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

Sharon Cohen, MD, FRCPC
Toronto Memory Program, Toronto, ON, Canada

Presented at the Alzheimer's Association International Conference (AAIC) in Toronto, Canada, July 27–31, 2025

Disclosures

Speaker: Sharon Cohen, MD, FRCPC

Conflict	Disclosure
Research Support	AbbVie,[a] AgeneBio,[a] Alector,[a] Alnylam Pharmaceuticals, Alzheon, Anavex,[a] Biogen, BMS, Cassava, Davos Alzheimer's Collaborative[a], Eisai, Eli Lilly, Global Alzheimer's Platform Foundation,[a] GSK, INmune Bio, Janssen, Novo Nordisk, RetiSpec, Roche, UCB Biopharma
Advisory Committee/Consultant	Alnylam Pharmaceuticals, Biogen, Biohaven, BMS, Cassava, Cognivue, Cogtate, Eisai, Eli Lilly, GSK, INmune Bio, Kisbee Therapeutics,[a] Lundbeck,[a] Novartis, Novo Nordisk, Parexel,[a] RetiSpec, Roche, SciNeuro Pharmaceuticals[a]

Mivelsiran:

Mivelsiran is an investigational drug being studied for the treatment of cerebral amyloid angiopathy and Alzheimer's disease. Mivelsiran is not approved by any health authority, and the safety and efficacy of mivelsiran have not been established.

Funding:

The mivelsiran clinical program has been funded by Alnylam Pharmaceuticals and Regeneron Pharmaceuticals. Medical writing support, provided by Valentina Bart PhD of PharmaGenesis Cardiff, Cardiff, UK, was funded by Alnylam Pharmaceuticals in accordance with Good Publication Practice guidelines.

[a]Relationship has ended.

RNA Interference in the CNS

Technology Advances have Enabled Development of RNAi Therapeutics to Reduce Production of Disease-Associated Proteins in the CNS[1]

Synthetic double-stranded small interfering RNA (siRNA) designed to target specific mRNA[2–4]

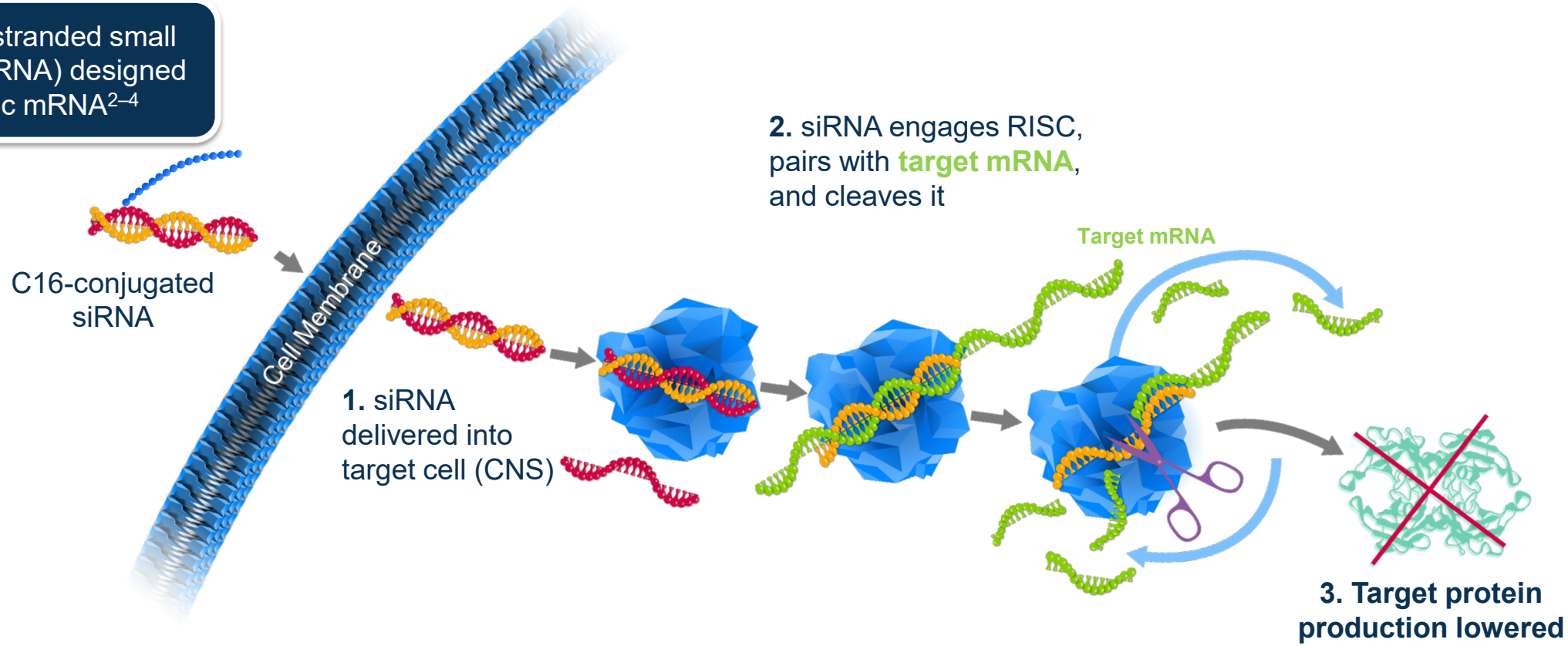


Image created by Alnylam Pharmaceuticals from data published in Jadhav *et al.* 2024.

C16, 2'-O-hexadecyl; CNS, central nervous system; mRNA, messenger RNA; RISC, RNA-induced silencing complex; RNAi, RNA interference; siRNA, small interfering RNA.

1. Brown KM *et al. Nat Biotechnol* 2022;40:1500–8. 2. Niemietz C *et al. Molecules* 2015;20:17944–75. 3. Ranasinghe R *et al. Br J Pharmacol* 2023;180:2697–720. 4. Jadhav V *et al. Nature Biotechnol* 2024;42:394–405.

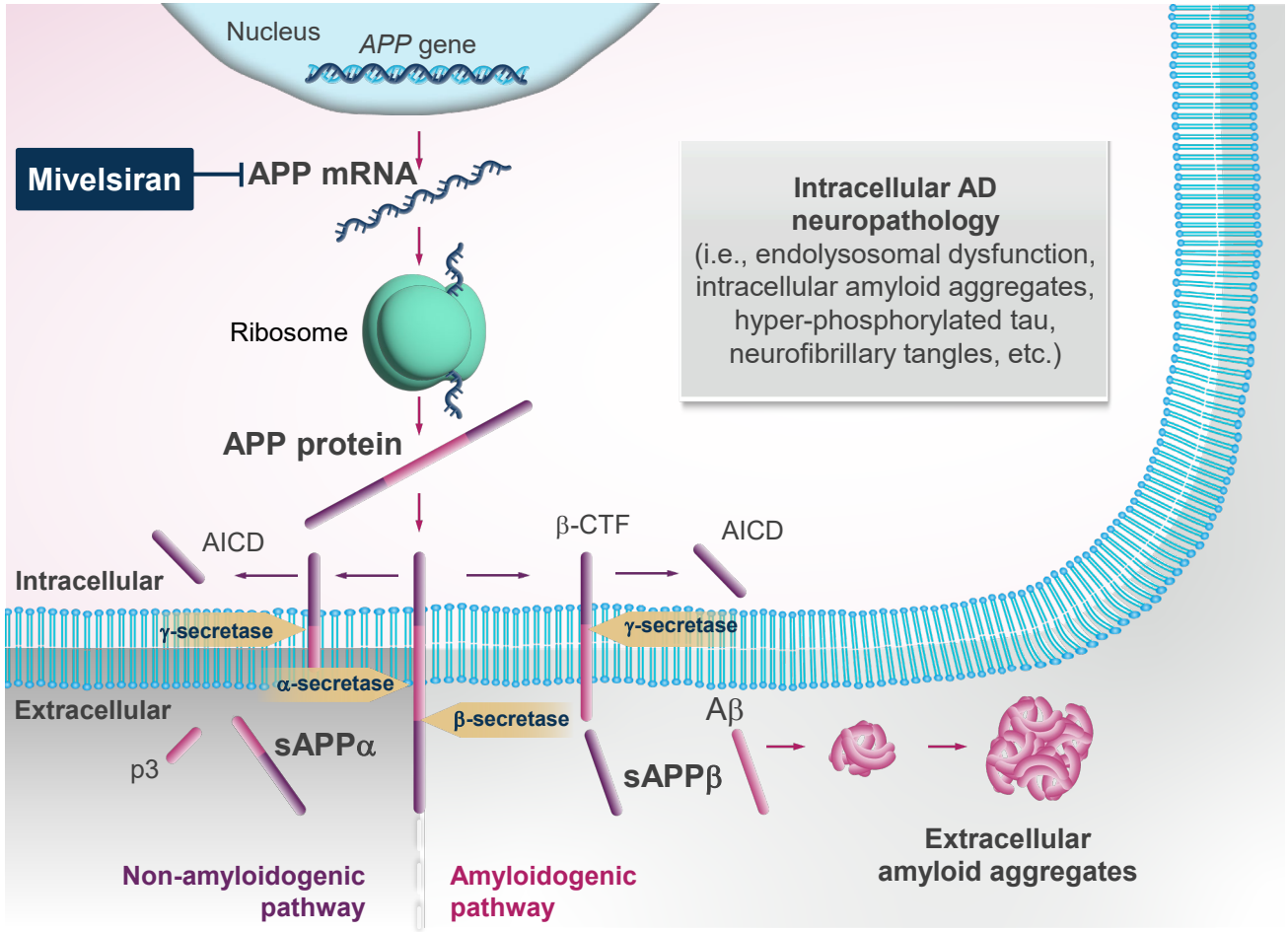
Mivelsiran Targets Aβ Precursor Protein (APP)

Scan to View Preclinical Congress Poster Presented

For US HCPs Only

- Despite recent therapeutic progress, an unmet need remains for AD[1]
- Mivelsiran is an investigational RNAi therapeutic for AD and CAA
  - Targets APP mRNA, upstream of APP cleavage to Aβ peptides[2–4]
- Lowering APP production may:
  - Reduce intracellular and extracellular drivers of AD pathology[5] to stabilize or improve clinical manifestations
  - Avoid safety risks, such as ARIA[a]

Here, we present original multiple-dose data on mivelsiran from an ongoing Phase 1 study in early-onset AD



[a]APP-targeting siRNA is not expected to directly interact with vascular amyloid or drive immuno-active Aβ clearance.

AD, Alzheimer's disease; AICD, APP intracellular domain; APP, Aβ precursor protein; ARIA, amyloid-related imaging abnormalities; Aβ, amyloid-beta; CAA, cerebral amyloid angiopathy; HCP, healthcare provider; mRNA, messenger RNA; p3, p3 peptide; RNAi, RNA interference; sAPP, soluble APP; β-CTF; C-terminal fragment beta.

1. Mummery CJ *et al. Nat Med* 2023;29:1437–47. 2. Cohen S *et al. Alzheimers Dement* 2024;20(Suppl 6):e084521. 3. ClinicalTrials.gov. NCT05231785. Available from: https://clinicaltrials.gov/study/NCT05231785 (Accessed June 5, 2025). 4. ClinicalTrials.gov. NCT06393712. Available from: https://clinicaltrials.gov/study/NCT06393712 (Accessed June 5, 2025). 5. Dang LTH *et al.* The International Conference on Alzheimer's and Parkinson's Disease (AD/PD) and Related Neurological Disorders. 2024. Poster. 6. Sperling RA *et al. Alzheimers Dement* 2011;7:367–85.

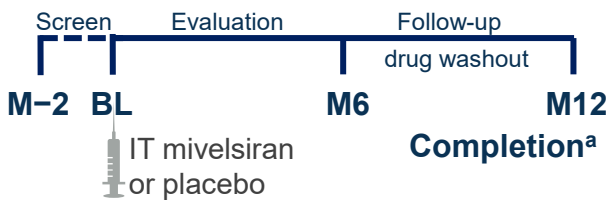
Ongoing Two-Part Phase 1 Study to Evaluate Mivelsiran in Early-Onset AD

Patient Population

- Symptom onset <65 years
- MCI or mild dementia due to AD
- AD confirmed by CSF biomarkers or Aβ-PET
- CDR® global score, 0.5 or 1.0
- MMSE >20

Part A: double-blind SAD

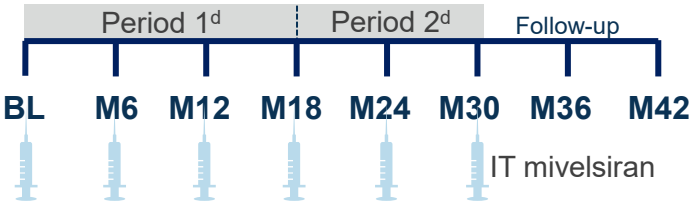
- **Mivelsiran 25 mg or PBO** (2:1 randomization, n=6)
- **Mivelsiran 35 mg or PBO** (3:1 randomization, n=8)
- **Mivelsiran 50 mg or PBO** (3:1 randomization, n=8)
- **Mivelsiran 75 mg or PBO** (5:2 randomization, n=14)
- **Mivelsiran 100 mg or PBO** (2:1 randomization, n=9)
- **Mivelsiran 150 mg or PBO** (3:1 randomization, n=8)



Part B: open-label MAD

- Dose cohorts selected based on Part A[b]
- Includes patients from Part A[c] or their replacements

- **Mivelsiran 50 mg Q6M** (n=10)
- **Mivelsiran 75 mg Q6M** (n=12)
- Other Potential Cohort(s)



Endpoints assessed for each part separately:

Primary

- Safety and tolerability

Select Secondary

- PD: CSF sAPPβ

Select Exploratory

- Disease biomarkers: CSF Aβ42, Aβ40, NfL

NCT05231785. [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.

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; IT, intrathecally; 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, once every 6 months; SAD, single ascending dose; sAPP, soluble Aβ precursor protein.

Baseline Characteristics Generally Balanced Across Cohorts

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)
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/m², 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)

Data shown as of May 15, 2025, patients with EOAD. [a]Unavailable at the time of presentation. [b]At least one E4 allele.

ApoE, apolipoprotein E; BMI, body mass index; CDR, Clinical Dementia Rating; EOAD, early-onset Alzheimer's disease; MAD, multiple ascending dose; MMSE, Mini Mental State Examination; SAD, single ascending dose; SD, standard deviation.

Mivelsiran Was Generally Well Tolerated Across Dose Levels

Patients with events	Part A: SAD (N=53)							Part B: MAD (N=22)	
n (%)	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)
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

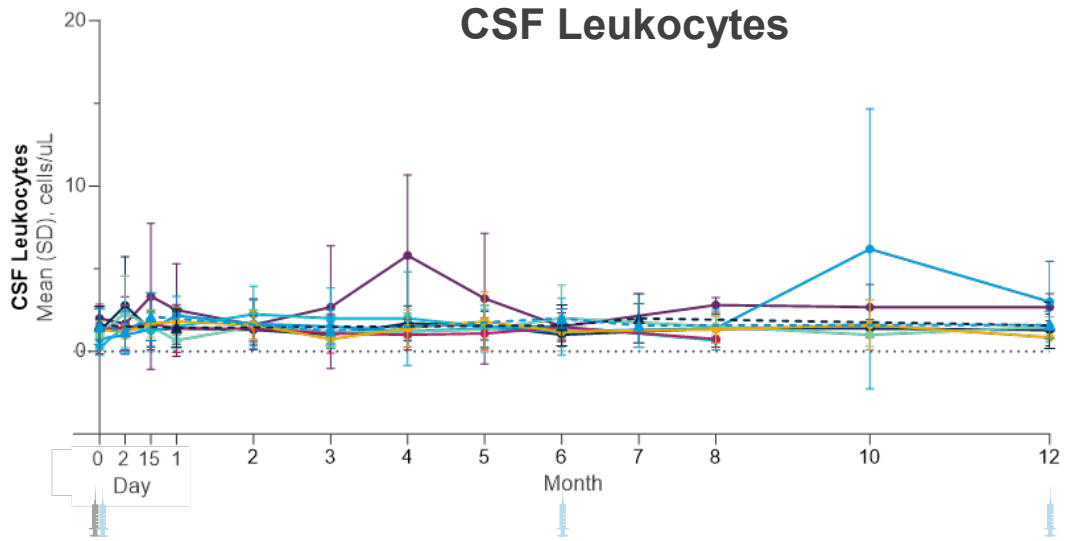
- Majority of AEs were nonserious, mild or moderate, and deemed unrelated to the study drug
- No serious or severe AEs were deemed related to study drug
- The two most common AEs were procedural pain and procedural headache
- No drug-related ARIA events have occurred in the study to date, and no ARIA-E was observed

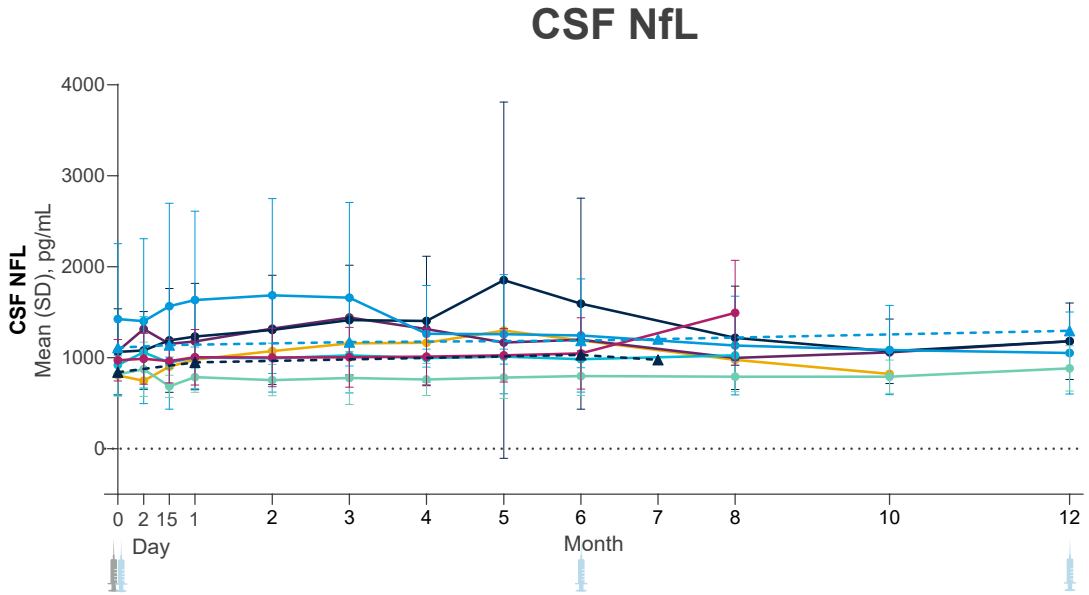
Data shown as of May 15, 2025, patients with EOAD. [a]One patient had one event of acute pancreatitis on Day 277 after dosing that was fatal on Day 288. The event was classified as serious, severe, and not related to study drug/LP.

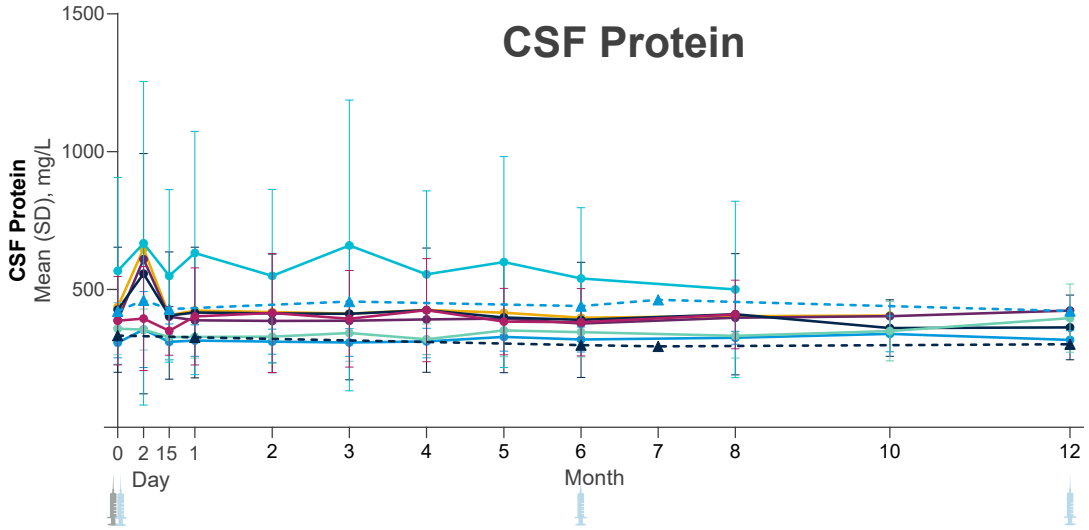
AE, adverse event; ARIA-E, amyloid-related imaging abnormality presenting as edema; EOAD, early-onset Alzheimer's disease; LP, lumbar puncture; MAD, multiple ascending dose; PY, patient years; SAD, single ascending dose; SD, standard deviation.

CSF Assessments Support Favorable Safety Profile

No Immune Responses Observed After Single or Multiple Doses of Mivelsiran







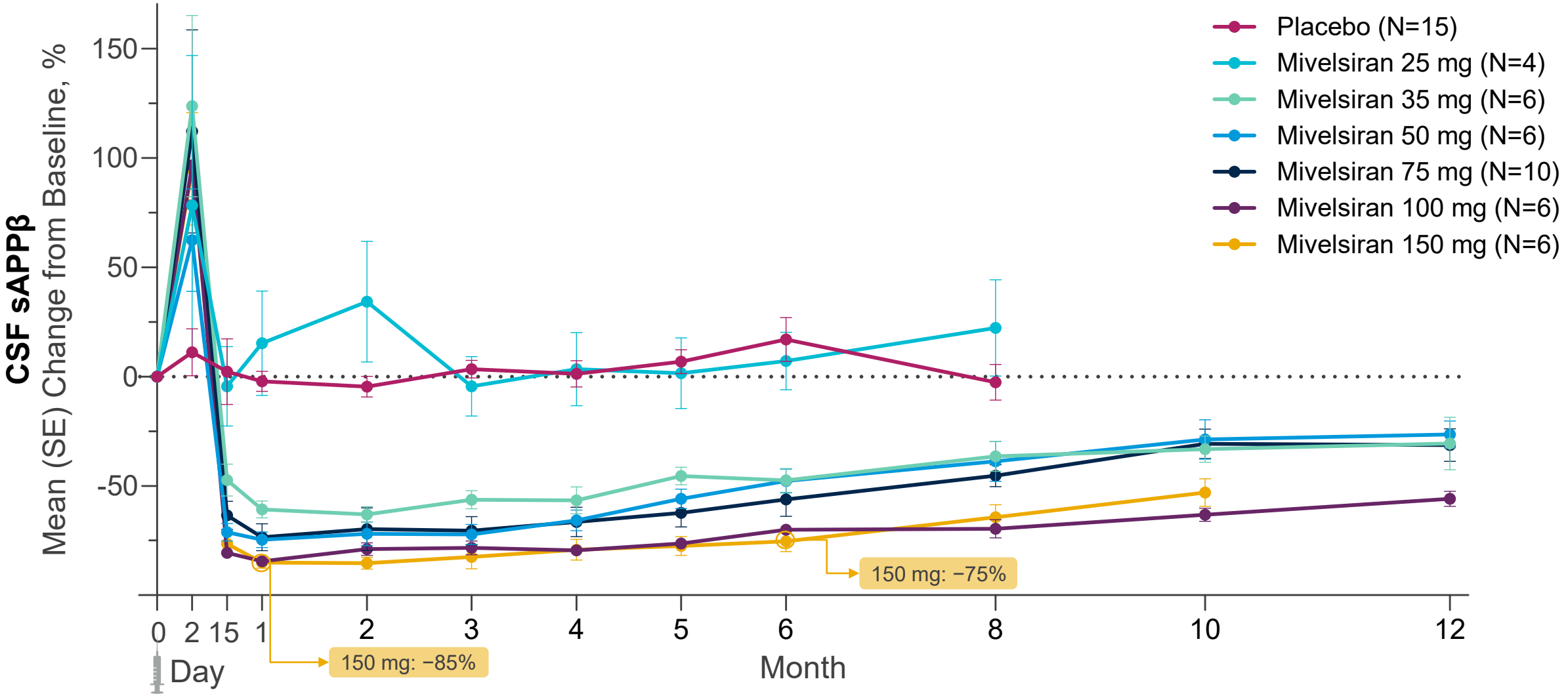
Single dose mivelsiran:
- 25 mg (N=4)
- 35 mg (N=6)
- 50 mg (N=6)
- 75 mg (N=10)
- 100 mg (N=6)
- 150 mg (N=6)
- Placebo (N=15)

Q6M mivelsiran:
- 50 mg (N=10)
- 75 mg (N=12)

Data shown as of May 15, 2025, patients with EOAD.

CSF, cerebrospinal fluid; EOAD, early-onset Alzheimer's disease; NfL, neurofilament light chain; Q6M, once every 6 months; SD, standard deviation.

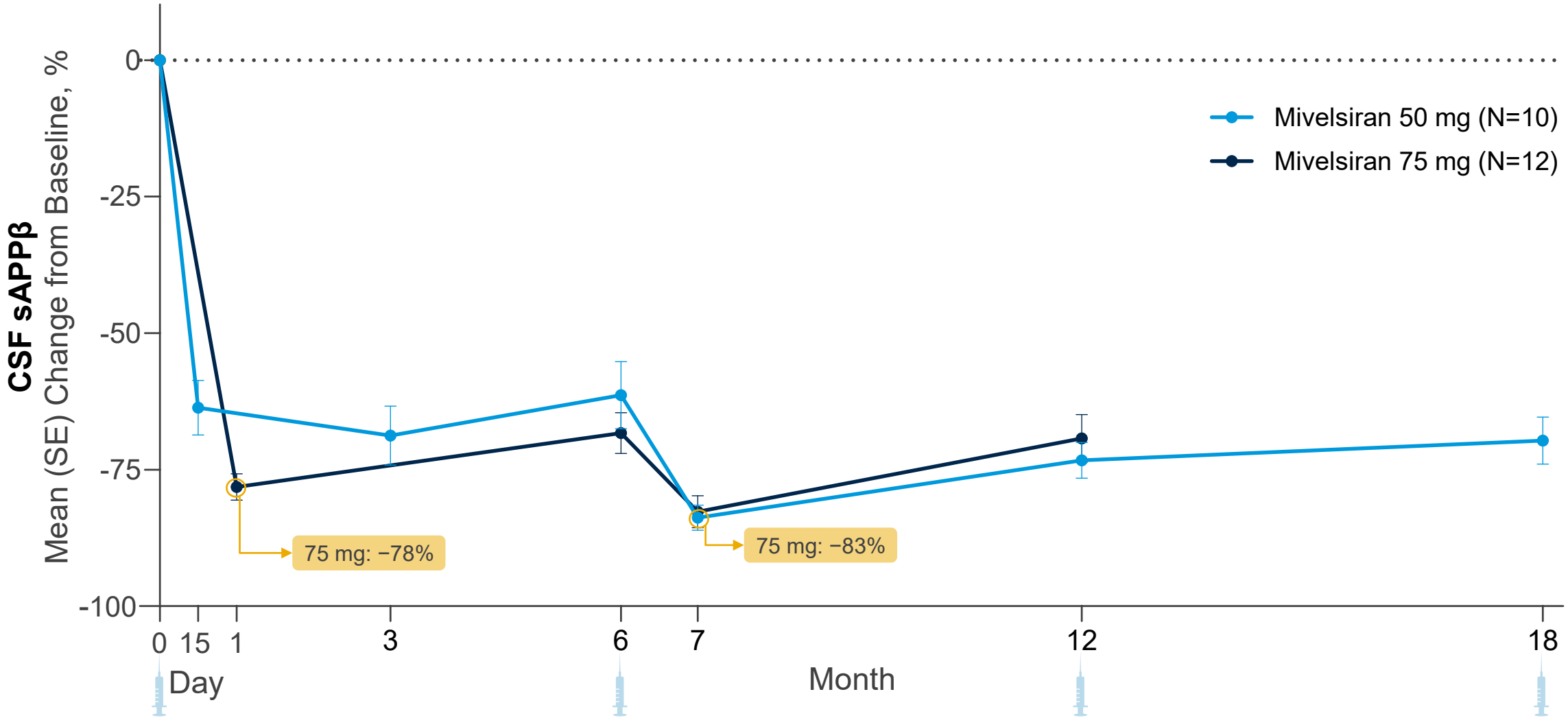
Robust, Durable Reductions in CSF sAPPβ with Single Doses of Mivelsiran



Data shown as of May 15, 2025, patients with EOAD. 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).

Aβ, amyloid-beta; CSF, cerebrospinal fluid; D, day; EOAD, early-onset Alzheimer's disease; M, month; sAPP, soluble Aβ precursor protein; SE, standard error.

Robust, Durable Reductions in CSF sAPPβ with Q6M Mivelsiran Dosing



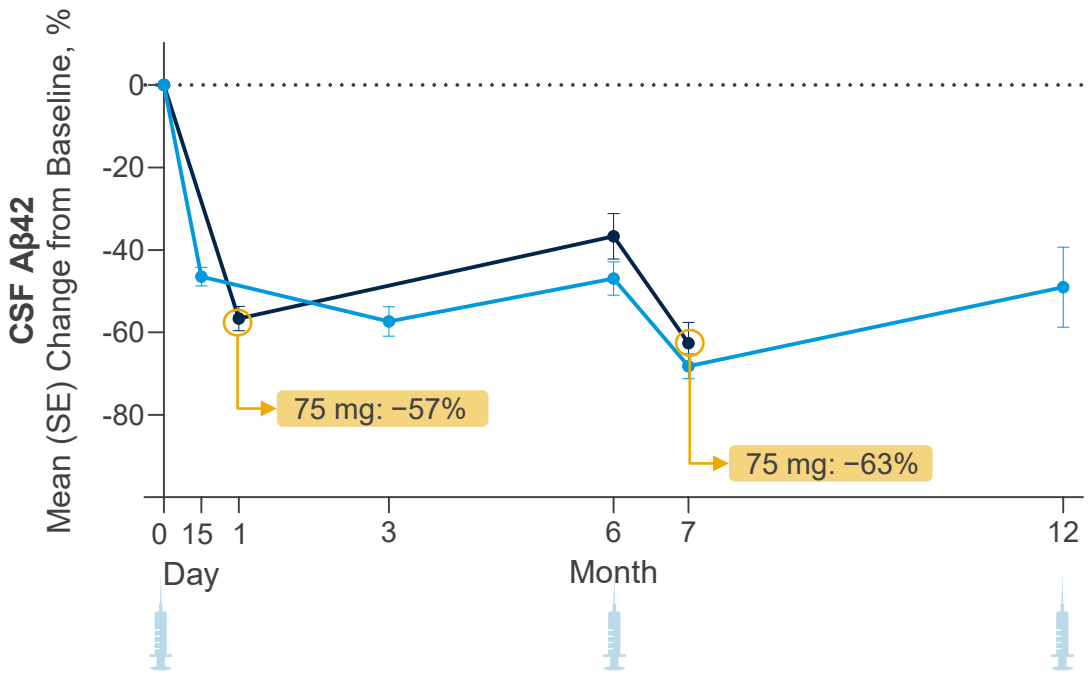
Data shown as of May 15, 2025, patients with EOAD. Time points with an n of <3 are not plotted. Mivelsiran 50 mg: n=8 (M3), n=9 (M7), n=5 (M18); mivelsiran 75 mg: n=10 (M6, M7), n=6 (M12).
Aβ, amyloid-beta; CSF, cerebrospinal fluid; EOAD, early-onset Alzheimer's disease; M, month; Q6M, once every 6 months; sAPP, soluble Aβ precursor protein; SE, Standard error.

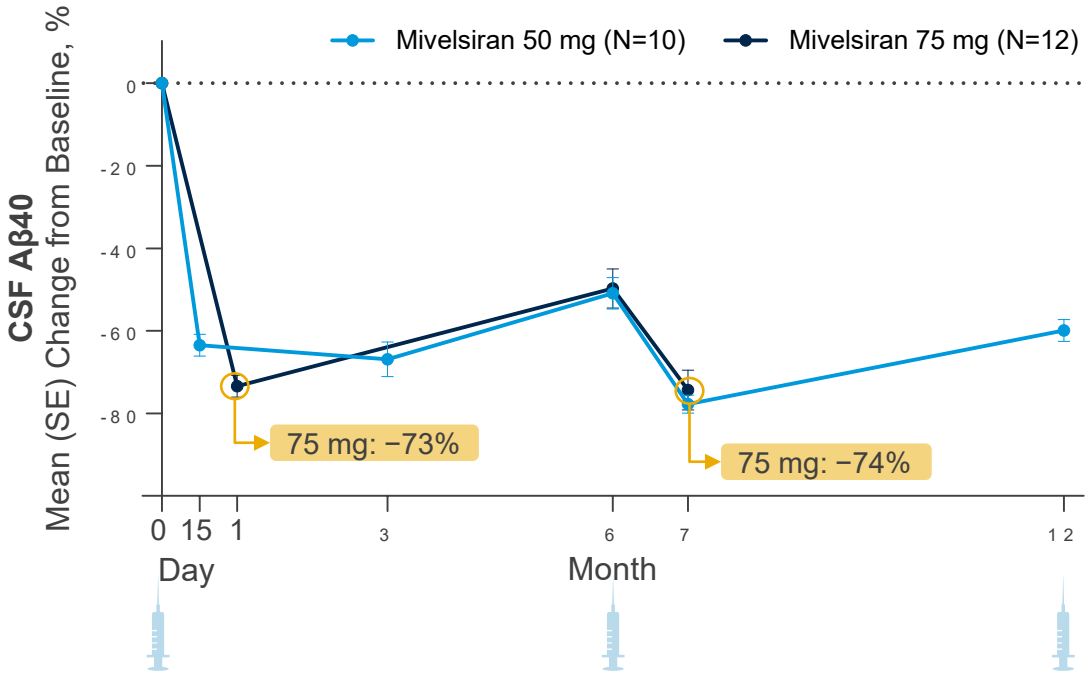
Marked Reductions in CSF Aβ42 and Aβ40 with Mivelsiran

Single Doses of Mivelsiran Reduced CSF Aβ42 and Aβ40 Levels

- Reductions in CSF Aβ42 and Aβ40 achieved with all doses at Day 15
  - Peak mean (SE) reductions in CSF Aβ42 (−61% [8]) and Aβ40 (−79% [5]) achieved in the 150 mg cohort at Month 2
  - For doses over 25 mg, mean reductions in Aβ42 (Aβ40) over 25% (30%) sustained to Month 6

Multiple Doses of Mivelsiran Provided Additional Reductions in CSF Aβ42 and Aβ40 Levels





Data shown as of May 15, 2025, patients with EOAD. Time points with an n of <3 are not plotted.

Aβ, amyloid-beta; Aβ40, Aβ peptide length 40 amino acids; Aβ42, Aβ peptide length 42 amino acids; CSF, cerebrospinal fluid; EOAD, early-onset Alzheimer's disease; SE, standard error.

Summary

Scan to View Congress Materials Presented

For US HCPs Only

- Multiple-dose data are reported for an investigational CNS-targeting RNAi therapeutic for the first time
- Single and multiple doses of mivelsiran were generally well tolerated at all dose levels
- Robust, durable, dose-dependent reductions in CSF sAPPβ were observed with single and multiple doses of mivelsiran above 25 mg
  - Continued lowering was observed after a second dose of mivelsiran, sustained to Month 18 with Q6M dosing
- Marked and sustained reductions in CSF Aβ42 and Aβ40 were observed through Month 12 following multiple doses of mivelsiran, based on available data
- Encouraging safety profile and robust reductions in CSF biomarkers support further evaluation of mivelsiran in patients with AD and CAA
  - MAD part has been extended to 42 months to enable evaluation of mivelsiran over a longer time period
  - cAPPricorn-1 (NCT06393712) is an ongoing Phase 2 study evaluating efficacy and safety of mivelsiran in patients with CAA

AD, Alzheimer's disease; APP, Aβ precursor protein; Aβ, amyloid-beta; Aβ40, Aβ peptide length 40 amino acids; Aβ42, Aβ peptide length 42 amino acids; CAA, cerebral amyloid angiopathy; CNS, central nervous system; CSF, cerebrospinal fluid; HCP, healthcare provider; MAD, multiple ascending dose; Q6M, once every 6 months; RNAi, RNA interference; sAPP, soluble APP.

Presented on behalf of the authors:

Sharon Cohen[1], Simon Ducharme[2], Jared Brosch[3], Everard Vijverberg[4], Daniel Blackburn[5], Eric McDade[6], Alexandre Sostelly[7], Sandeep Chaudhari[7], Lynn Farrugia[7], Robert Deering[7], Julia Shirvan[7], Catherine Mummery[8]

1. Toronto Memory Program, Toronto, ON, Canada
2. Montreal Neurological Institute, Department of Neurology & Neurosurgery, McGill University, Montreal, QC, Canada
3. Indiana University School of Medicine, Indianapolis, IN, USA
4. Alzheimer Center Amsterdam, Department of Neurology, Amsterdam Neuroscience, Amsterdam UMC, Vrije Universiteit Amsterdam, Amsterdam, Netherlands
5. University of Sheffield, Sheffield, UK
6. Washington University in St. Louis, St. Louis, MO, USA
7. Alnylam Pharmaceuticals, Cambridge, MA, USA
8. University College London, London, UK

Thank you to the patients, their families, investigators, study staff, and collaborators for their participation in the Phase 1 mivelsiran study

Backup Slides

Mivelsiran Was Generally Well Tolerated Across Dose Levels

Patients with events	Part A: SAD (N=53)							Part B: MAD (N=22)	
n (%)	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
Events occurring in >3 patients in Part A or Part B									
Back pain	0	2 (33.3)	0	1 (10.0)	0	2 (33.3)	2 (13.3)	0	0
Fall	0	1 (16.7)	0	3 (30.0)	1 (16.7)	0	1 (6.7)	1 (10.0)	1 (8.3)
Headache	0	0	0	2 (20.0)	1 (16.7)	1 (16.7)	2 (13.3)	2 (20.0)	1 (8.3)
Nasopharyngitis	0	1 (16.7)	0	3 (30.0)	0	1 (16.7)	1 (6.7)	0	1 (8.3)
Presyncope	0	0	1 (16.7)	1 (10.0)	0	0	2 (13.3)	1 (10.0)	0
Post-procedural discomfort	0	0	0	2 (20.0)	2 (33.3)	0	0	0	1 (8.3)
Procedural headache	2 (50.0)	4 (66.7)	5 (83.3)	2 (20.0)	3 (50.0)	1 (16.7)	6 (40.0)	3 (30.0)	2 (16.7)
Procedural pain	3 (75.0)	0	2 (33.3)	3 (30.0)	5 (83.3)	2 (33.3)	4 (26.7)	5 (50.0)	2 (16.7)
Procedural vomiting	0	0	0	2 (20.0)	0	0	3 (20.0)	NR	NR

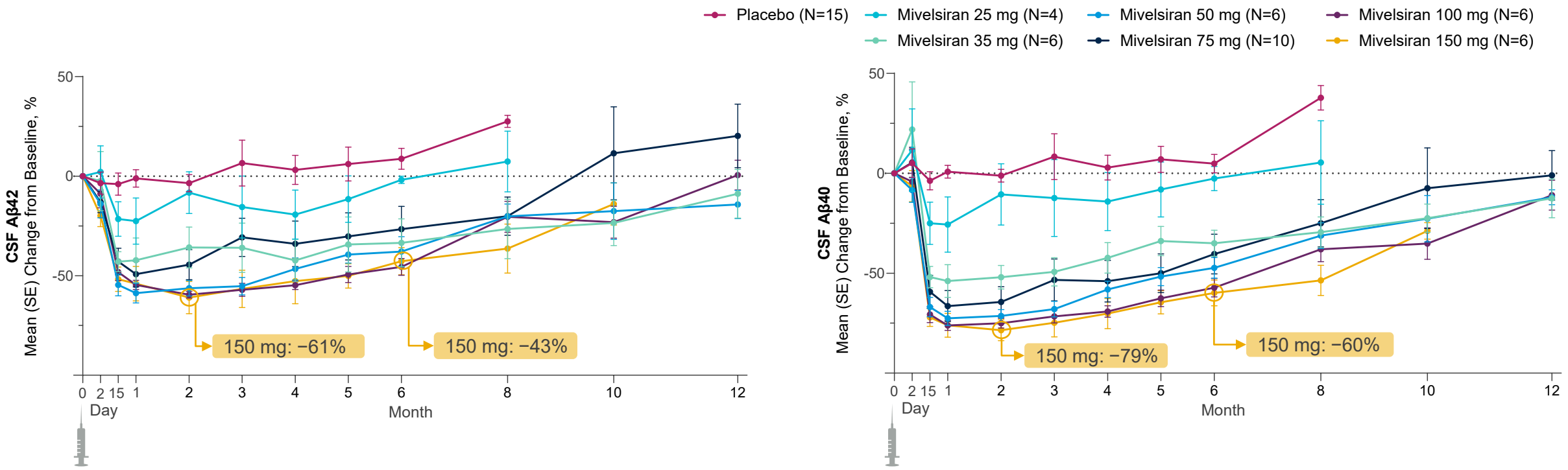
Data shown as of May 15, 2025, patients with EOAD.

EOAD, early-onset Alzheimer's disease; MAD, multiple ascending dose; NR, not recorded; PY, patient years; SAD, single ascending dose.

Marked Reductions in CSF Aβ42 and Aβ40 with Mivelsiran

Single Doses of Mivelsiran Reduced CSF Aβ42 and Aβ40 Levels

- Reductions in CSF Aβ42 and Aβ40 achieved with all doses at Day 15
  - Peak mean (SE) reductions in CSF Aβ42 (−61% [8]) and Aβ40 (−79% [5]) achieved in the 150 mg cohort at Month 2
  - For doses over 25 mg, mean reductions in Aβ42 (Aβ40) over 25% (30%) sustained to Month 6



Data shown as of May 15, 2025, patients with EOAD. Time points with an n of <3 are not plotted.

Aβ, amyloid-beta; Aβ40, Aβ peptide length 40 amino acids; Aβ42, Aβ peptide length 42 amino acids; CSF, cerebrospinal fluid; EOAD, early-onset Alzheimer's disease; SE, standard error.