

Mivelsiran: APPlauDS Study

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

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SUMMARY

- Mivelsiran is an intrathecally administered 2'-O-hexadecyl (C16)-conjugated RNAi therapeutic being investigated in adults for the treatment of AD and CAA.^{1,2}
- 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 A β protein species to be reduced.¹
- People with DS have an additional copy of chromosome 21, the locus of the *APP* gene, resulting in overexpression of APP and increased production of A β peptides implicated in AD pathogenesis.¹
- The efficacy, safety, tolerability, PK, and PD of mivelsiran in people with early stage DS-AD are being evaluated in a global, multicenter, randomized, double-blind, placebo-controlled, phase 2 study (NCT07636811).^{1,3}

ABBREVIATIONS

A β 42 = amyloid-beta peptide-42; AD = Alzheimer's Disease; AE = adverse event; APP = amyloid-beta precursor protein; BL = baseline; CAA = cerebral amyloid angiopathy; CL = centiloid; CSF = cerebrospinal fluid; DB = double-blind; DS = Down syndrome; DS-AD = Down syndrome-associated Alzheimer's disease; ID = intellectual disability; M = month; MCI = mild cognitive impairment; mCRT = modified Cued Recall Test; OLE = open-label extension; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; p-tau217 = phosphorylated tau protein at threonine 217; Q6M = every 6 months; R = randomized; sAPP = soluble amyloid-beta precursor protein.

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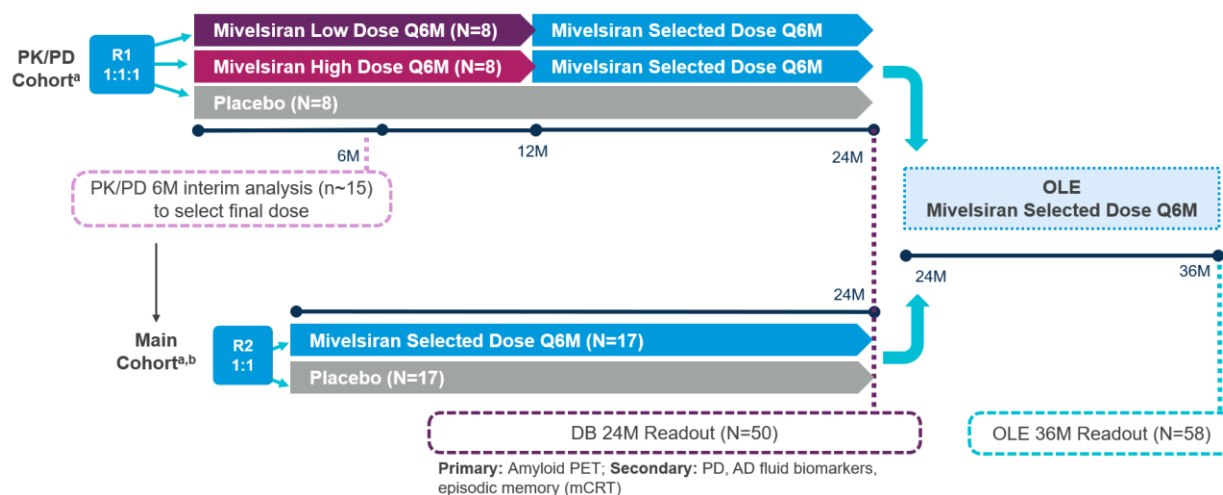
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STUDY DESIGN

The APPlauDS study is a global, multicenter, randomized, double-blind, placebo-controlled, phase 2 study designed to evaluate the efficacy, safety, tolerability, PK, and PD of mivelsiran in people with DS-AD. In the PK/PD cohort, participants will be randomized 1:1:1 to receive intrathecal injections of a low dose or high dose of mivelsiran or placebo every 6 months. Following an interim PK/PD analysis for final dose selection, the main cohort will be randomized 1:1 to the selected dose of mivelsiran or

placebo for a 24-month, double-blind treatment period. All participants will be eligible to receive mivelsiran in the OLE (**Figure 1**).¹

Figure 1. APPlauDS Study Design.^{1,a}



Abbreviations: BL = baseline; CL = centiloid; DB = double-blind; M = month; OLE = open-label extension; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; Q6M = every 6 months; R = randomized.

^aIndividuals will be randomized sequentially into two cohorts, with the PK/PD cohort enrolled first and the main cohort beginning once enrollment in the PK/PD cohort completes and the main cohort dose has been selected.

^bRandomization of the main cohort will be stratified by amyloid PET at baseline (high and low CL values).

From Rafii et al.¹

Select inclusion criteria include¹:

- Clinical diagnosis of DS associated with trisomy 21
- Aged 40-55 years
- Positive amyloid PET scan
- Cognitively stable with no MRI or dementia
- No prior on ongoing treatment with anti-amyloid antibodies
- Individuals with mild or moderate ID

Select exclusion criteria include³:

- Individuals with severe ID
- History of DS regression disorder
- ALT or AST >2x ULN at screening
- eGFR <45 mL/min/1.73m²
- Comorbidities such as obstructive sleep apnea and hypothyroidism that are not well-controlled

The primary endpoint is the change from baseline in amyloid PET at 24 months. The primary endpoint will include all participants who received the selected dose of mivelsiran or placebo in the pooled PK/PD and main cohorts.¹

Secondary endpoints include the change from baseline at 24 months in the following¹:

- CSF sAPP α and sAPP β
- CSF A β 42
- Plasma p-tau217

- mCRT

Safety will be assessed by the frequency of AEs through 36 months.¹

REFERENCES

1. Rafii MS, Ances B, Levin J, et al. Design of APPlauDS, a phase 2 study of mivelsiran in people with Down syndrome and early-stage Alzheimer's disease. Presented at: Alzheimer's Disease International Conference (AAIC); July 12-15, 2026. London, UK.
2. 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.
3. Alnylam Pharmaceuticals: A study to evaluate mivelsiran in adult participants with early-stage down syndrome-associated Alzheimer's disease (DS-AD). Available from: <https://clinicaltrials.gov/study/NCT07636811>. Accessed October 6, 2026.

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