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HUMAN

Multiple-Dose Results from an Ongoing Phase 1 Study of Mivelsiran, an Investigational RNA Interference Therapeutic Targeting Amyloid-Beta Precursor Protein for Alzheimer's Disease

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Abstract

Background: Single doses of mivelsiran, an investigational RNA interference (RNAi) therapeutic, have demonstrated robust amyloid-beta precursor protein (APP) lowering in the CNS. We report additional interim safety and pharmacodynamic data in patients with early-onset Alzheimer's disease (EOAD) who received single ascending doses (SAD) and, for the first time, multiple doses of mivelsiran in the ongoing Phase 1 study (NCT05231785).

Methods: Patients with EOAD (symptom onset <65 years of age, Clinical Dementia Rating global score 0.5 or 1.0, Mini-Mental State Examination score >20) were randomized to a single intrathecal dose of mivelsiran 25–100mg or placebo for 6 months (plus up to 6 months follow-up if needed for washout). After washout, patients could enter a separate multiple ascending dose (MAD) portion and receive open-label mivelsiran. Presented here are data from a SAD cohort of mivelsiran 100mg and a MAD cohort of mivelsiran 50mg every 6 months (Q6M). Frequency of adverse events (AEs) and pharmacodynamics were primary and secondary endpoints, respectively.

Results: Forty-five patients were enrolled in SAD cohorts (as of 11/20/2024). Of those, 9 patients were randomized to mivelsiran 100mg or placebo (mean [SD] age, 64.1 [3.7] years; 33.3% male; 100% white). Most AEs were mild or moderate. Peak mean (SE) change from baseline in cerebrospinal fluid (CSF) soluble APP beta (sAPPβ) at Month 1 (—84.5% [1.3]) was largely sustained through Month 10 (—61.1% [2.8]).

After meeting washout criteria, 10 patients from SAD cohorts received mivelsiran 50mg Q6M (mean [SD] age, 59.9 [4.4] years; 70.0% male; 70.0% white). No serious or severe AEs were reported. At Day 15 after the first dose, mean (SE) change from

baseline in CSF sAPPβ was —63.7% (5.0); at Month 1 after the second dose, change was —83.8% (2.3). Additional data will be presented.

Conclusions: In this first report of multiple-dose clinical data for a CNS-targeting RNAi therapeutic, single and multiple doses of mivelsiran were generally well tolerated and continued to demonstrate robust, durable, dose-dependent CSF sAPPβ reductions. Further sAPPβ lowering was observed after a second dose of mivelsiran 50mg. These results support further evaluation of mivelsiran in patients with Alzheimer's disease or cerebral amyloid angiopathy.