Mivelsiran: Phase 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 the FDA or any health authority.

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SUMMARY

- Mivelsiran is an IT administered RNAi therapeutic being investigated in adults for the treatment of EOAD and CAA.[1]
- Mivelsiran is an investigational 2'-O-hexadecyl (C16)-conjugated RNAi therapeutic that 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 (including Aβ40 and Aβ42). This downstream effect may thereby reduce amyloidogenic protein fragments and amyloid deposition in tissues.[1,2]
- The safety, tolerability, PD, and PK of mivelsiran in patients with EOAD are being evaluated in an ongoing randomized, double-blind, placebo-controlled, 2-part Phase 1 study (NCT05231785).[1,3]

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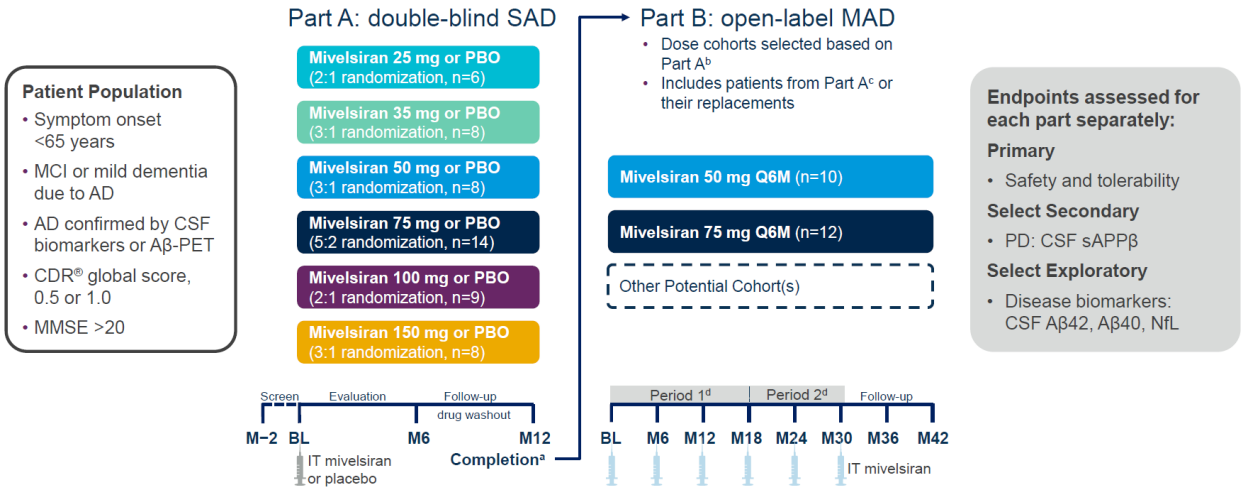
STUDY DESIGN

The Phase 1 study (NCT05231785) is an ongoing, global, randomized, double-blind, placebo-controlled, 2-part study designed to evaluate the safety, tolerability, PD, and PK of mivelsiran in patients with EOAD. Part A of the study is a double-blind, single-ascending dose study, while Part B of the study is an open-label multi-dose study of mivelsiran.[1,3]

In Part A, study participants (N=36) were dosed with a single dose of mivelsiran or placebo via IT administration. Following completion of Part A, eligible patients were sequentially assigned to Part B cohorts (**Figure 1**).[3]

Figure 1. Phase 1 Study Design of Mivelsiran in EOAD.[3]



Abbreviations: AD = Alzheimer's disease; Aβ = amyloid-beta; Aβ40 = Aβ peptide length 40 amino acids; Aβ42 = Aβ peptide length 42 amino acids; BL = baseline; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; EOAD = early onset Alzheimer's disease; IT = intrathecal; M = month; MAD = multiple ascending dose; MCI = mild cognitive impairment; MMSE = Mini Mental State Examination; NfL = neurofilament light chain protein; PBO = placebo; PD = pharmacodynamics; PET = positron emission tomography; Q6M = every 6 months; SAD = single ascending dose; sAPP = soluble amyloid precursor protein.

[a]Patients are determined to have completed Part A at or after Month 6 when sAPPα and sAPPβ levels have returned to ≥75% of the patient's Day 1 sAPPα and sAPPβ level for two consecutive visits or at Month 12, whichever is earlier.

[b]Acceptable safety profile in Part A, and ≥25% reduction in CSF sAPPα and sAPPβ in ≥3 patients.

[c]Eligible patients from Part A are sequentially assigned to Part B cohorts based on the order of Part A study completion.

[d]In period 1, up to four dosing regimens will be evaluated; in period 2, cohorts are consolidated into up to two dosing regimens at the Month 18 visit.

From Cohen et al.[3]

The primary endpoint assessed for each part separately is the safety and tolerability of mivelsiran as measured by the frequency of AEs. The secondary endpoints of the study are to assess the PK profile of mivelsiran in CSF and plasma and the PD of mivelsiran through change from baseline in CSF levels of sAPPα and sAPPβ. Exploratory endpoints assess biomarkers of disease progression through change from baseline in CSF levels of Aβ42, Aβ40, and NfL.[1,3]

PATIENT DEMOGRAPHICS & BASELINE CHARACTERISTICS

The patient demographics and baseline characteristics of patients enrolled in Part A and Part B are presented in **Table 1**.[3]

Table 1. Patient Demographics and Baseline Characteristics Across Cohorts in Parts A and B.[3]

Characteristic	Part A: SAD (N=53)							Part B: MAD (N=22)	
	25 mg (n=4)	35 mg (n=6)	50 mg (n=6)	75 mg (n=10)	100 mg (n=6)	150 mg (n=6)	Placebo (n=15)	50 mg (n=10)	75 mg (n=12)
Age, years, mean (SD)	56.5 (3.3)	60.7 (4.7)	62.0 (5.4)	62.2 (6.7)	66.0 (2.4)	62.2 (5.4)	61.1 (4.9)	59.9 (4.4)	64.3 (4.7)
Male, n (%)	4 (100.0)	4 (66.7)	2 (33.3)	6 (60.0)	3 (50.0)	3 (50.0)	7 (46.7)	7 (70.0)	6 (50.0)
Race, n (%)									
White	2 (50.0)	5 (83.3)	5 (83.3)	10 (100.0)	6 (100.0)	6 (100.0)	13 (86.7)	7 (70.0)	10 (83.3)

Characteristic	Part A: SAD (N=53)							Part B: MAD (N=22)	
	25 mg (n=4)	35 mg (n=6)	50 mg (n=6)	75 mg (n=10)	100 mg (n=6)	150 mg (n=6)	Placebo (n=15)	50 mg (n=10)	75 mg (n=12)
Asian	1 (25.0)	0	1 (16.7)	0	0	0	2 (13.3)	2 (20.0)	2 (16.7)
Black/African American	1 (25.5)	0	0	0	0	0	0	1 (10.0)	0
Unknown/ Other	0	1	0	0	0	0	0	0	0
CDR global score, n (%)									
0.0	0	0	0	0	0	1 (16.7)	0	0	0
0.5	4 (100.0)	6 (100.0)	5 (83.3)	8 (80.0)	5 (83.3)	4 (66.7)	10 (66.7)	3 (30.0)	9 (75.0)
1.0	0	0	1 (16.7)	2 (20.0)	1 (16.7)	1 (16.7)	5 (33.3)	6 (60.0)	2 (16.7)
2.0	0	0	0	0	0	0	0	1 (10.0)	0
Missing data	0	0	0	0	0	0	0	0	1
MMSE score, mean (SD)	22.8 (1.0)	25.2 (3.2)	25.0 (3.0)	25.4 (3.1)	27.2 (2.6)	26.0 (3.6)	24.1 (2.9)	–[a]	–[a]
BMI, kg/m^2, mean (SD)	26.1 (1.8)	26.5 (2.8)	25.6 (4.1)	25.0 (3.6)	23.9 (4.7)	26.3 (4.6)	25.5 (4.1)	26.7 (3.4)	27.1 (4.3)
APOE4 carrier[b], n (%)	2 (50.0)	4 (66.7)	4 (66.7)	7 (70.0)	6 (100.0)	3 (50.0)	9 (60.0)	4 (40.0)	10 (83.3)

Abbreviations: ApoE = apolipoprotein E; BMI = body mass index; CDR = Clinical Dementia Rating; MAD = multiple ascending dose; MMSE = Mini Mental State Examination; SAD = single ascending dose; SD = standard deviation.

Data shown as of May 15, 2025.

[a]Unavailable at the time of presentation.

[b]At least one E4 allele.

SAFETY RESULTS

The safety and tolerability of mivelsiran was monitored throughout the study and in the follow-up period as a primary endpoint. A majority of the AEs were nonserious, mild or moderate, and considered not related to study drug. There were no serious or severe AEs that were considered related to study drug. The most common AEs were procedural pain and procedural headache. No drug-related ARIA events have occurred in the study as of a data cut-off of May 15, 2025, and no ARIA-E was observed. A safety summary of AEs across cohorts in Part A and Part B is shown in **Table 2**.[3]

Table 2. Safety Summary Across Cohorts in Parts A and B.[3]

Events, n (%)	Part A: SAD (N=53)							Part B: MAD (N=22)	
	25 mg (n=4) PY=4.5	35 mg (n=6) PY=6.4	50 mg (n=6) PY=6.2	75 mg (n=10) PY=11.6	100 mg (n=6) PY=7.3	150 mg (n=6) PY=5.6	Placebo (n=15) PY=11.9	50 mg (n=10) PY=14.6	75 mg (n=12) PY=10.6
Duration on study months, mean (SD)	13.6 (1.5)	12.8 (2.8)	12.4 (4.5)	13.9 (2.5)	14.7 (1.3)	11.1 (1.2)	9.5 (3.3)	17.6 (2.1)	10.7 (3.0)
At least 1 AE	4 (100.0)	6 (100.0)	6 (100.0)	10 (100.0)	6 (100.0)	6 (100.0)	14 (93.3)	10 (100.0)	10 (83.3)
Related to study drug	0	0	1 (16.7)	2 (20.0)	0	2 (33.3)	1 (6.7)	0	1 (8.3)

Events, n (%)	Part A: SAD (N=53)							Part B: MAD (N=22)	
	25 mg (n=4) PY=4.5	35 mg (n=6) PY=6.4	50 mg (n=6) PY=6.2	75 mg (n=10) PY=11.6	100 mg (n=6) PY=7.3	150 mg (n=6) PY=5.6	Placebo (n=15) PY=11.9	50 mg (n=10) PY=14.6	75 mg (n=12) PY=10.6
Related to LP	3 (75.0)	5 (83.3)	5 (83.3)	5 (50.0)	6 (100.0)	2 (33.3)	10 (66.7)	7 (70.0)	5 (41.7)
At least 1 severe AE	0	0	0	1 (10.0)[a]	0	1 (16.7)	1 (6.7)	0	0
At least 1 serious AE	0	0	0	1 (10.0)[a]	0	1 (16.7)	0	0	1 (8.3)
Death	0	0	0	1 (10.0)[a]	0	0	0	0	0

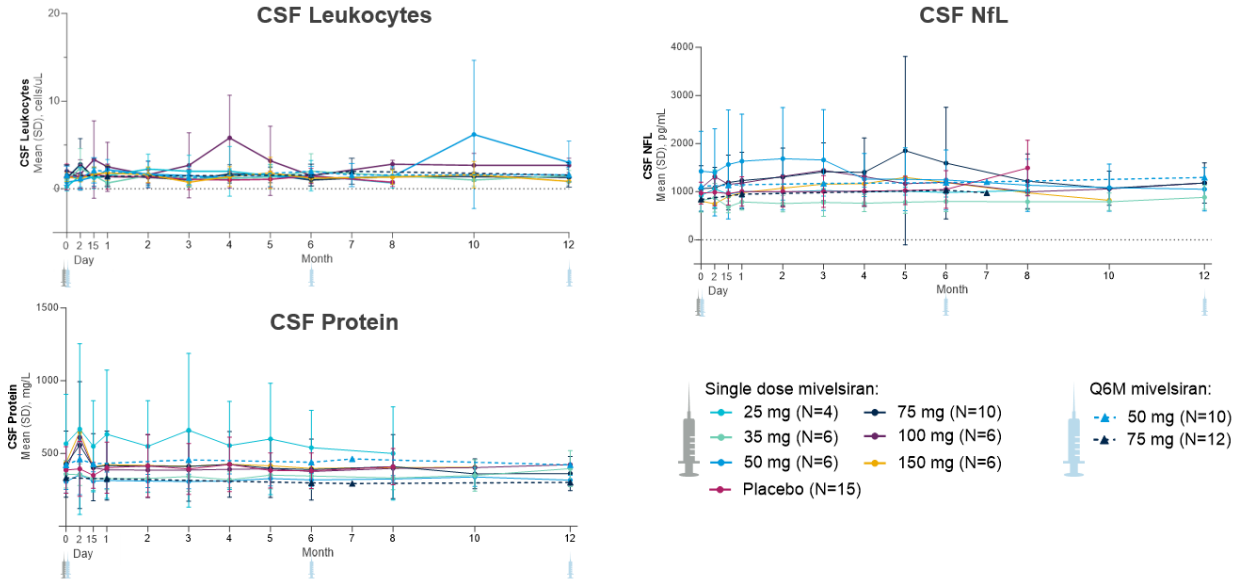
Abbreviations: AE = adverse event; ARIA-E = amyloid-related imaging abnormality presenting as edema; LP = lumbar puncture; MAD = multiple ascending dose; PY = patient years; SAD = single ascending dose; SD = standard deviation.

[a]One patient had one event of acute pancreatitis on Day 277 after dosing that was fatal on Day 288. The event was classified as serious, severe, and not related to study drug/LP.

Data shown as of May 15, 2025.

Immune responses were not observed following single or multiple doses of mivelsiran, as assessed by routine CSF laboratory assessments (**Figure 2**).[3]

Figure 2. CSF Safety Laboratory Assessments of Mivelsiran.[3]



Abbreviations: CSF = cerebrospinal fluid; NfL = neurofilament light chain; Q6M = every 6 months; SD = standard deviation.

Data shown as of May 15, 2025.

From Cohen et al.[3]

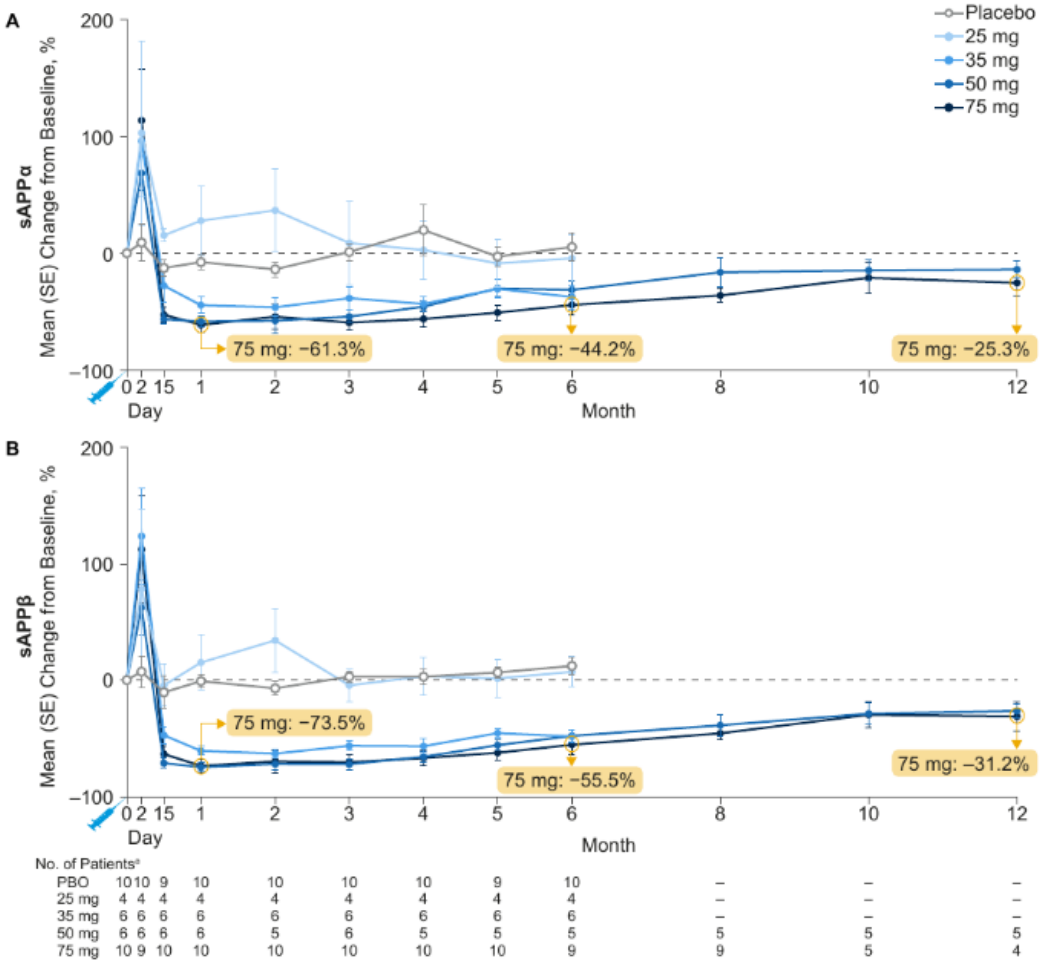
PHARMACODYNAMIC RESULTS

CSF sAPPα and sAPPβ

In an interim analysis of Part A (25 mg, 35 mg, 50 mg, and 75 mg cohorts), there was a rapid reduction in CSF sAPPα and sAPPβ levels following a single dose of mivelsiran above 25 mg (**Figure 2**). At Month 1 following a single dose of mivelsiran 75 mg, peak mean reductions from baseline were 61.3% and 73.5%

for sAPPα and sAPPβ, respectively. Dose-dependent reductions were sustained through Month 6, and reductions were observed through 12 months with the single 50 or 75 mg doses.[1]

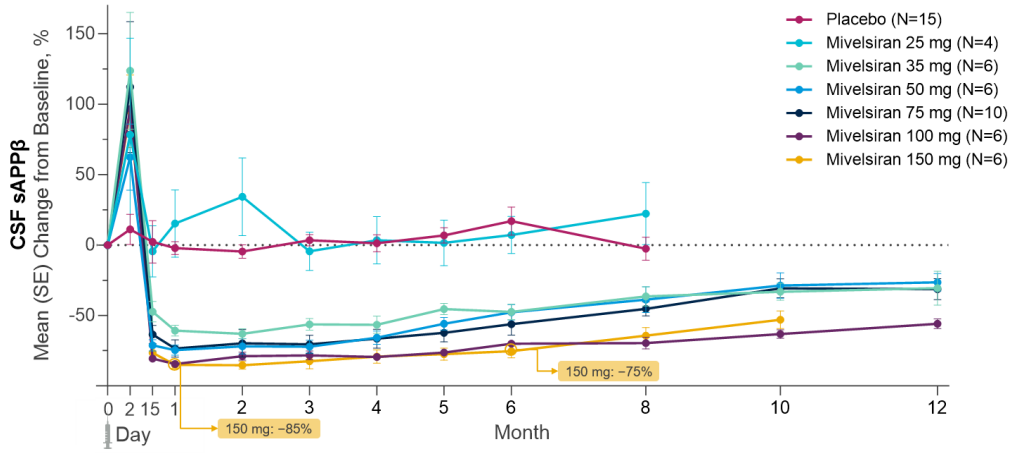
Figure 3. Mean Percent Change from Baseline in CSF sAPPα and sAPPβ After Single Dose of Mivelsiran.[1]



Abbreviations: CSF = cerebrospinal fluid; PBO = placebo; sAPP = soluble amyloid precursor protein; SE = standard error.
[a]Number of patients are the same for both panels A and B.
Data shown as of July 10, 2024. Time points with n≤3 are not plotted.
From Cohen et al.[1]

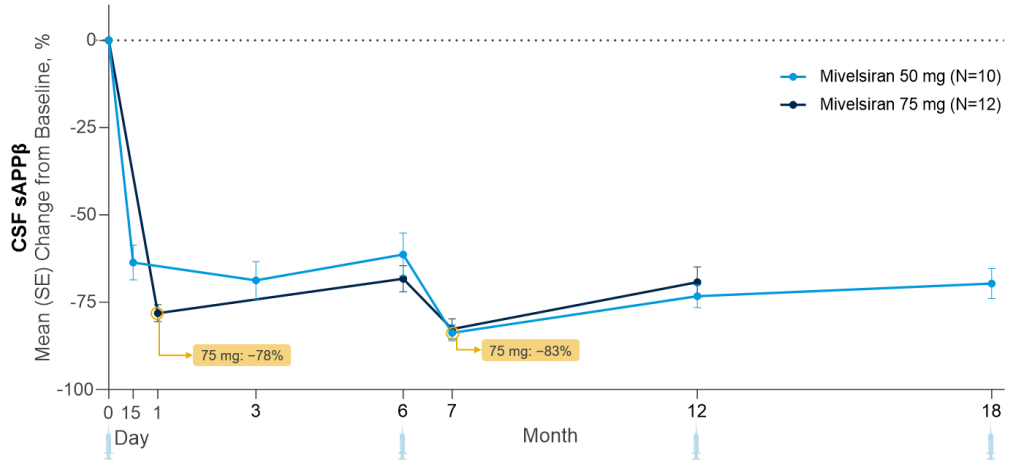
Additional data on the mean percent change from baseline in CSF sAPPβ levels after single and multiple doses of mivelsiran are presented in **Figures 4 and 5,** respectively. Following a single dose of mivelsiran 150 mg, the peak mean reduction from baseline in sAPPβ was 85% and 75% at Month 1 and Month 6, respectively.[3]

Figure 4. Mean Percent Change from Baseline in CSF sAPPβ After Single Dose of Mivelsiran.[3]



Abbreviations: CSF = cerebrospinal fluid; D = day; M, month; sAPP = soluble amyloid precursor protein; SE = standard error.
Data shown as of May 15, 2025. Time points with an n of <3 are not plotted.
Placebo: n=14 (D2), n= 13 (D15, M1–3, M6), n=12 (M4), n=11 (M5), n=3 (M8); mivelsiran 25 mg: n=4 (M6), n=3 (M8); mivelsiran 35 mg: n=5 (M8, M10), n=4 (M12); mivelsiran 50 mg: n=5 (M2, M4–12), mivelsiran 75 mg: n=9 (D2), n=8 (M10, M12); mivelsiran 100 mg: n=5 (M2, M4, M8, M12); mivelsiran 150 mg: n=5 (M1, M2, M4–6, M10), n=4 (M3).
From Cohen et al.[3]

Figure 5. Change from Baseline in CSF sAPPβ With Mivelsiran Q6M Dosing.[3]



Abbreviations: CSF = cerebrospinal fluid; M, month; Q6M = every 6 months; sAPP = soluble amyloid precursor protein; SE = standard error.
Data shown as of May 15, 2025. Time points with an n of <3 are not plotted.
Mivelsiran 50 mg: n=8 (M3), n=9 (M7), n=5 (M18); mivelsiran 75 mg: n=10 (M6, M7), n=6 (M12).
From Cohen et al.[3]

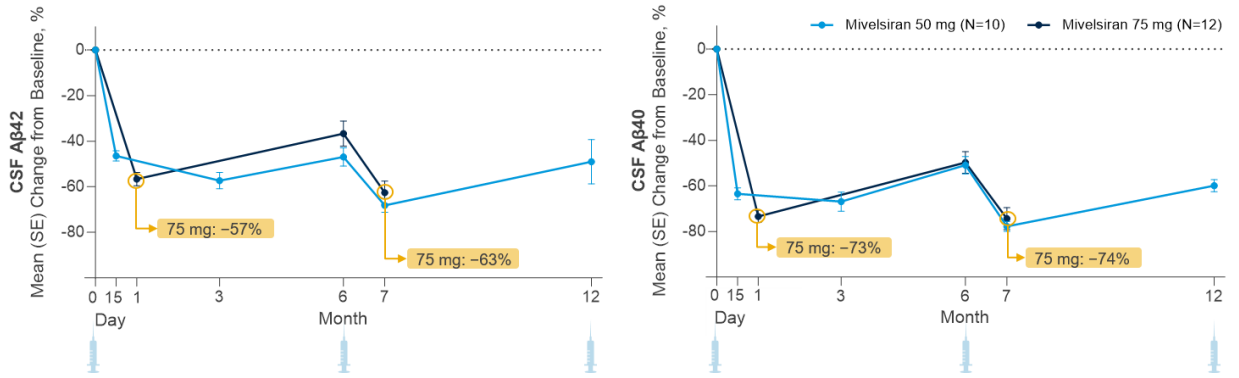
EXPLORATORY RESULTS

CSF Aβ42 and Aβ40

In Part A, reductions in CSF Aβ42 and Aβ40 were observed with all doses at Day 15. In the 150 mg cohort, the peak mean (SE) reductions from baseline in CSF Aβ42 and Aβ40 were 61% (8) and 79% (5), respectively, at Month 2. Following a single dose of mivelsiran over 25 mg, mean reductions in Aβ42 over 25% and in Aβ40 over 30% were sustained to Month 6.[3]

The change from baseline in CSF Aβ42 and Aβ40 observed with multiple doses of mivelsiran in Part B is presented in **Figure 6**.[3]

Figure 6. Mean Percent Change from Baseline in CSF Aβ42 and Aβ40 After Multiple Doses of Mivelsiran.[3]



Abbreviations: Aβ = amyloid beta; Aβ40 = Aβ peptide length 40 amino acids; Aβ42 = Aβ peptide length 42 amino acids; CSF = cerebrospinal fluid; SE = standard error.
Data shown as of May 15, 2025. Time points with an n of <3 are not plotted.
From Cohen et al.[3]

ABBREVIATIONS

Aβ = amyloid beta; Aβ40 = amyloid beta peptide length 40 amino acids; Aβ42 = amyloid beta peptide length 42 amino acids; AD = Alzheimer's disease; AE = adverse event; ApoE = apolipoprotein E; APP = amyloid precursor protein; ARIA-E = amyloid-related imaging abnormality presenting as edema; BL = baseline; BMI = body mass index; CAA = cerebral amyloid angiopathy; CDR = Clinical Dementia Rating; CNS = central nervous system; CSF = cerebrospinal fluid; EOAD = early onset Alzheimer's disease; IT = intrathecal; LP = lumbar puncture; M = month; MAD = multiple ascending dose; MCI = mild cognitive impairment; MMSE = Mini Mental State Examination; NfL = neurofilament light chain protein; PBO = placebo; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; PY = patient-years; Q6M = every 6 months; RNAi = ribonucleic acid interference; SAD = single ascending dose; sAPP = soluble amyloid precursor protein; SD = standard deviation; SE = standard error; ULN = upper limit of normal.

Updated 05 August 2025

REFERENCES

1. Cohen S, Ducharme S, Brosch J, et al. 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. Presented at: Alzheimer's Association International Conference (AAIC); July 28-August 1, 2024; Philadelphia, PA, USA.
2. Cohen S, Ducharme S, Brosch J, et al. Interim phase 1 part A results for ALN-APP, the first investigational RNAi therapeutic in development for Alzheimer's disease. Presented at: Alzheimer's Association International Conference (AAIC); July 16-20, 2023; Amsterdam, Netherlands.
3. Cohen S, Ducharme S, Brosch J, et al. 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. Presented at: Alzheimer's Association International Conference (AAIC); July 27-31, 2025; Toronto, Canada.