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Single Ascending Dose Results From an Ongoing Phase 1 Study of Mivelsiran (ALN-APP), the First Investigational RNA Interference Therapeutic Targeting Amyloid Precursor Protein for Alzheimer's Disease

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Conclusions

- **Single doses of mivelsiran tested in this ongoing Phase 1 study in patients with early-onset Alzheimer's disease (EOAD) were generally well tolerated.**
  - **Most adverse events (AEs) were mild or moderate in severity and nonserious; one serious AE deemed unrelated to study drug was reported.**
- **Robust, durable, and dose-dependent reductions in soluble amyloid precursor protein (sAPP) α and β levels in the cerebrospinal fluid (CSF) were sustained through Month 6, with reductions observed through Month 12 at higher doses evaluated.**
- **Marked reductions in CSF amyloid beta (Aβ) 42 and 40 were observed through Month 6.**
- **Encouraging safety profile and robust, durable reductions in APP CSF biomarkers support further evaluation of mivelsiran as a potential treatment for cerebral disorders of Aβ, namely Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA).**
  - **Single and multiple ascending dose studies of mivelsiran in EOAD are ongoing.**
  - **cAPPricorn-1 (NCT06393712), a Phase 2 study of mivelsiran in CAA, has initiated.**

Introduction

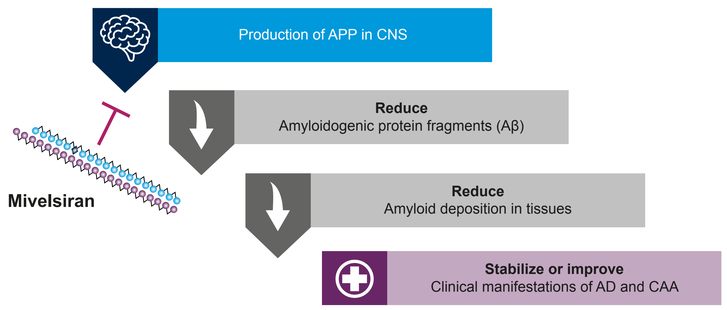
Background

- AD and CAA are distinct but related diseases of the central nervous system associated with significant morbidity and mortality and high unmet need for improved treatment options.[1–3]
- Both diseases are characterized by accumulation of Aβ deposits, primarily Aβ42 and Aβ40.
  - Accumulation occurs in the brain tissue in AD and cerebral blood vessels in CAA, causing progressive structural and functional impairment and leading to clinical symptoms.[4,5]

Mivelsiran

- Mivelsiran (ALN-APP) is an investigational, intrathecally administered RNA interference therapeutic targeting amyloid precursor protein (APP) (**Figure 1**).
  - Mivelsiran lowers levels of Aβ peptide by reducing upstream production of APP, the source of all Aβ protein species.[6]

Figure 1. Therapeutic Hypothesis



Aβ, amyloid beta; AD, Alzheimer's disease; APP, amyloid precursor protein; CAA, cerebral amyloid angiopathy; CNS, central nervous system.

Aim

- To investigate the safety, tolerability, pharmacodynamics, and effect on exploratory biomarkers of disease activity of mivelsiran in patients with EOAD.

Methods

Study Design and Patients

- Phase 1, double-blind, placebo-controlled, single ascending dose study (NCT05231785) (**Figure 2**).
- Patients were evaluated at Month 6 with additional follow-up of up to 6 months for drug washout.
- Interim safety, pharmacodynamic, and exploratory biomarker data are reported.
- Baseline characteristics and safety data are reported in pooled cohorts of mivelsiran and placebo, to preserve blinding in this ongoing study.

Figure 2. Mivelsiran Phase 1 Part A Study Design

Study Population

- Patients with EOAD
- Mild cognitive impairment or mild dementia with symptom onset <65 years of age
- MMSE score >20
- CDR global score 0.5 or 1.0
- Confirmed AD via CSF biomarkers or Aβ-PET

Dose Cohorts[a] (6-month minimum observation period)	R (IT mivelsiran or PBO)	N
25 mg	2:1	N=6
35 mg	3:1	N=8
50 mg	3:1	N=8
75 mg	2:1	Pooled analysis: N=6
75 mg	3:1	Pooled analysis: N=8

Endpoints

Primary Endpoint
- Safety and tolerability measured by frequency of AEs

Secondary Endpoints
- PK: mivelsiran CSF and plasma profile
- PD: change from baseline in CSF levels of sAPPα and sAPPβ

Exploratory Endpoints
- Biomarkers of disease progression: change from baseline in CSF levels of Aβ42 and Aβ40

[a]Cohorts were not enrolled by ascending dose temporally; cohort enrollment initiated with 25 mg and then 75 mg, in which 6 patients were randomized 2:1 each. Following this, further dose exploration occurred through enrollment of cohorts randomized in a 3:1 fashion.
Aβ, amyloid beta; AD, Alzheimer's disease; AE, adverse event; CDR, Clinical Dementia Rating; CSF, cerebrospinal fluid; EOAD, early-onset Alzheimer's disease; IT, intrathecal; MMSE, Mini-Mental State Examination; PBO, placebo; PD, pharmacodynamics; PET, positron emission tomography; PK, pharmacokinetics; R, randomization; sAPP, soluble amyloid precursor protein.

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Results

Patient Population and Disposition

- A total of 36 patients with EOAD were enrolled (**Table 1**).
- There were three discontinuations during the 12-month observation and follow-up period; none were deemed related to study drug.
  - Withdrawal by the patient ([n=2] 35 mg or placebo and 50 mg or placebo cohorts).
  - Death (75 mg or placebo cohort).

Table 1. Pooled Demographics and Baseline Disease Characteristics

Characteristic	All patients (N=36)
Mean age, years (SD)	60.9 (5.4)
Male, n (%)	21 (58.3)
Race, n (%)	
White	30 (83.3)
Asian	4 (11.1)
Black/African American	1 (2.8)
CDR global score, n (%)	
0.5	30 (83.3)
1.0	6 (16.7)
Mean MMSE score (SD)	24.6 (2.8)
Mean BMI, kg/m² (SD)	26.0 (3.4)

Data shown as of 18 April 2024.
BMI, body mass index; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; SD, standard deviation.

Blinded Safety

- Most AEs were mild or moderate in severity and nonserious (**Table 2**).
- Three patients had AEs deemed related to study drug by the investigator; all events resolved.
  - One patient receiving mivelsiran 50 mg or placebo had two mild AEs (post-lumbar puncture [LP] headache and nausea), each deemed study drug-related and LP-related.
  - One patient receiving mivelsiran 75 mg or placebo had three moderate AEs (post-LP headache, neck pain, and vomiting), each deemed study drug-related and LP-related.
    - The same patient had one mild AE (lymphocytopenia), deemed study drug-related and not LP-related.
  - One patient receiving mivelsiran 75 mg or placebo had two moderate AEs (post-LP vomiting and post-LP headache), each deemed study drug-related and LP-related.
- One patient experienced a serious and severe AE of acute pancreatitis on day 277 after receiving a single dose of mivelsiran 75 mg or placebo, deemed unrelated to study drug.
  - The event resulted in a fatal outcome on day 288.
- CSF safety biomarkers, routine lab assessments, and preliminary data for the exploratory biomarker neurofilament light chain all continued to show no significant abnormalities.

Table 2. AE Summary in Blinded Cohorts

Patients with events	Mivelsiran 25 mg or placebo (N=6, PY=6.9)	Mivelsiran 35 mg or placebo (N=8, PY=4.8)	Mivelsiran 50 mg or placebo (N=8, PY=7.6)	Mivelsiran 75 mg or placebo (N=14, PY=13.5)
Time from randomization, months, mean (SD)	13.89 (1.46)	7.27 (0.79)	11.45 (3.66)	11.60 (2.86)
At least one AE, n (%)	6 (100.0)	8 (100.0)	7 (87.5)	14 (100.0)
Related to study drug	0	0	1 (12.5)	2 (14.3)
Related to LP	4 (66.7)	7 (87.5)	6 (75.0)	7 (50.0)
At least one moderate AE, n (%)	4 (66.7)	4 (50.0)	5 (62.5)	10 (71.4)
At least one severe AE, n (%)	0	0	0	1 (7.1)[a]
At least one serious AE, n (%)	0	0	0	1 (7.1)[a]
Deaths, n (%)	0	0	0	1 (7.1)[a]
Related to study drug	0	0	0	0

Data shown as of 18 April 2024.
[a]One AE of acute pancreatitis.
AE, adverse event; LP, lumbar puncture; PY, patient-years; SD, standard deviation.

- Procedural headache AE occurred in the most patients (41.7% of patients) (**Table 3**); all were mild or moderate in severity.

Table 3. AEs by Preferred Term in Blinded Cohorts

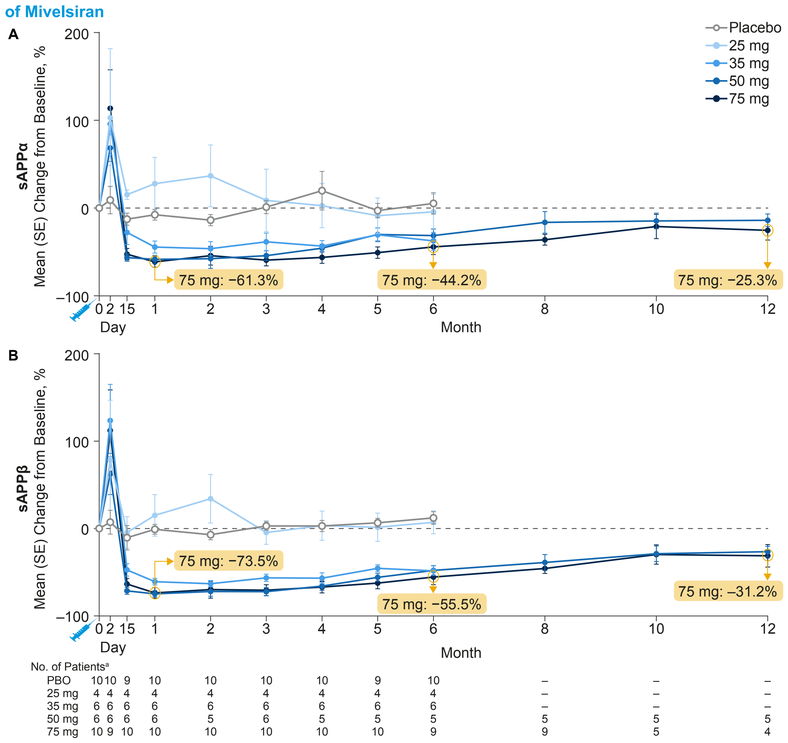
Patients with event, n (%)	Mivelsiran 25 mg or placebo (N=6, PY=6.9)	Mivelsiran 35 mg or placebo (N=8, PY=4.8)	Mivelsiran 50 mg or placebo (N=8, PY=7.6)	Mivelsiran 75 mg or placebo (N=14, PY=13.5)	Total (N=36)
AEs reported in at least three patients					
Procedural headache	3 (50.0)	4 (50.0)	6 (75.0)	2 (14.3)	15 (41.7)
Related to LP	3 (50.0)	4 (50.0)	6 (75.0)	2 (14.3)	15 (41.7)
Procedural pain	3 (50.0)	2 (25.0)	3 (37.5)	2 (14.3)	10 (27.8)
Related to LP	2 (33.3)	2 (25.0)	3 (37.5)	2 (14.3)	9 (25.0)
Back pain	0	3 (37.5)	0	2 (14.3)	5 (13.9)
Fall	0	1 (12.5)	0	4 (28.6)	5 (13.9)
Nasopharyngitis	0	1 (12.5)	0	4 (28.6)	5 (13.9)
Procedural vomiting	1 (16.7)	1 (12.5)	0	2 (14.3)	4 (11.1)
Related to LP	1 (16.7)	1 (12.5)	0	2 (14.3)	4 (11.1)
Headache	0	1 (12.5)	1 (12.5)	1 (7.1)	3 (8.3)
Presyncope	0	0	1 (12.5)	2 (14.3)	3 (8.3)
Related to LP	0	0	0	1 (7.1)	1 (2.8)
Syncope	2 (33.3)	0	0	1 (7.1)	3 (8.3)

Data shown as of 18 April 2024.
AE, adverse event; LP, lumbar puncture; PY, patient-years.

Pharmacodynamics – CSF sAPPα and sAPPβ

- A single dose of mivelsiran above 25 mg rapidly reduced CSF sAPPα and sAPPβ levels.
  - Peak mean reductions from baseline with mivelsiran 75 mg were 61.3% for sAPPα and 73.5% for sAPPβ at Month 1 (**Figure 3**).
- Dose-dependent reductions were sustained through Month 6.
- Reductions were observed through 12 months with single 50 mg or 75 mg doses.

Figure 3. Robust and Durable Reductions from Baseline in CSF sAPPα and sAPPβ after Single Dose of Mivelsiran



No. of Patients[a]

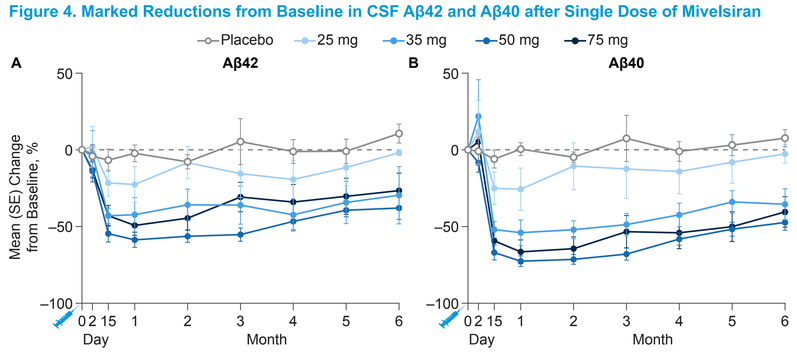
PBO	10	10	9	10	10	10	10	9	10	–	–	–
25 mg	4	4	4	4	4	4	4	4	4	–	–	–
35 mg	6	6	6	6	6	6	6	6	6	–	–	–
50 mg	6	6	6	6	5	6	5	5	5	5	5	5
75 mg	10	9	10	10	10	10	10	9	9	5	5	4

Data shown as of July 10, 2024. Time points with n≤3 are not plotted. [a]Numbers of patients are the same for both panels A and B.
CSF, cerebrospinal fluid; PBO, placebo; sAPP, soluble amyloid precursor protein; SE, standard error.

Exploratory Biomarkers – CSF Aβ42 and Aβ40

- A single dose of mivelsiran above 25 mg reduced CSF Aβ42 and Aβ40 levels.
  - Peak mean reductions with mivelsiran 75 mg were –49.3% for Aβ42 and –66.5% for Aβ40 at Month 1.
- Reductions were sustained through Month 6 at doses of 35 mg or higher (**Figure 4**).

Figure 4. Marked Reductions from Baseline in CSF Aβ42 and Aβ40 after Single Dose of Mivelsiran



Data shown as of July 10, 2024. Placebo: n=10, except Days 2 and 15, Months 5 and 6: n=9; 25 mg mivelseran: n=4; 35 mg mivelsiran: n=6, except Month 6: n=4; 50 mg mivelsiran: n=6, except Months 4–6: n=5; 75 mg mivelsiran: n=10, except for Aβ42 assessment on Day 2: n=9.
Aβ40, amyloid beta peptide length 40 amino acids; Aβ42, amyloid beta peptide length 42 amino acids; CSF, cerebrospinal fluid; PBO, placebo; SE, standard error.

DISCLOSURES

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