Design of APPlauDS, a Phase 2 Study of Mivelsiran in People with Down Syndrome and Early-Stage Alzheimer's Disease

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Takeaways

- **Triplication of chromosome 21, the locus of the *amyloid-beta precursor protein* (*APP*) gene, and resulting overproduction of APP causes a near-complete risk of Alzheimer's disease (AD) in people with Down syndrome (DS).**
- **APPlauDS will investigate the disease-modifying potential of APP reduction with the investigational RNA interference (RNAi) therapeutic mivelsiran in people with early-stage Down syndrome-associated Alzheimer's disease (DS-AD), and evaluate whether mivelsiran can slow, halt, or reverse AD progression in people with DS who are not yet experiencing cognitive decline.**

Background

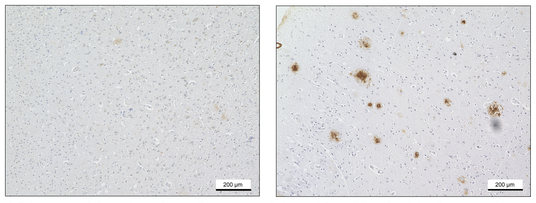
Down Syndrome-Associated Alzheimer's Disease (DS-AD)

- People with DS have a near-complete risk of developing symptomatic AD in late adulthood (>50 years); AD has become the leading cause of death in adults with DS.[1,2]
- DS-AD follows the same biomarker cascade as sporadic AD but is clinically distinct with earlier onset and more rapid progression.[2–4]

Rationale for Mivelsiran in DS-AD

DS-AD is Caused by Overexpression of APP Due to Trisomy 21

- People with DS have an additional copy of chromosome 21, the locus of the *APP* gene; this results in overexpression of APP and increases the production of amyloid-beta (Aβ) peptides implicated in AD pathogenesis.[5–7]
- Two rare case studies of people with DS with partial trisomy 21, in whom the *APP* locus had not been triplicated, showed no dementia and no signs of AD neuropathology at their time of death in their 70s.[8,9]

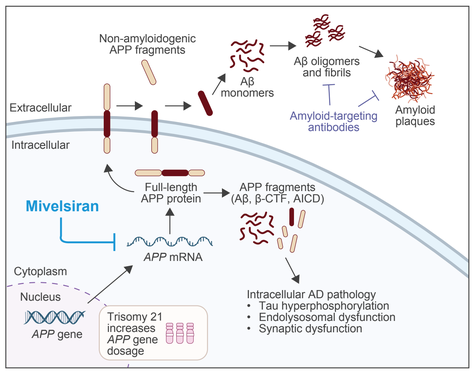


Aβ immunohistochemistry (brown staining; 10× objective) in the superior temporal gyrus from a 72-year-old patient with partial trisomy 21 (left) and a 45-year-old patient with full trisomy 21 and AD dementia (right). Images courtesy of Elizabeth Head PhD and Lisi Flores-Aguilar PhD.
Aβ, amyloid-beta; AD, Alzheimer's disease.

Mivelsiran is an RNAi Therapeutic that Targets APP

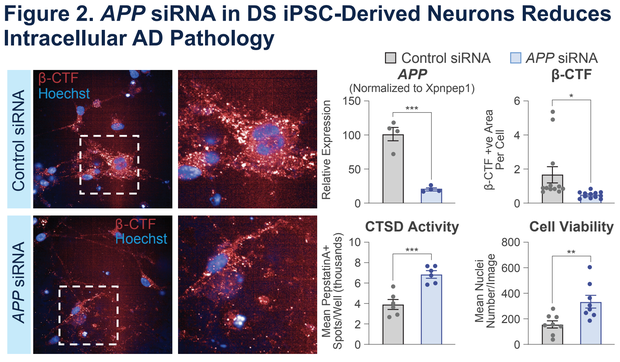
- Mivelsiran contains a small interfering RNA (siRNA) that binds and cleaves *APP* mRNA, reducing APP expression and Aβ production to reduce downstream intracellular and extracellular drivers of AD progression (**Figure 1**).[10,11]
- APP reduction has been shown to reduce amyloid plaques, reduce glial fibrillary acidic protein and neurofilament light chain, and correct behavior in a five times familial AD (5xFAD) mouse model.[12]
- Preclinical studies in induced pluripotent stem cell-derived neurons of people with DS have shown that APP-lowering siRNA can lower β-C-terminal fragment, improve lysosomal activity, and increase cell viability (**Figure 2**).

Figure 1. Mivelsiran is an Investigational RNAi Therapeutic that Targets *APP*



Aβ, amyloid-beta; AD, Alzheimer's disease; AICD, amyloid-beta precursor protein intracellular domain; APP, amyloid-beta precursor protein; β-CTF, β-C-terminal fragment.

Figure 2. *APP* siRNA in DS iPSC-Derived Neurons Reduces Intracellular AD Pathology



AG28801 cells (human iPSCs carrying trisomy 21) were differentiated into neurons and astrocytes and treated with control or *APP*-targeting siRNA. *APP*, β-CTF, and CTSD activity (marker of lysosomal activity) measured at 30 days; cell viability measured at 56 days. *$p<0.05$; **$p<0.01$; ***$p<0.001$.
AD, Alzheimer's disease; APP, amyloid-beta precursor protein; β-CTF, β-C-terminal fragment; CTSD, cathepsin D; DS, Down syndrome; iPSC, induced pluripotent stem cell; siRNA, small interfering RNA.

Mivelsiran Phase 1: Rapid, Robust APP-Lowering with Encouraging Safety[11]

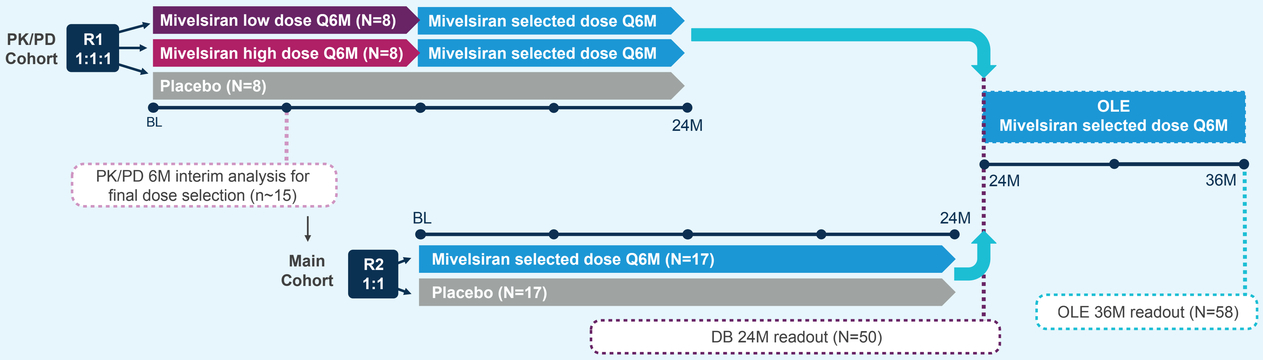
- The Phase 1 study investigated the safety and tolerability of single and multiple ascending doses of mivelsiran in patients with early-onset AD.
- Mivelsiran was generally well tolerated across dose levels with single and multiple doses, with no immune responses or evidence of drug-related amyloid-related imaging abnormalities observed.
- Marked reductions in cerebrospinal fluid soluble APPβ and Aβ peptides (Aβ42 and Aβ40) were observed with single and multiple doses of mivelsiran above 25 mg versus placebo.

Methods

APPlauDS is a Phase 2, Global, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study

Objective
Evaluate the efficacy, safety, tolerability, PK, and PD of mivelsiran versus placebo in individuals with DS-AD

Key Inclusion Criteria
- Clinical diagnosis of DS associated with trisomy 21
- Aged 40–55 years, inclusive
- Positive amyloid PET scan
- Cognitively stable with no MCI or dementia
- No prior or ongoing treatment with anti-amyloid antibodies
- Individuals with mild or moderate ID



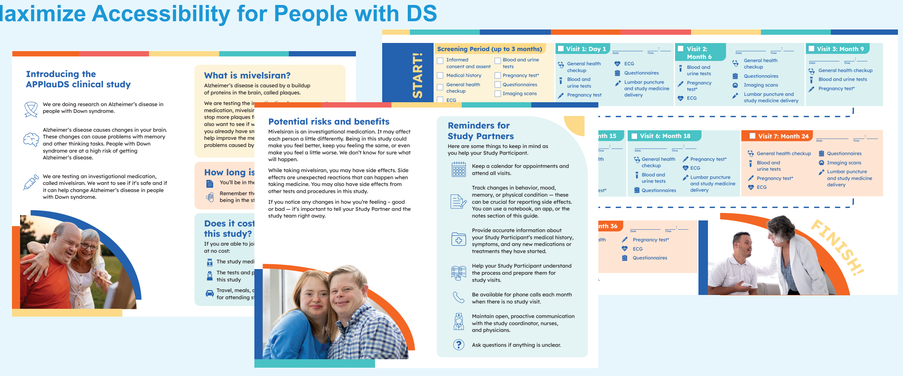
Outcome Measures

Primary Endpoint	Amyloid PET (CL)	**Secondary Endpoints**	• CSF sAPPα and sAPPβ • CSF Aβ42 • Plasma p-tau217 • mCRT	**Safety**	Frequency of AEs

APPlauDS has been Designed to Maximize Accessibility for People with DS

APPlauDS design was informed by DS community engagement with accommodations made to ensure accessibility including:

- assessments designed for people with DS
- study schedule with minimal assessment frequency, high visit flexibility, and an extended 90-day screening window
- trial materials developed in collaboration with the DS community
- large site footprint across USA and Europe.



Randomization of the main cohort will be stratified by amyloid PET at BL (high and low CL values). All endpoints are measured as change from BL to Month 24, with the exception of safety endpoints, which are measured through Month 36. The primary endpoint will include all participants who received the selected dose of mivelsiran or placebo in the pooled PK/PD and main cohorts.
Aβ42, amyloid-beta peptide-42; AE, adverse event; BL, baseline; 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.

Enrollment

- Enrollment will begin in 2026 across ~30 sites worldwide.
- Interested investigators and referring physicians may contact clinicaltrials@alnylam.com.

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