Mivelsiran: cAPPricorn-1 Study

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The safety and efficacy of mivelsiran are currently being investigated in clinical studies and have not been evaluated by FDA or any health authority.

If you are seeking additional scientific information related to Alnylam medicines, you may visit the Alnylam US Medical Affairs website at RNAiScience.com.

SUMMARY

- Mivelsiran is an intrathecally administered 2'-O-hexadecyl (C16)-conjugated RNAi therapeutic being investigated in adults for the treatment of EOAD and CAA.[1]
- Mivelsiran targets intracellular and extracellular APP production in the CNS, upstream of amyloidogenic processing, through reduction of APP mRNA. The investigational hypothesis for mivelsiran suggests that the reduction of APP production causes the downstream Aβ protein species to be reduced. This downstream effect may thereby reduce amyloidogenic protein fragments and amyloid deposition in cerebral blood vessels.[1]
- The efficacy, safety, tolerability, and PD of mivelsiran in patients with sporadic or hereditary CAA are being evaluated in an ongoing, global, randomized, double-blind, placebo-controlled, phase 2 study (NCT06393712).[2]

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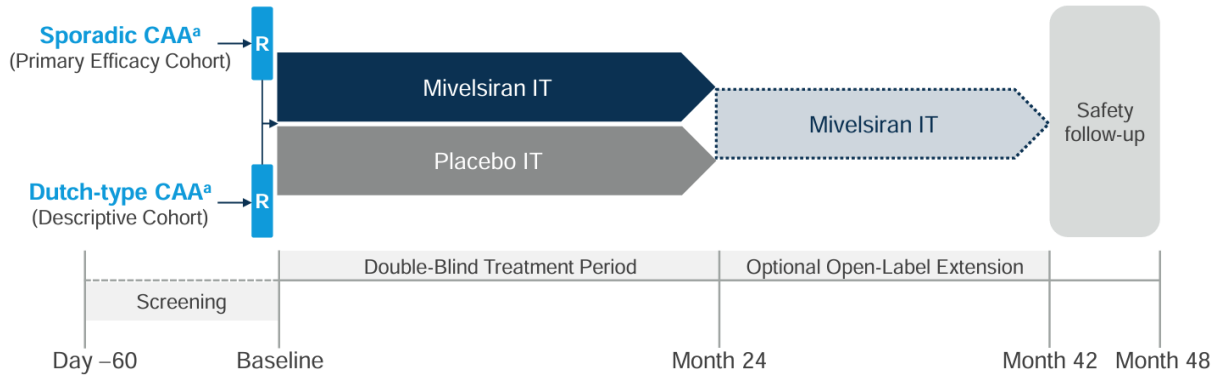
STUDY DESIGN

The cAPPricorn-1 study is an ongoing, global, randomized, double-blind, placebo-controlled, phase 2 study designed to evaluate the efficacy, safety, tolerability, and PD of mivelsiran (ALN-APP-02) in patients with sporadic or Dutch-type CAA. Enrolled patients will be randomized to receive intrathecal injections of mivelsiran or placebo during the 24-month double-blind treatment period, followed by an optional 18-month OLE period. The estimated duration of study participation, inclusive of the 60-day screening period, the double-blind treatment period, the optional OLE, and the 6-month additional safety follow-up, is up to 50 months (**Figure 1**).[1,2]

Figure 1. cAPPricorn-1 Study Design.[1]



Abbreviations: CAA = cerebral amyloid angiopathy; IT = intrathecal; R = randomization.
[a]Sporadic and Dutch-type CAA cohorts will be analyzed separately.
From: Lee et al.[1]

The primary endpoint is the annualized rate of new lobar CMBs on brain MRI in patients with sporadic CAA.[1]

Secondary endpoints include:[1,2]

- Global rank based on severity, count, symptom burden, and timing of new clinical hemorrhagic events and hemorrhagic lesions on brain MRI
- Change from baseline in the total CAA small vessel disease score on brain MRI
- Incidence of new cerebral hemorrhagic lesions
- Assessment of vascular physiology through the change from baseline in cerebrovascular vasoreactivity on BOLD-fMR
- Assessment of non-hemorrhagic disease progression through the incidence of white matter hyperintensities assessed on brain MRI
- Pharmacodynamic evaluation of the change from baseline in CSF sAPPα and sAPPβ concentrations

Safety will be assessed by the frequency of AEs for up to 48 months.

Key study inclusion criteria are:[1]

- Able to complete MRI and tolerate lumbar puncture
- BMI ≥18 and ≤34 kg/m^2
- Supportive psychosocial circumstances
- Sporadic CAA patients: ≥50 years with a probable CAA per the Boston criteria version 2.0 with adaptations
- Dutch-type CAA patients: ≥30 years with a known E693Q *APP* gene variant

Key study exclusion criteria are:[1]

- Moderate or severe AD (CDR global score 2.0 or 3.0) or severe CI (MMSE <22)
- History of previous ICH with onset <90 days prior to randomization

- Any treatment with amyloid-targeting antibody

The trial is listed as recruiting as of November 8, 2024.[2]

ABBREVIATIONS

Aβ = amyloid beta; AD = Alzheimer's disease; AE = adverse event; APP = Aβ precursor protein; BMI = body mass index; BOLD = blood oxygenation level dependent; CAA = cerebral amyloid angiopathy; CDR = clinical dementia rating; CI = cognitive impairment; CMB = cerebral microbleed; CNS = central nervous system; CSF = cerebral spinal fluid; EOAD = early onset Alzheimer's disease; eGFR = estimated glomerular filtration rate; ICH = clinical intracerebral hemorrhage; IT = intrathecal; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; mRNA = messenger ribonucleic acid; OLE = open-label extension; PD = pharmacodynamics; R = randomization; RNA = ribonucleic acid; sAPPα = soluble amyloid precursor protein alpha; sAPPβ = amyloid precursor protein beta; ULN = upper limit of normal.

Updated 8 November 2024

REFERENCES

1. Lee J, van Etten ES, van Osch MJP, et al. Design and rationale of cAPPricorn-1, a phase 2 study of mivelsiran in patients with cerebral amyloid angiopathy. Presented at: Clinical Trials on Alzheimer's Disease (CTAD) Conference; October 29–November 1, 2024; Madrid, Spain.
2. Alnylam Pharmaceuticals: A phase 2 trial of ALN-APP in patients with cerebral amyloid angiopathy (cAPPricorn-1). Available from: https://clinicaltrials.gov/study/NCT06393712. Accessed November 08, 2024.