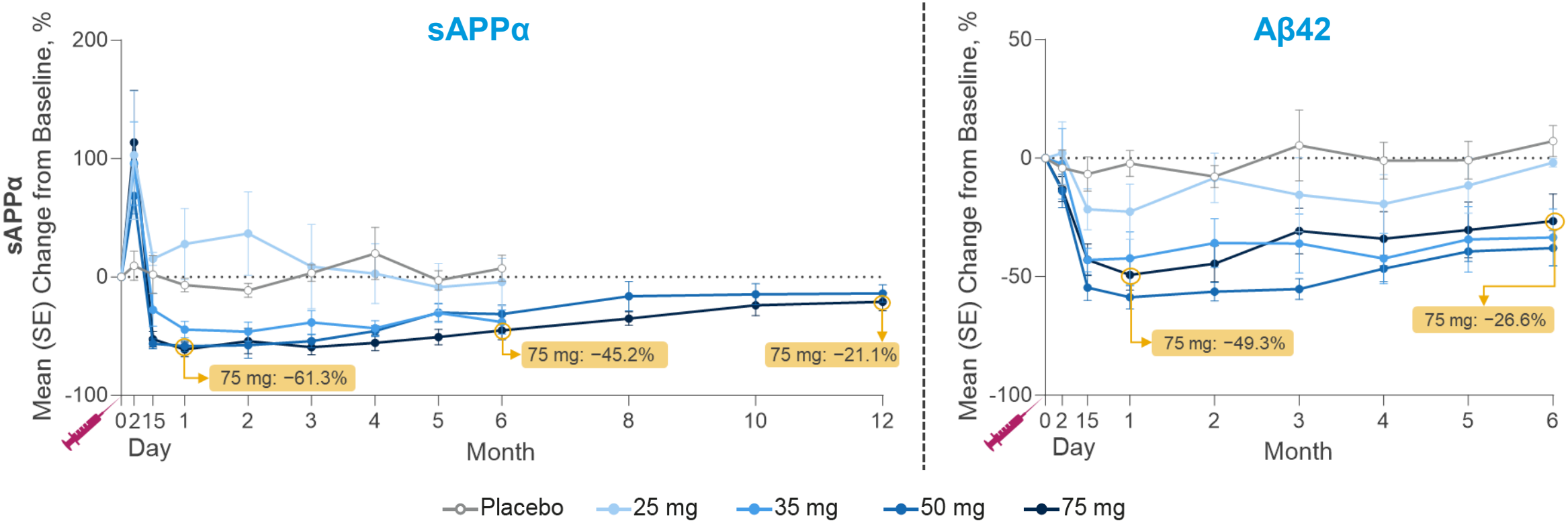
Select Exploratory Endpoints

- Biomarkers of disease progression: change from baseline in CSF levels of Aβ42 and Aβ40

- Patients were evaluated through Month 6 with additional follow-up of up to 6 months for drug washout
- Baseline characteristics and safety data are reported in pooled cohorts of mivelsiran and placebo to preserve blinding

NCT05231785. Enrollment initiated with the 25 mg cohort and then the 75 mg cohort, in each of which, 6 patients were randomized 2:1. Further dose exploration occurred through enrollment of cohorts randomized in a 3:1 ratio.
[a]Symptom onset at <65 years of age.
Aβ, amyloid beta; Aβ40, Aβ peptide length 40 amino acids; Aβ42, Aβ peptide length 42 amino acids; AD, Alzheimer's disease; AE, adverse event; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; IT, intrathecally; MMSE, Mini-Mental State Examination; PD, pharmacodynamics; PET, positron emission tomography; PK, pharmacokinetics; sAPP, soluble Aβ precursor protein.
1. Deering R *et al.* Oral Presentation at the International Cerebral Amyloid Angiopathy (ICAA) Conference, October 15–17, 2024, Munich, Germany.

Single Doses of Mivelsiran Reduced CSF sAPPα and Aβ42 in a Phase 1 Study of Patients With Early-Onset AD[1]



Mivelsiran has shown robust and durable reductions of APP cleavage products in early-onset AD, supporting its further evaluation in CAA[1,2]

NCT05231785. Data shown as of August 2, 2024.
Aβ, amyloid beta; Aβ42, Aβ peptide length 42 amino acids; AD, Alzheimer's disease; CAA, cerebral amyloid angiopathy; CSF, cerebrospinal fluid; sAPP, soluble Aβ precursor protein; SE, standard error.
1. Deering R *et al*. Oral Presentation at the International Cerebral Amyloid Angiopathy (ICAA) Conference, October 15–17, 2024, Munich, Germany. 2. Kozberg MG *et al. Int J Stroke* 2021;16:356–69.