A Phase 2 Study Evaluating the Effects of Mivelsiran, an Investigational RNA Interference Therapeutic, on Hemorrhagic and Nonhemorrhagic Manifestations of Cerebral Amyloid Angiopathy

Steven M. Greenberg[1]; Ellis S. van Etten[2]; Matthias J. P. van Osch[2]; Catharina J. M. Klijn[3]; Alexandre Sostelly[4]; Sasikiran Goteti[4]; Farshid Sepehrband[5]; Andreja Avbersek[5]; Robert W. Deering[4]; Neal S. Parikh[4]; Jin-Moo Lee[6]

[1]Harvard Medical School, Massachusetts General Hospital, Boston, MA, USA; [2]Leiden University Medical Center, Leiden, Netherlands; [3]Department of Neurology, Donders Institute for Brain, Cognition, and Behaviour, Radboud University Medical Center, Nijmegen, Netherlands; [4]Alnylam Pharmaceuticals, Inc., Cambridge, MA, USA; [5]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [6]Washington University School of Medicine, St. Louis, MO, USA

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Key Points

- **Cerebral amyloid angiopathy (CAA) is a leading cause of hemorrhagic stroke; no disease-modifying therapies are available.**
- **Mivelsiran is an investigational RNA interference (RNAi) therapeutic in development for the treatment of CAA.**
- **Mivelsiran has been shown to lower biomarkers related to CAA in a Phase 1 trial in patients with early-onset Alzheimer's disease.**
- **The Phase 2 cAPPricorn-1 study of mivelsiran is the only active global, multicenter, interventional study for patients with CAA and is currently enrolling at select sites in North America, Europe, and Australia.**

Background

Cerebral Amyloid Angiopathy

- CAA is a debilitating disease characterized by cerebrovascular deposition of amyloid-beta (Aβ).[1]
  - In patients with CAA, insoluble amyloid aggregates – predominantly made up of Aβ40 – are deposited in cerebral vessels.[1,2]
  - All Aβ peptides are derived from Aβ precursor protein (APP).[3]
- Patients with CAA are affected by progressive cerebrovascular dysfunction.[1]
  - Hemorrhagic manifestations include cerebral microbleeds, cortical superficial siderosis, acute convexity subarachnoid hemorrhage, and recurrent intracerebral hemorrhage (ICH).[1,4]
  - Nonhemorrhagic manifestations include white matter hyperintensities, impaired cerebrovascular reactivity, cortical microinfarcts, and cognitive decline and dementia.[1,5]
- CAA is often comorbid with Alzheimer's disease (AD), but also independently contributes to cognitive decline.[6]
- CAA can be sporadic or hereditary.[7]
  - Sporadic CAA is the more prevalent form and has later onset of symptoms.
  - Dutch-type CAA is an autosomal dominant hereditary form with an earlier onset of symptoms and rapid disease progression.
- There are no disease-modifying therapies for CAA.[1]

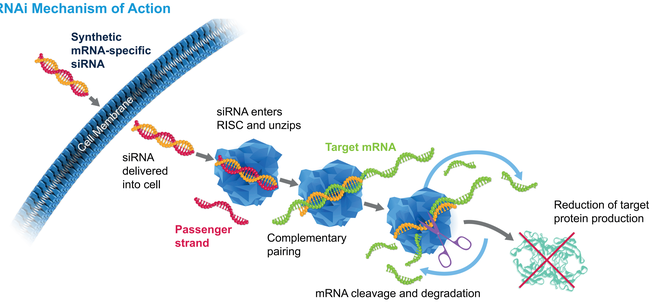
RNA Interference

- RNAi is a natural process that regulates gene expression.[8]
- Synthetic small interfering RNAs (siRNAs) are designed to specifically degrade messenger RNA encoding a disease-associated protein.[8]
- RNAi works catalytically, reducing target protein expression while leaving DNA intact (**Figure 1**).[8,9]

Mivelsiran

- Mivelsiran is an investigational, first-in-class RNAi therapeutic designed to target the underlying pathophysiology of CAA by reducing production of APP and downstream Aβ peptides.
- Mivelsiran is conjugated to a C16 lipid chain, which enhances cellular uptake and biodistribution in the central nervous system following intrathecal delivery.
- By reducing production of APP and downstream Aβ peptides, mivelsiran is designed to decrease Aβ deposition in the cerebral vessels and thereby potentially stabilize or improve clinical manifestations of CAA.

Figure 1. RNAi Mechanism of Action

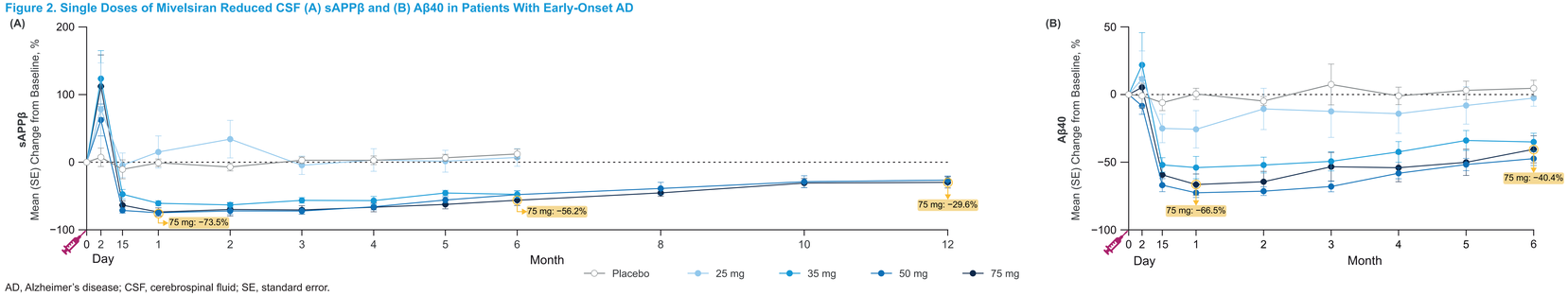


mRNA, messenger RNA; RISC, RNA-induced silencing complex; RNAi, RNA interference; siRNA, small interfering RNA.

Phase 1 Study of Mivelsiran in Early-Onset AD (NCT05231785)

- An ongoing Phase 1 study of mivelsiran in early-onset AD has shown encouraging safety data and robust, durable reductions of soluble APP (sAPP) and Aβ peptides in cerebrospinal fluid.[10]
- Most adverse events (AEs) were mild or moderate in severity.
- One patient had a serious and severe AE of acute pancreatitis that was fatal; this was deemed unrelated to study drug or lumbar puncture (LP) by the investigator.
- Three patients had AEs deemed related to study drug; all events but one were also assessed as related to LP.
  - Mild: post-LP headache, nausea.
  - Mild: lymphocytopenia (day 59, normal total white blood cell count, resolved without treatment).
  - Moderate: post-LP headache, neck pain, vomiting.
- A single mivelsiran dose of more than 25 mg resulted in robust and durable reductions in sAPPβ and Aβ40 levels (**Figure 2**).
  - Peak mean reductions with mivelsiran 75 mg were 73.5% for sAPPβ and 66.5% for Aβ40 at Month 1.

Figure 2. Single Doses of Mivelsiran Reduced CSF (A) sAPPβ and (B) Aβ40 in Patients With Early-Onset AD



AD, Alzheimer's disease; CSF, cerebrospinal fluid; SE, standard error.

cAPPricorn-1: A Phase 2 Study of Mivelsiran in CAA (NCT06393712)

Objective

- To evaluate the efficacy, safety, and pharmacodynamics of mivelsiran in patients with sporadic CAA or Dutch-type CAA.

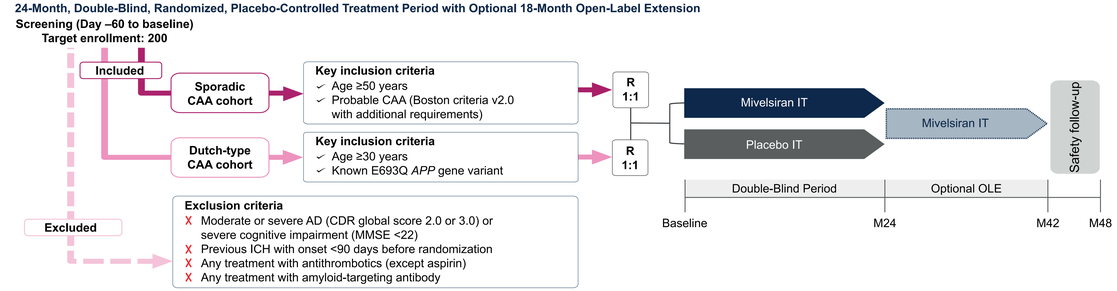
Study Design

- Patients randomized 1:1 to receive mivelsiran or placebo in a 24-month double-blind treatment period (**Figure 3**).
  - Patients with prior ICH are included.
- Optional 18-month open-label extension period; all patients will be eligible to receive mivelsiran.
  - The open-label extension will use the same dosing regimen as the double-blind period.
- Hemorrhagic and nonhemorrhagic outcome measures will be assessed.

cAPPricorn-1 Study Status

- Initiated in memory clinics and stroke care centers in Australia, Canada, Switzerland, the UK, and the USA.
  - Enrollment at additional sites is planned pending regulatory and ethical review.
- First patient enrolled in mid-2024; enrollment will continue through 2025.
- Interested investigators and referring physicians may visit cappricorn1.com or contact clinicaltrials@alnylam.com

Figure 3. cAPPricorn-1 Study Evaluating Efficacy, Safety, and Pharmacodynamics



Efficacy outcome measures	
Hemorrhagic disease progression	**Primary:** Annualized rate of new lobar cerebral microbleeds on MRI Novel CAA endpoint that ranks clinical and imaging findings based on severity Change in the total CAA small vessel disease score on MRI Incidence of new cerebral hemorrhagic lesions
Vascular physiology	Change in cerebral vasoreactivity on BOLD-fMRI
Nonhemorrhagic disease progression	Incidence of white matter hyperintensities on MRI
Pharmacodynamics	Change in CSF sAPPα concentration Change in CSF sAPPβ concentration
Safety outcome measure	
Frequency of adverse events	

Sporadic and Dutch-type CAA cohorts will be analyzed separately. The primary endpoint will be formally analyzed in the sporadic CAA cohort only; all other outcome measures shown are secondary. Changes in outcomes are measured from baseline. Imaging endpoints will be determined by blinded, centrally adjudicated MRI.
AD, Alzheimer's disease; APP, amyloid-beta precursor protein; BOLD-fMRI, blood-oxygenation-level-dependent functional MRI; CAA, cerebral amyloid angiopathy; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; ICH, intracerebral hemorrhage; IT, intrathecal; M, month; MMSE, Mini Mental State Examination; MRI, magnetic resonance imaging; OLE, open-label extension; R, randomized; sAPP, soluble amyloid-beta precursor protein.

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REFERENCES

1. Kozberg MG *et al. Int J Stroke* 2021;16:356–69.
2. Greenberg SM *et al. Nat Rev Neurol* 2020;16:30–42.
3. Zheng H, Koo EH. *Mol Neurodegener* 2006;1:5.
4. Raposo N *et al. Eur J Neurol* 2018;25:253–9.
5. Beaudin AE *et al. Neurology* 2022;98:e1716–28.
6. Boyle PA *et al. Neurology* 2015;85:1930–6.
7. Banerjee G *et al. J Neurol Neurosurg Psychiatry* 2017;88:982–94.
8. Jadhav V *et al. Nature Biotechnol* 2024;42:394–405.
9. Ranasinghe P *et al. Br J Pharmacol* 2023;180:2697–720.
10. Deering R *et al.* Oral presentation at the International Cerebral Amyloid Angiopathy Conference, October 15–17, 2024, Munich, Germany

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