Dementia Research Centre, Institute of Neurology, UCL, London

ARO-MAPT, a Subcutaneous Shuttled siRNA Silencing Tau Production: Early Phase 1 Safety, Tolerability, and Pharmacodynamic Results in Healthy Volunteers

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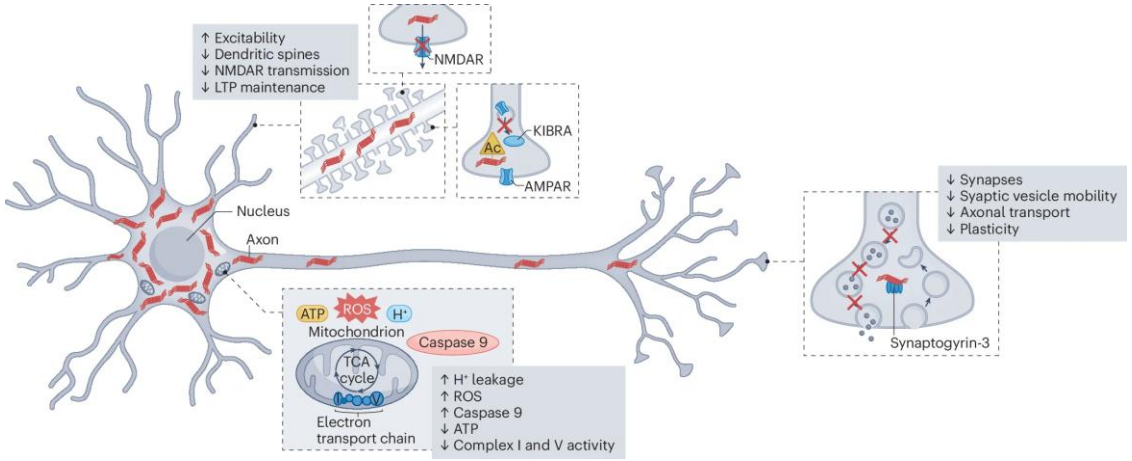
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Disclosures

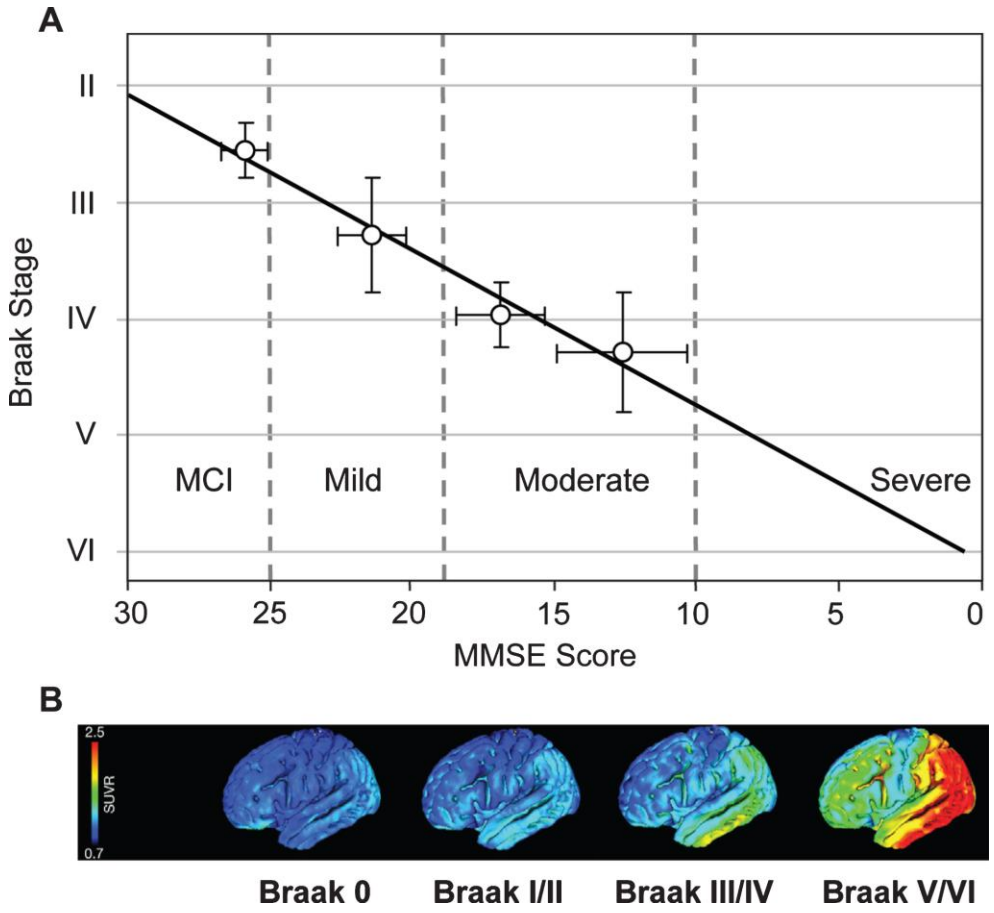
- This study was sponsored by Arrowhead Pharmaceuticals.
- CM has served on advisory board or consulted for AC Immune, Biogen, Roche, WAVE, IONIS, Prevail, Lilly, Eisai, Alector, Neurimmune, Novartis, Switch, Voyager, Alnylam, Denali, Arrowhead, Vectory, Aviadobio, Sanofi, UCB Pharma. She has received grant funding from Biogen and from NIHR, she has received honorarium for presentations from Biogen, Roche, EISAI, IONIS, Lilly, MSD, Sanofi
- IC has received unrestricted speaking honorarium from Eisai and Lilly.
- DJ has received an honorarium from Eisai.
- ED has severed on advisory board, received grant funding and received honorarium for presentations from Eli Lilly and Roche Diagnostics.
- SC has served as a consultant or on the advisory board (with no personal fees) for AbbVie, Alnylam, Alzheon, Banner Alzheimer's Institute, Biogen, BMS, Cogstate, Eisai, Eli Lilly, GSK, INmune Bio, J&J, Novartis, Novo Nordisk, RetiSpec, Roche, and UCB Biopharma. SC's affiliated institution has received research funding from Acumen, Alnylam, Alzheon, Arrowhead, Biogen, BMS, Eisai, Eli Lilly, GAP, INmune Bio, J&J, Novartis, RetiSpec, Roche, UCB Biopharma, and Voyager.
- RC, DC, GS, RF, and JH are employees of Arrowhead Pharmaceuticals.

MAPT Encodes Tau: A Central Mediator of Neurodegeneration

Pathologic Tau

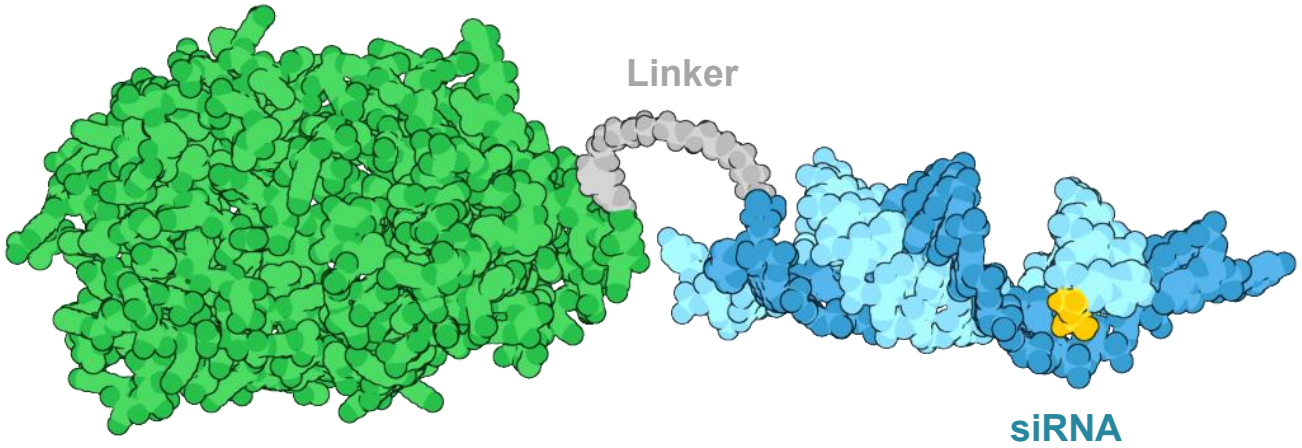


Tau Burden and Cognitive Decline



Parra Bravo, C., Naguib, S.A. & Gan, L. *Nat Rev Mol Cell Biol* 25, 845–864 (2024).
Wischik et al., *Biochem Pharmacol* 88, 529-539, 2014
Schöll et al., *Neuron* 89, 971-982, 2016

ARO-MAPT-SC

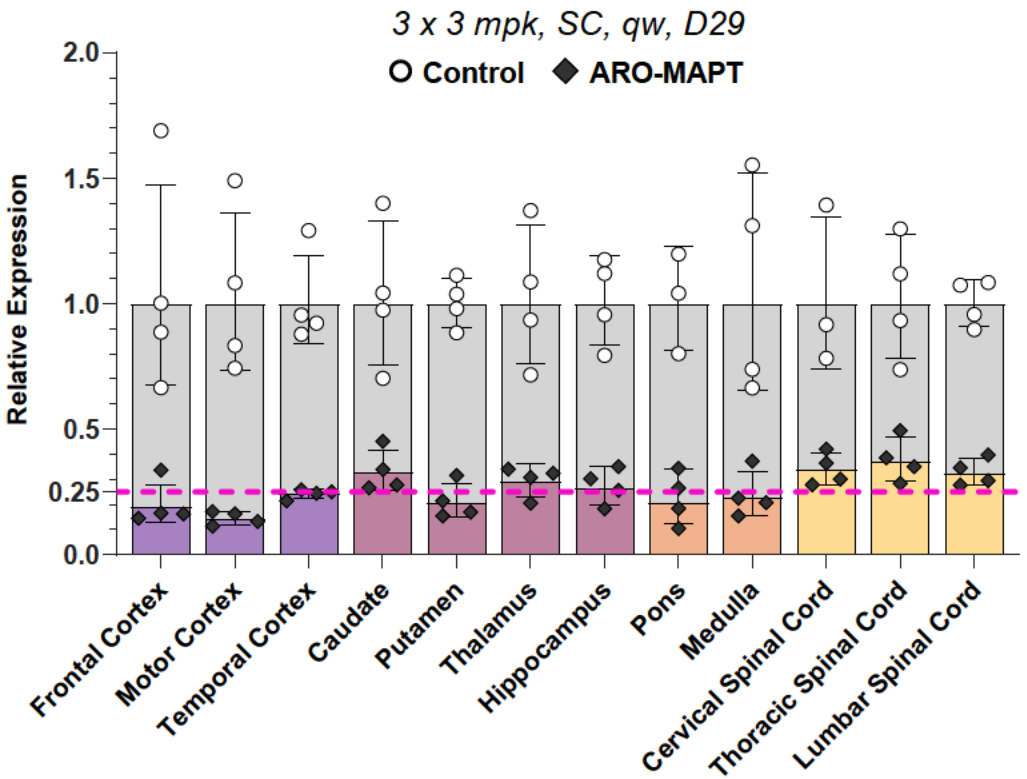


- **Shuttles siRNA across the Blood-Brain Barrier** using a conjugated TfR1 Fab ligand
- Targets **tau in all compartments** and **all six tau isoforms**
- **Infrequent**, **subcutaneous** (SC) administration

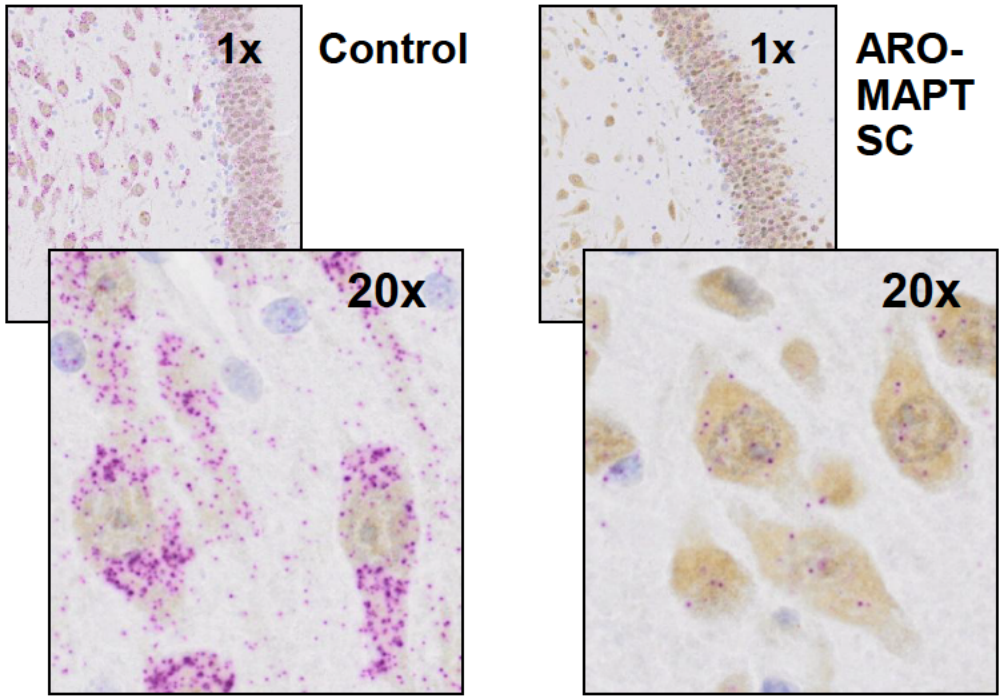
ARO-MAPT Achieves Deep Knockdown of *MAPT* mRNA Homogenously Throughout the CNS with Subcutaneous Administration in NHPs



MAPT mRNA Reduction in NHP CNS Regions



MAPT mRNA Depletion in Hippocampus



MAPT mRNA shown in purple

mRNA Knockdown Corroborated by RNAscope

Sustained CSF Tau Protein Reduction in NHPs

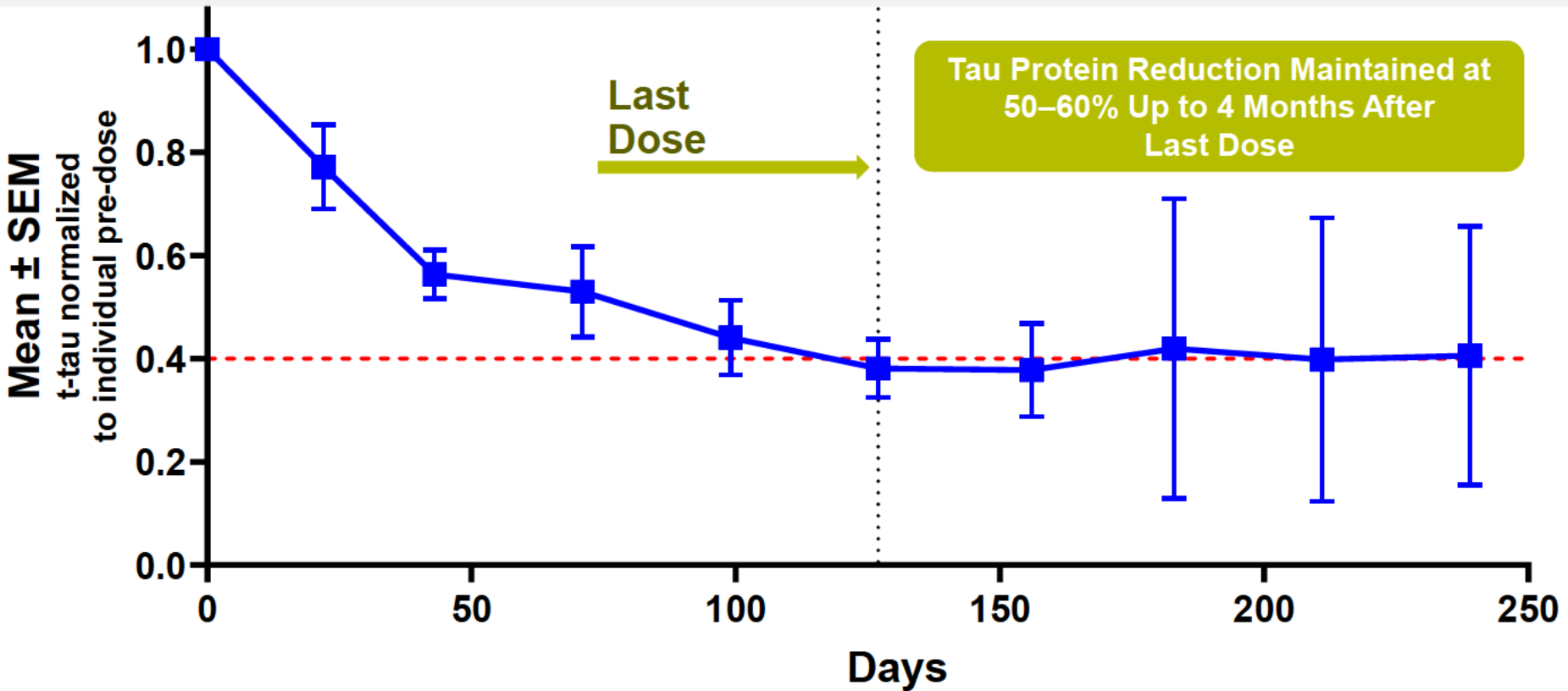


7x3 mg MAPT siRNA/kg SC: 3 Weekly Loading Doses + 4 Monthly Maintenance Doses

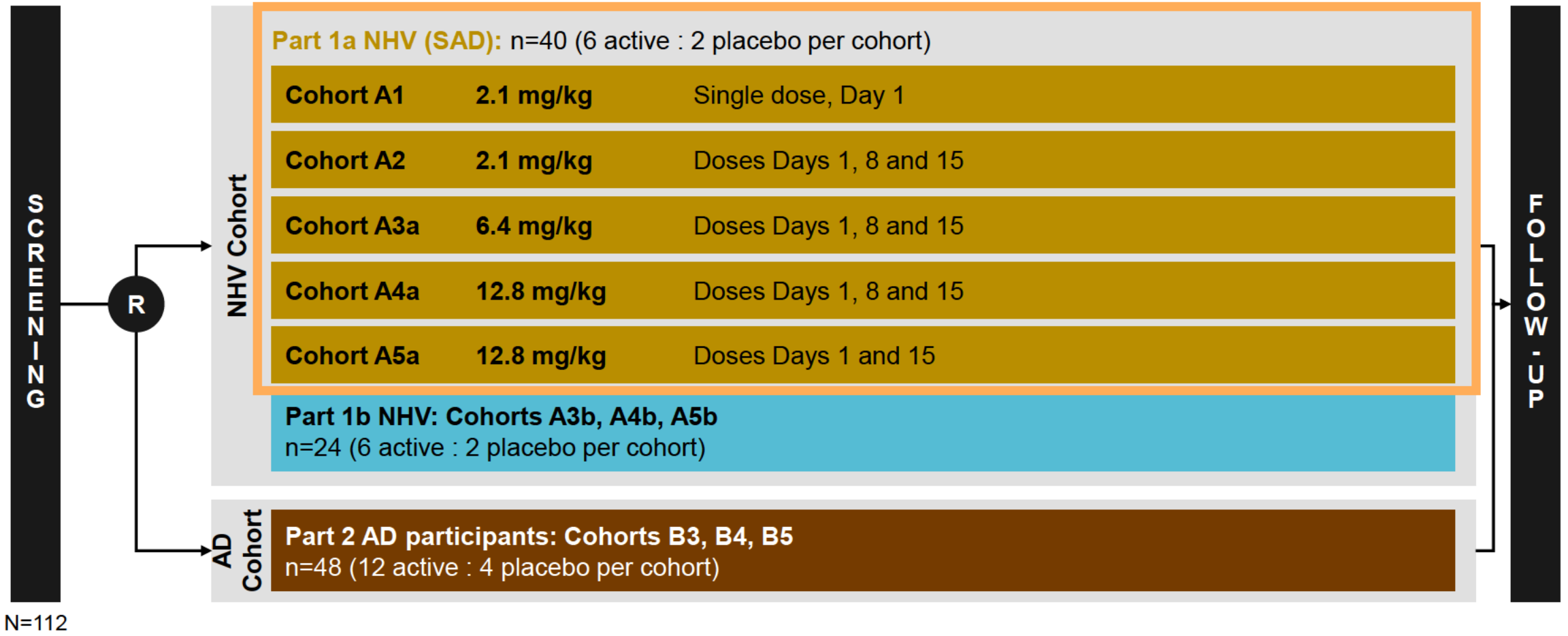


Study Day: 1 8 15 43 71 99 127 156 183 211 239

CSF T-Tau Levels



AROMAPT-SC-1001: Study Design and SAD Cohort Doses



Doses represent total conjugate dose. All healthy volunteer cohorts (Parts 1A and 1B) are fully enrolled.

Key Endpoints



NHVs

- CSF total tau (t-tau)
- Plasma brain-derived (BD) tau

AD Patients:

- Plasma and CSF Biomarkers
- Tau-PET SUVR change
- MRI Brain volumetry
- Cognitive and functional scores
  - CDR-SB, ADAS-Cog13, ADCS-ADL

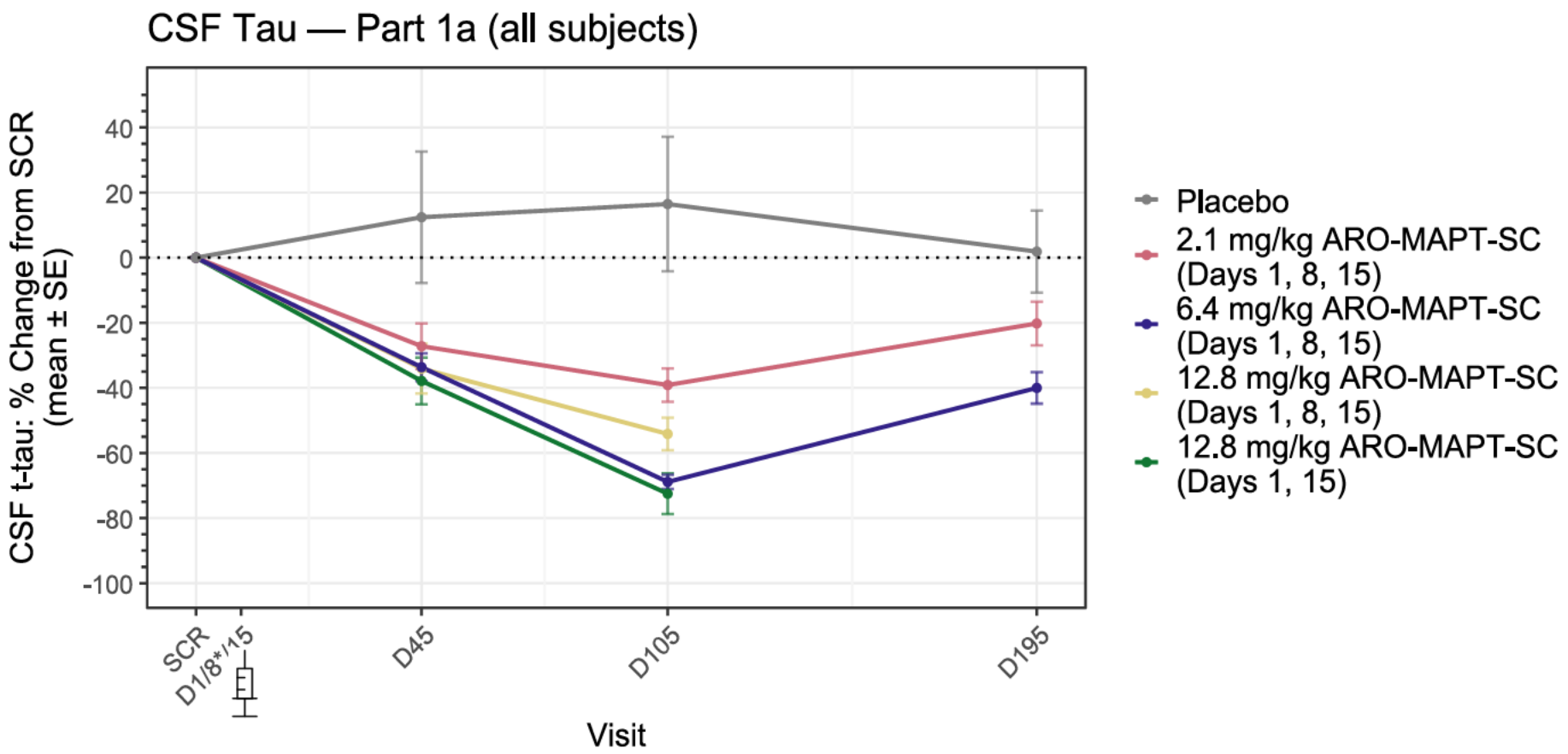
CSF = cerebrospinal fluid; BD = brain-derived; NfL = neurofilament light chain; GFAP = glial fibrillary acid protein; NHV = Normal Healthy Volunteer

Baseline NHV Characteristics

	AROMAPT-SC-1001	
Characteristic	**Part 1a (N=41)**	**Part 1b (N=16)[2]**
Age, mean (SD), years	**42.2 (12.6)**	**41.7 (11.4)**
Sex		
Female, n (%)	21 (51.2)	9 (56.2)
Male, n (%)	20 (48.8)	7 (43.8)
Race		
American Indian or Alaska Native, n (%)	3 (7.3)	0 (0.0)
Asian, n (%)	3 (7.3)	3 (18.8)
Black or African American, n (%)	0 (0.0)	0 (0.0)
Native Hawaiian or Pacific Islander, n (%)	2 (4.9)	1 (6.2)
White, n (%)	26 (63.4)	10 (62.5)
Other, n (%)	2 (4.9)	0 (0.0)
Multiple, n (%)	5 (12.2)	2 (12.5)
Baseline CSF Tau, mean (SD), pg/mL	**63.7 (71.3)[1]** [n=32]	**48.8 (18.0)** [n=8]
Baseline plasma BD-tau, mean (SD), pg/mL	8.5 (3.1) [n=32]	8.3 (2.4) [n=8]

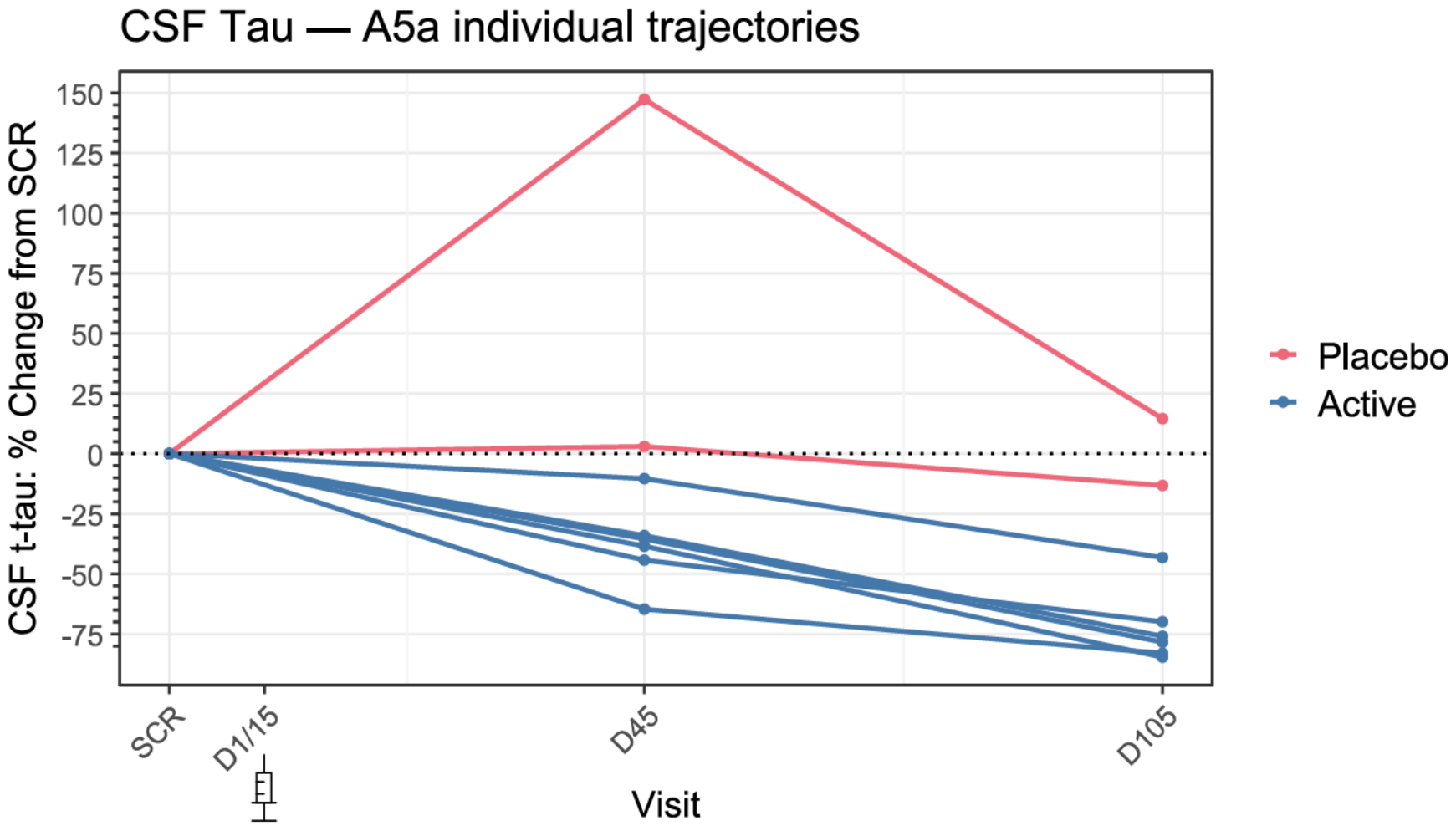
SD = standard deviation; CSF = cerebrospinal fluid; BD = brain-derived; NHV = Normal Healthy Volunteer
1. High SD due to single healthy volunteer with elevated CSF tau at baseline; when excluded, mean (SD) = 51.4 (34.2) pg/mL.
2. Data cutoff: 25Aug26

Loading Dose of ARO-MAPT:
Individual CSF tau reduction up to 85% | Mean Reduction up to 73% at Day 105
Duration Supports Dosing Every 3 Months



*Cohort A5a is not dosed on Day 8.

Loading Dose of ARO-MAPT:
Consistent individual response to ARO-MAPT
Maximal individual response of 85%



ARO-MAPT Demonstrates a Favorable Safety Profile

Subjects with Treatment-Emergent AEs

Characteristic	Placebo (N=15)	ARO-MAPT Part 1A (N=30)	ARO-MAPT Part 1B (N=12)
Overall			
Any TEAEs, n (%)	8 (53.3)	27 (90.0)	10 (83.3)
Serious TEAEs, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Deaths, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Discontinuations due to TEAE, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Reported in >10% of the Study Participants			
Injection site reaction, n (%)	1 (6.7)	6 (20.0)	3 (25.0)
Vessel puncture site bruise, n (%)	0 (0.0)	4 (13.3)	3 (25.0)
Upper respiratory tract infection, n (%)	0 (0.0)	5 (16.7)	2 (16.7)
Back pain, n (%)	1 (6.7)	5 (16.7)	0 (0.0)
Headache, n (%)	2 (13.3)	6 (20.0)	4 (33.3)

Data cutoff Aug 25, 2026

- ARO-MAPT was **well tolerated** in normal healthy volunteers.
  - Most TEAEs were Grade 1 (mild)
  - No serious TEAEs
  - No TEAEs led to study or study drug discontinuation
- No neurobehavioral AEs. No persistent anemia.

Conclusions

- ARO-MAPT-SC is a subcutaneously administered siRNA-Fab conjugate designed to cross BBB and silence *MAPT* expression throughout the CNS
- Subcutaneous administration of ARO-MAPT in NHVs has been well tolerated, demonstrating deep, dose-dependent, and durable knockdown of CSF t-tau
- No neurobehavioral adverse events and no persistent anemia
- Ongoing dosing in MAD NHVs and early Alzheimer's disease Cohorts (2027)
- Engagement with regulatory agencies in anticipation of studies in MAPT-FTD and PSP

We would like to thank all the patients and healthy volunteer participants as well as the site investigators and staff who are conducting this ongoing study.


Questions?
Answers.