



ARO-MAPT Phase 1/2a Study Interim Clinical Data Update

October 14, 2026

ARO-MAPT Phase 1/2a Study Clinical Data Update

Introduction and Agenda

Vince Anzalone, CFA

Senior Vice President



Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, entering into new collaborations and achieving existing projected milestones, rapid technological changes in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K, recent and forthcoming Quarterly Reports on Form 10-Q, recent Current Reports on Forms 8-K, and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

Agenda

Topic	Presenter
Introduction	Vince Anzalone, CFA Arrowhead SVP
A New Era for RNAi Therapeutics	Chris Anzalone, Ph.D. Arrowhead CEO
Silencing <i>MAPT</i> in Alzheimer's Disease and Other Tauopathies	Adam Boxer, M.D., Ph.D. UCSF
TRiM™ CNS-SC Platform & Overview of ARO-MAPT	James Hamilton, M.D., MBA Arrowhead CMO/R&D Head
Interim Results from Phase 1/2a Study	James Hamilton, M.D., MBA
Key Takeaways	Chris Anzalone, Ph.D.
Q&A	Panel

Neurology Key Opinion Leader

Adam Boxer, M.D., PhD

Professor, Neurology

Endowed Professor in Memory and Aging

UCSF Weill Institute for Neurosciences

Adam L. Boxer, MD, PhD, is a fellowship-trained, clinically active behavioral neurologist and Endowed Professor in Memory and Aging in the Department of Neurology at the University of California, San Francisco (UCSF), where he directs the Neurosciences Clinical Research Unit and the Alzheimer's Disease and Frontotemporal Dementia Clinical Trials Programs.

Dr. Boxer is a co-principal investigator of ALLFTD, a 27-site North American research network focused on preparing for FTD clinical trials through biomarker and clinical endpoint development. He is the lead principal investigator for both the NIH Alzheimer's Disease Tau Platform (ATP) and the PSP Trial Platform (PTP), two new multidrug public-private clinical trial partnerships designed to accelerate the development of effective therapies. He has initiated and led multiple public-private partnerships focused on accelerating drug development for neurodegenerative disease, including the Neurofilament Surveillance Project, the FTD Treatment Study Group (now the FTD Research Roundtable), and the PSP Research Roundtable.



ARO-MAPT Phase 1/2a Study Clinical Data Update

A New Era for RNAi Therapeutics Led by Arrowhead

Chris Anzalone, Ph.D.

President and CEO



Expanding TRiM™: Solving the Challenges of RNAi in the Brain

-  Crossing the blood-brain barrier: Breaking through a major delivery challenge
-  Preclinical studies demonstrate broad distribution and uniform target suppression across CNS, including deep brain
-  Demonstrating functional/productive delivery: Deep and durable gene silencing
-  Eliminating the need for IT administration: quarterly subcutaneous dosing simplifies treatment and opens opportunities to treat a variety of indications

Current Clinical Programs using New CNS Delivery

Therapeutic Area		Pre-clinical	Phase 1	Phase 2	Phase 3	Product Rights
Cardiometabolic	Plozasiran* FCS, SHTG					
	Zodasiran HoFH					
	Olpasiran ASCVD					
	GSK4532990 MASH/ALD					
	ARO-DIMER-PA Mixed Hyperlipidemia					
	ARO-PNPLA3 MASH					
	ARO-INHBE Obesity					
	ARO-ALK7 Obesity					
Pulmonary	ARO-RAGE Inflammatory Lung Diseases					
	ARO-MMP7 Idiopathic Pulmonary Fibrosis					
Liver	Fazirsiran Alpha-1 Liver Disease					 
	Daplusiran/Tomligisiran Hepatitis B Virus					
Neuromuscular	ARO-MAPT Alzheimer's/Tauopathies					
	ARO-SNCA Parkinson's					
	ARO-DUX4 FSHD					
	ARO-DM1 Myotonic Dystrophy Type 1					
	ARO-ATXN2 Spinocerebellar Ataxia 2					
	ARO-HTT Huntington's					
Other	ARO-C3 Complement Mediated Disease					
	ARO-CFB Complement Mediated Disease					

ARO-MAPT Phase 1/2a Study Clinical Data Update

Silencing MAPT in Alzheimer's Disease and other Tauopathies

Adam Boxer, M.D., Ph.D.

Professor, Neurology

Endowed Professor in Memory and Aging

UCSF Weill Institute for Neurosciences

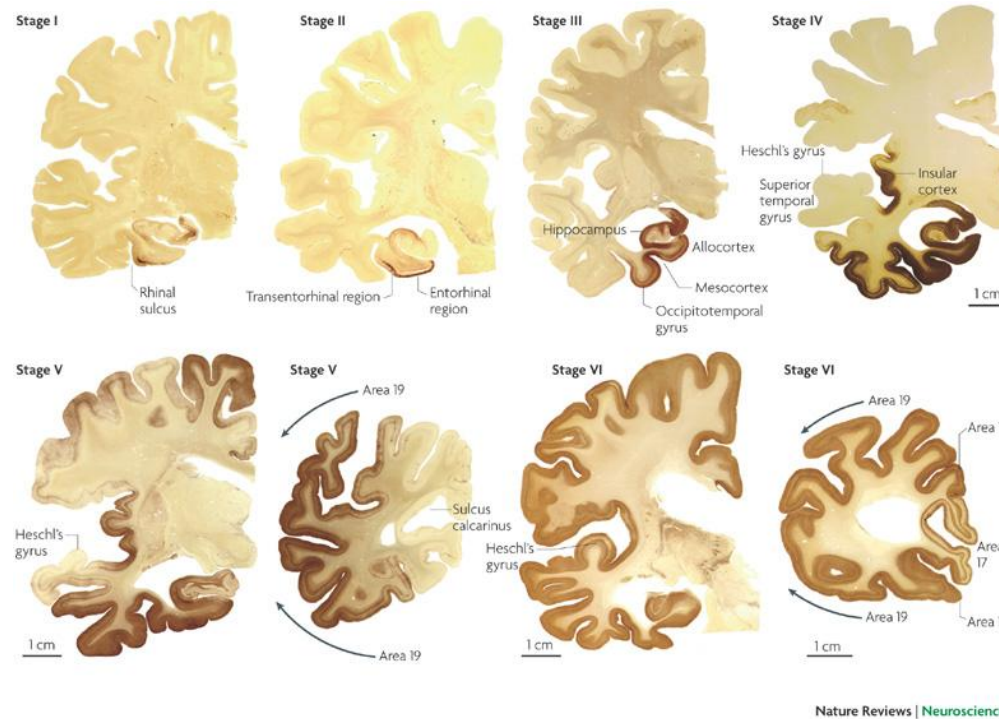


Objectives

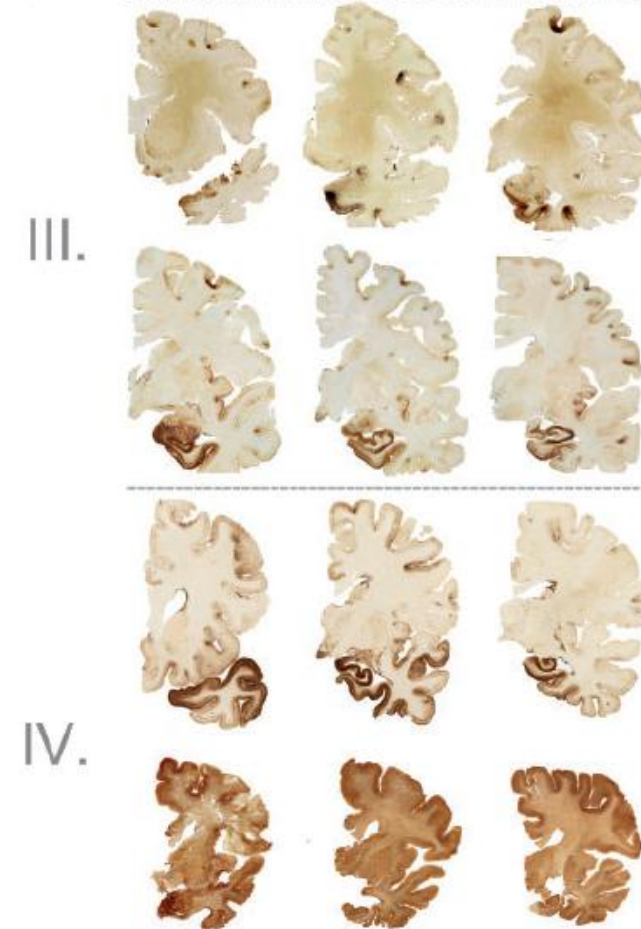
- Review the current treatment landscape in Alzheimer's disease
- Understand the implications of recent therapeutic advances
- Evaluate the rationale for tau-targeting approaches
- Frame key considerations for next-generation therapies
- Tau reduction for treatment of primary tauopathies

Insoluble tau correlates with clinical features in tauopathies

AD



PSP-RS

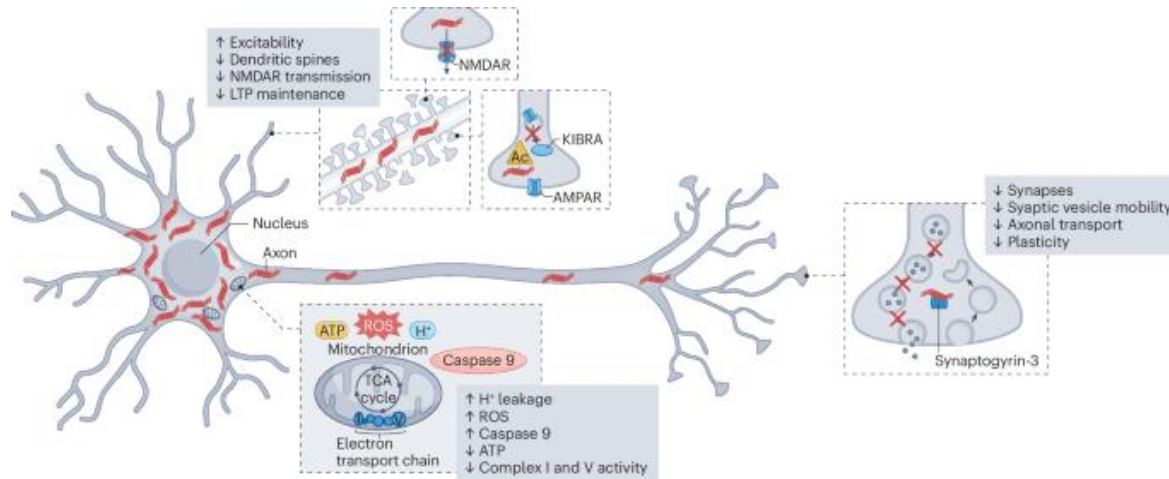


CTE

Targeting Tau in Tauopathies

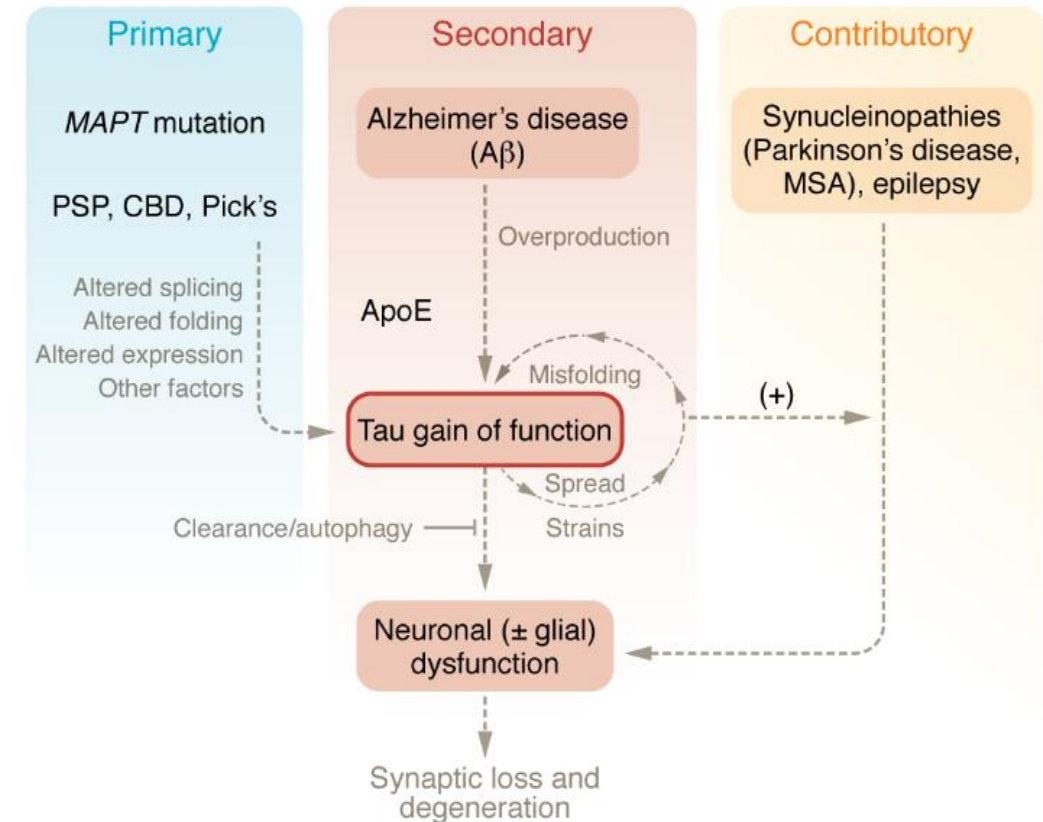
- Pathophysiology
 - Tau is the key pathogenic driver
 - Not secondary
 - Multiple mechanisms → “tau gain of function”

Neuronal Mechanisms of Tau Pathology



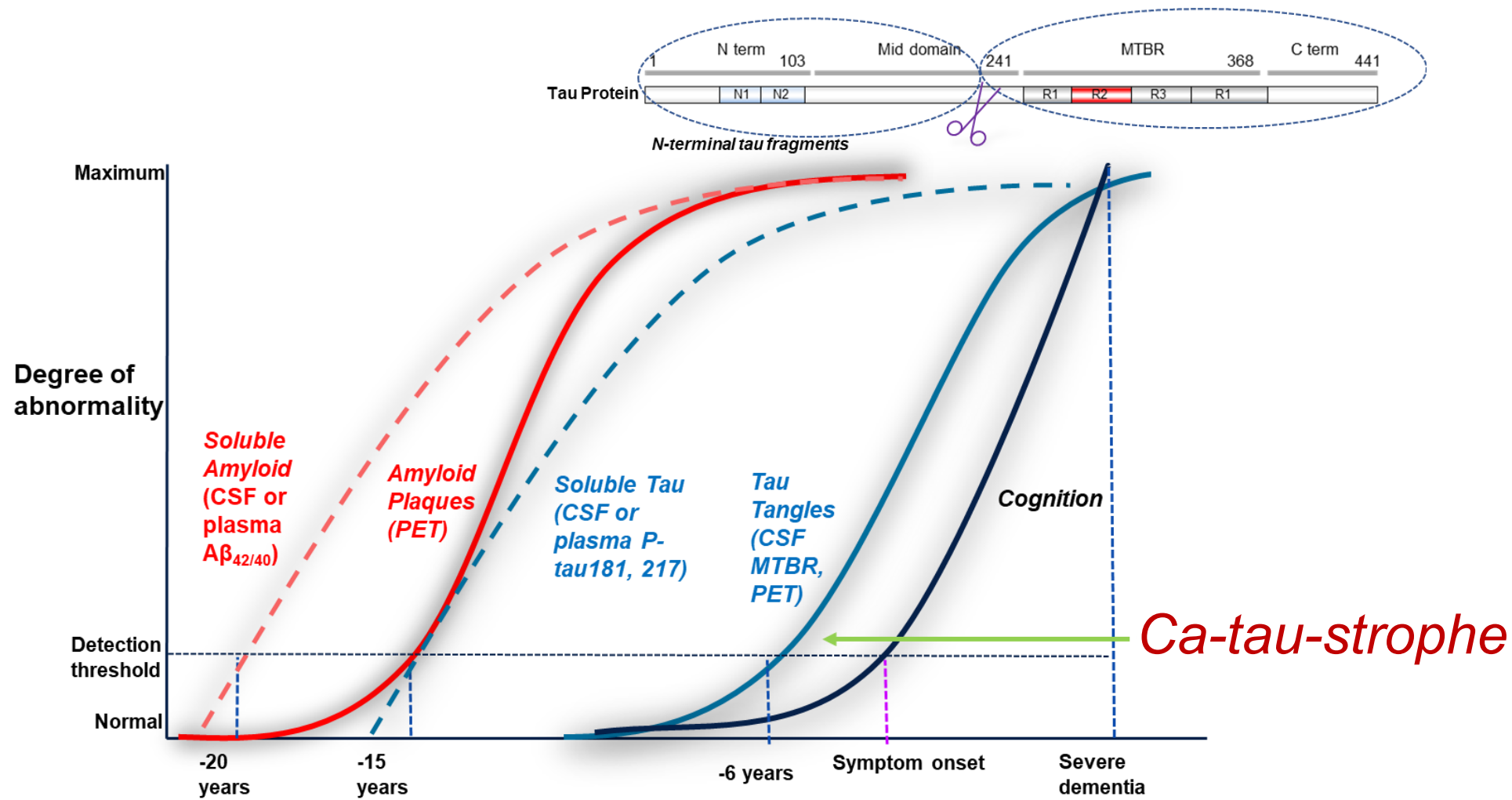
[Parra Bravo et al. Nature Reviews Molecular Cell Biology 2024.](#)

Role of Tau in Various Tauopathies



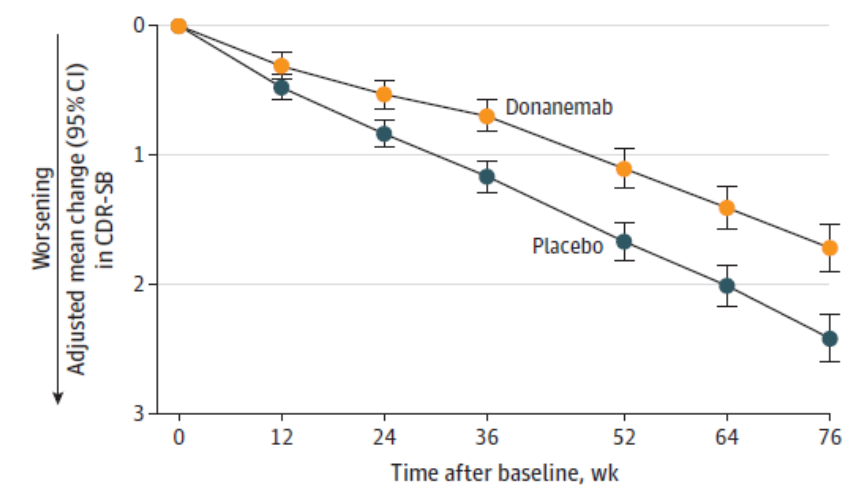
[Samudra and Boxer et al. Journal of Clinical Investigation. 2023.](#)

Biomarkers of AD Pathogenesis



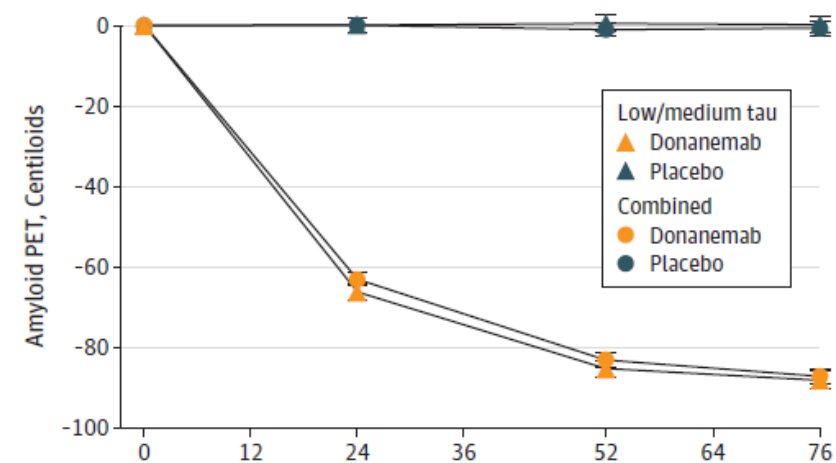
Donanemab Effects in Prodromal- Mild AD (Ph3)

D CDR-SB in combined population

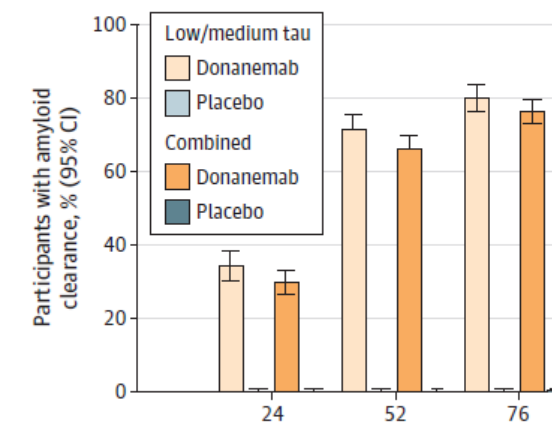


No. of participants							
Placebo	838	825	784	752	713	678	672
Donanemab	794	774	731	682	650	603	598

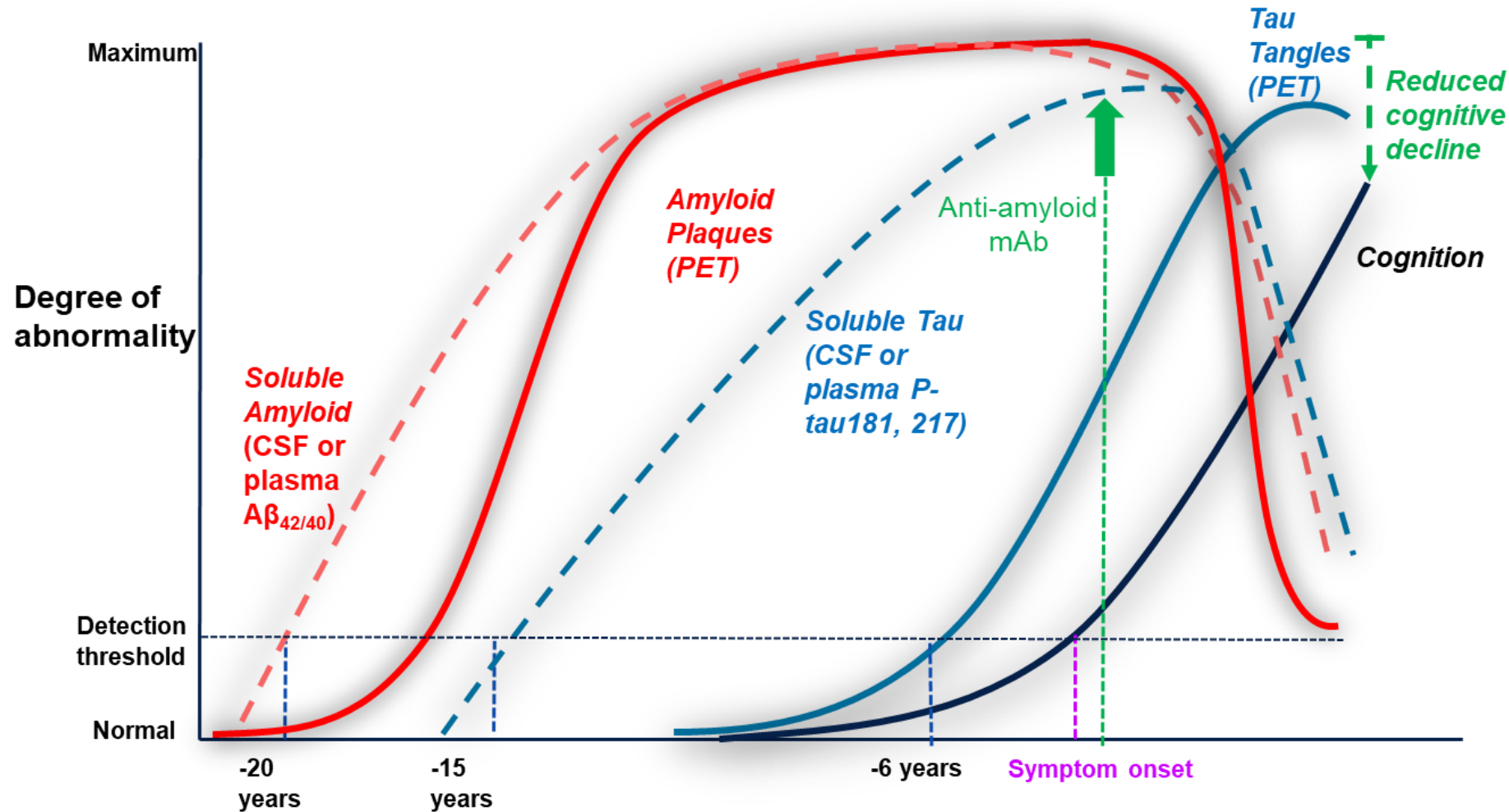
Adjusted mean change (95% CI) in amyloid PET



Participants with amyloid clearance (<24.1 Centiloids)



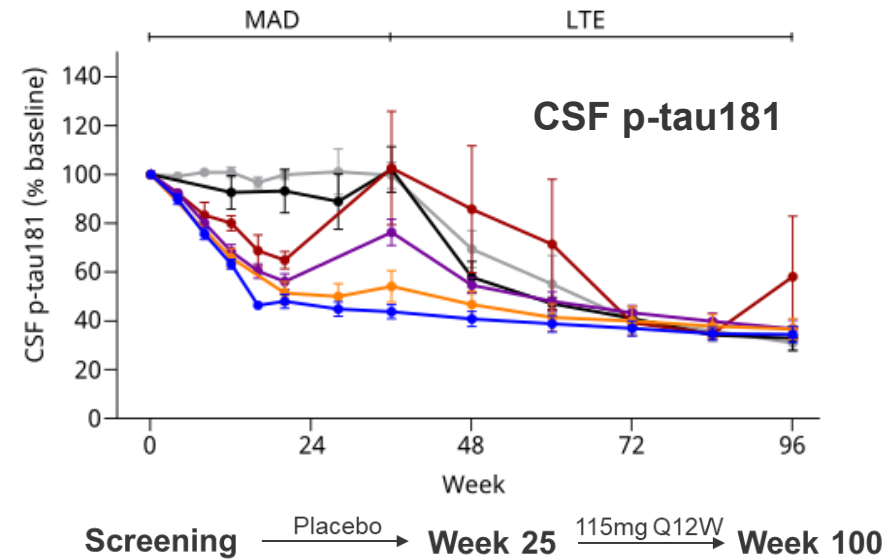
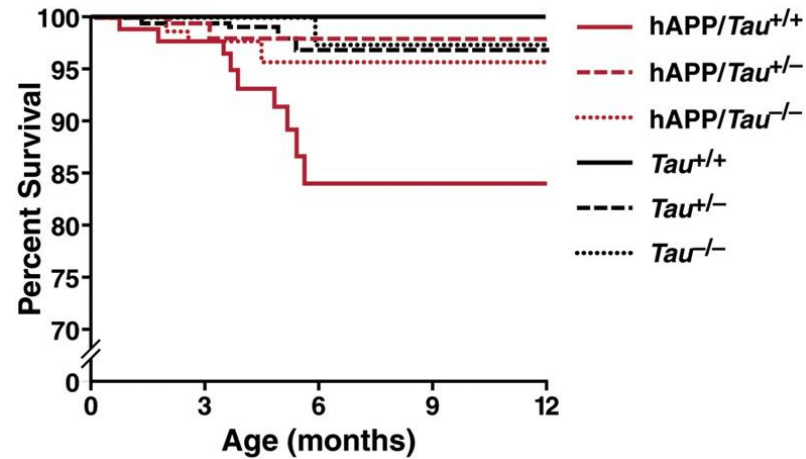
Hypothetical effects of current anti-amyloid immunotherapies



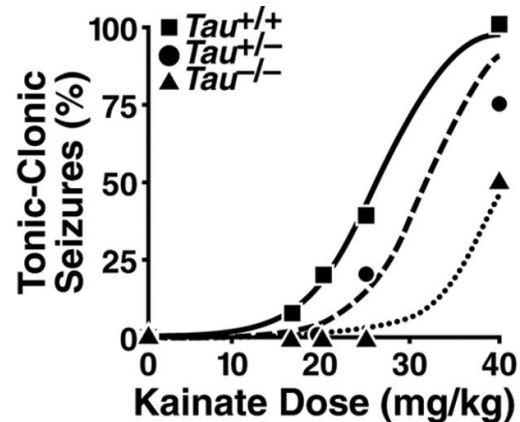
After Bateman & McDade, 2022; Boxer and Sperling, Cell, 2023

Tau reduction as a therapeutic strategy (mice & humans)

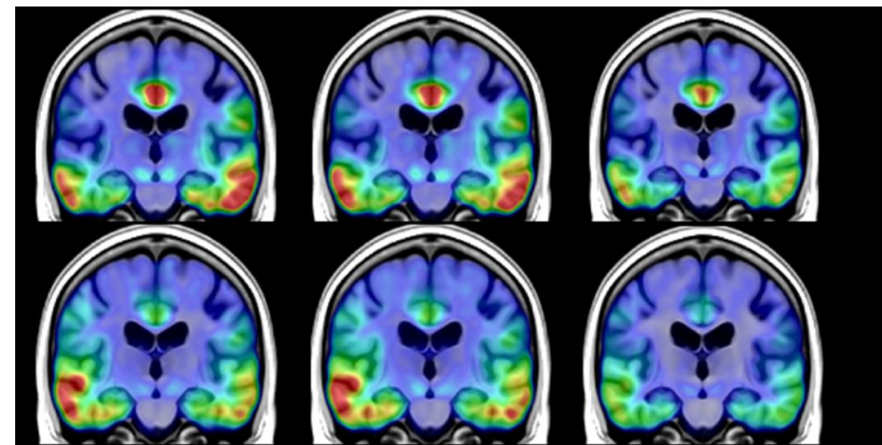
Alzheimer Mice



Neurotoxin seizures



2380-4011
67 y/o
Male
CDR = 0.5
MMSE = 26



Ph2 results negative, but moving to Ph3

Roberson et al. *Science* 2007;316:750-754; Mummery, *Nat Med*, 2022; Edwards, *JAMA Neurology*, 2023

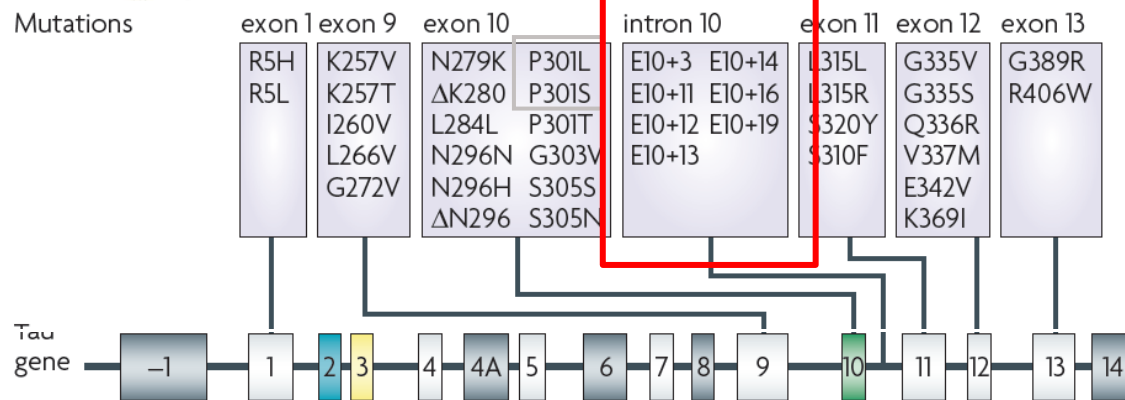
Tau genetics: strong links to primary tauopathies (but not AD)

probability of success for drugs with genetic support is 2.6x greater

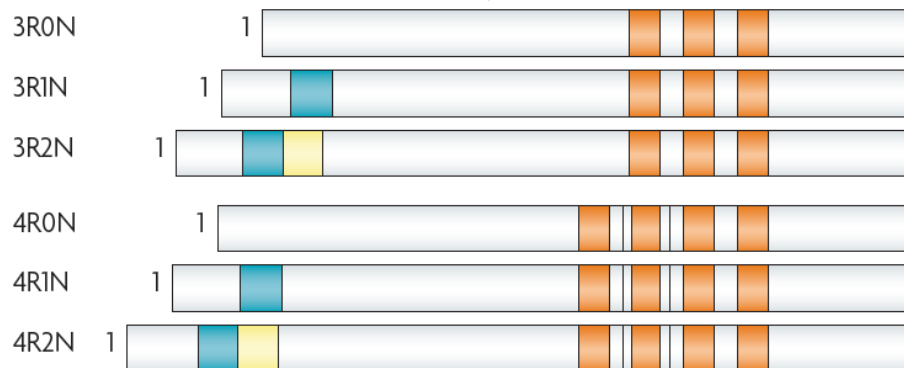


Mouse models

Mutations



Alternative splicing and translation



3R

Pick's

4R

CBD
PSP

AD
norm

PSP, CBD GWAS

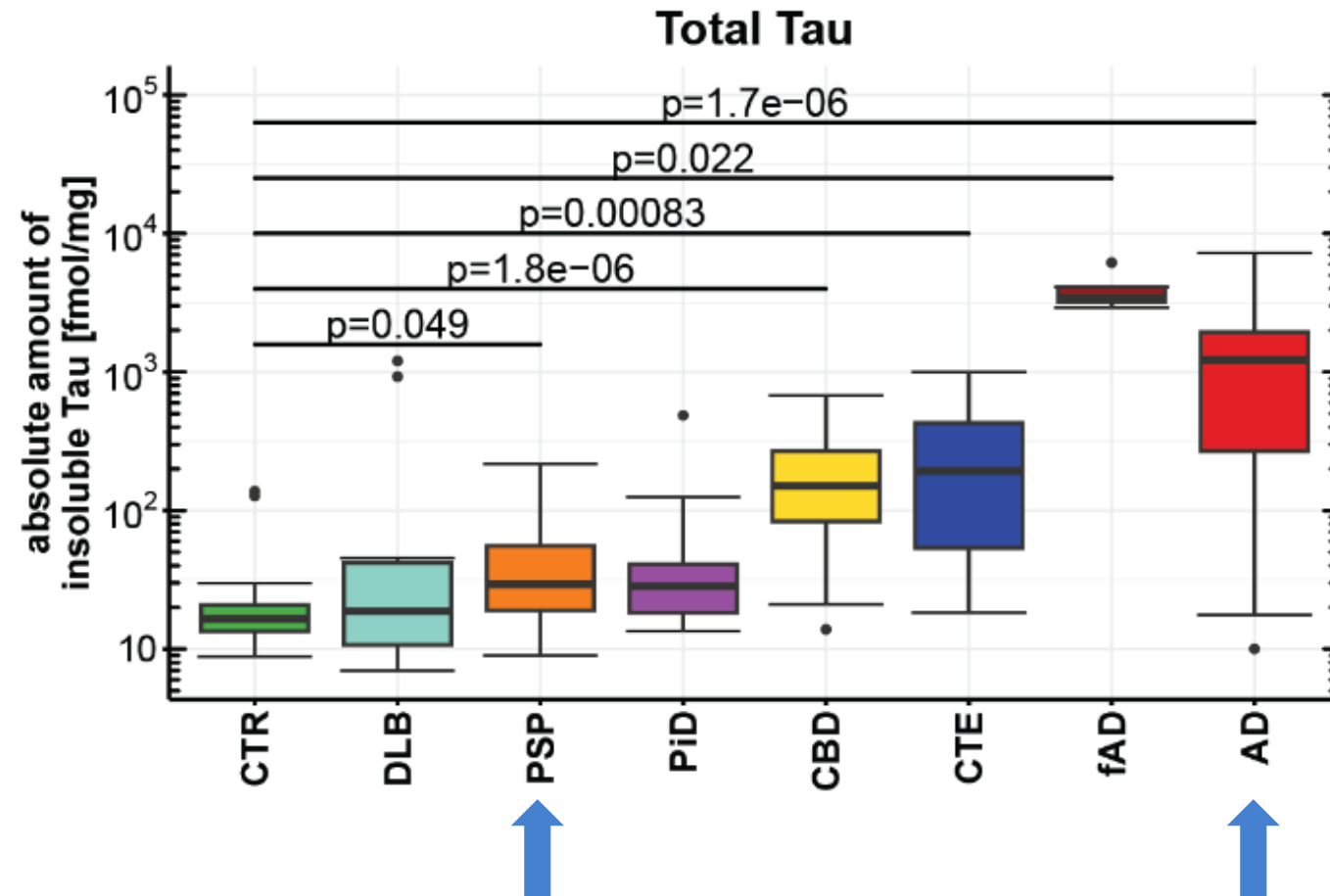
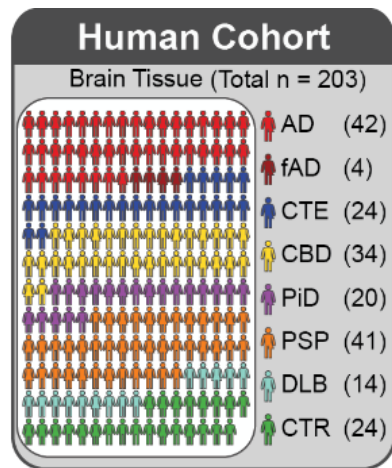
H1/H1 Tau haplotype
OR 5.46 (4.72–6.31) p
= 1.5×10^{-116}

H2 (protective allele) not present in Asia

Greater tau risk
PSP & CBD H1c

TRIM11/17 & LRRK2 protective SNPs

Insoluble tau >50 fold higher in AD than PSP (signal/ noise)



Judith Steen lab: Kumar, et al, *Cell*, 2026

Is tau the central pathogenic species in tauopathies?

AD



or



PSP

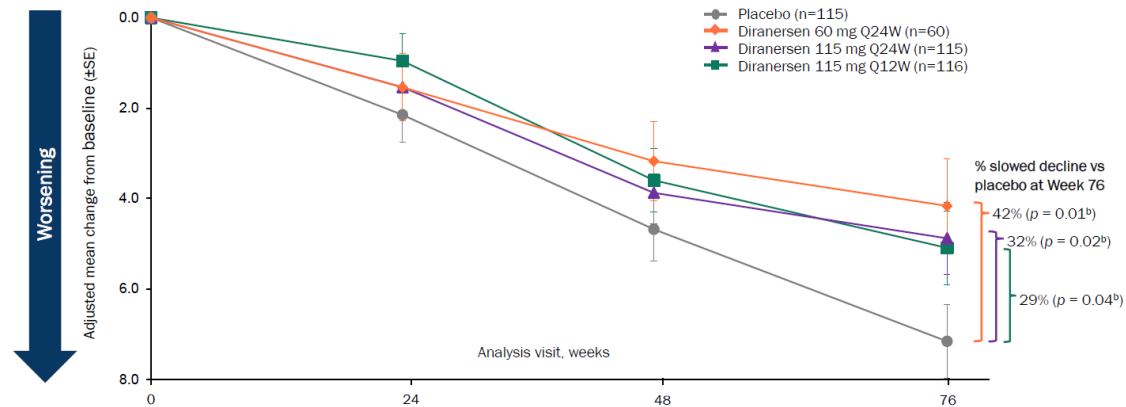


FTLD-MAPT

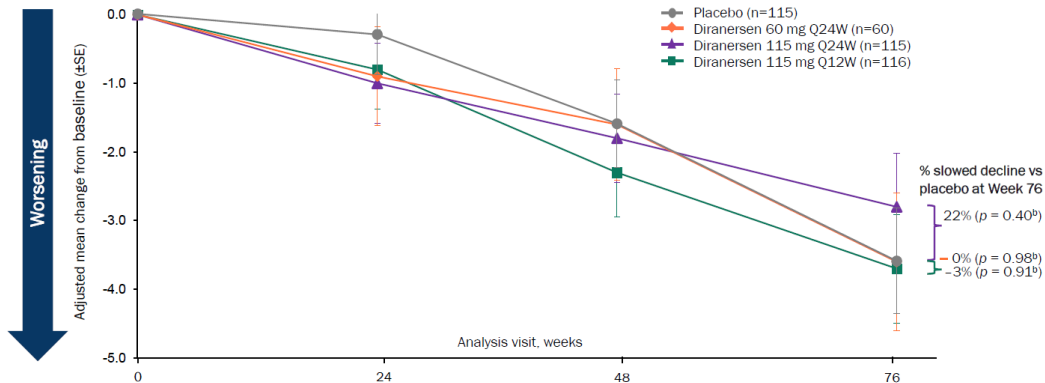


Reducing tau leads to cognitive benefits in AD with A β still present

Improved: Cognitive function (ADAS-cog): 42% slowing

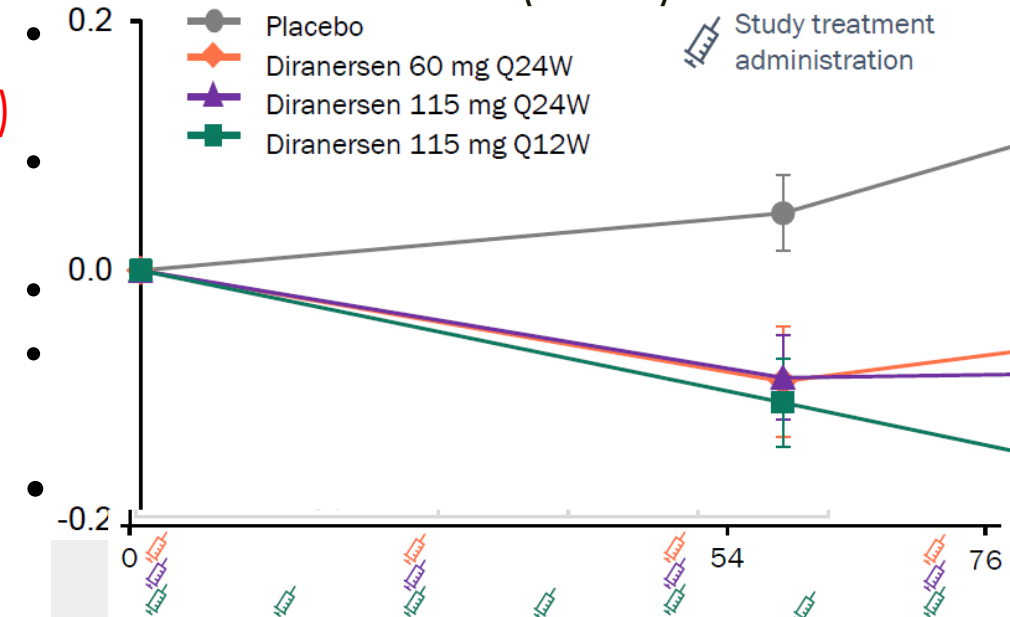


No effect: Activities of daily living (ADCS-ADL-MCI)

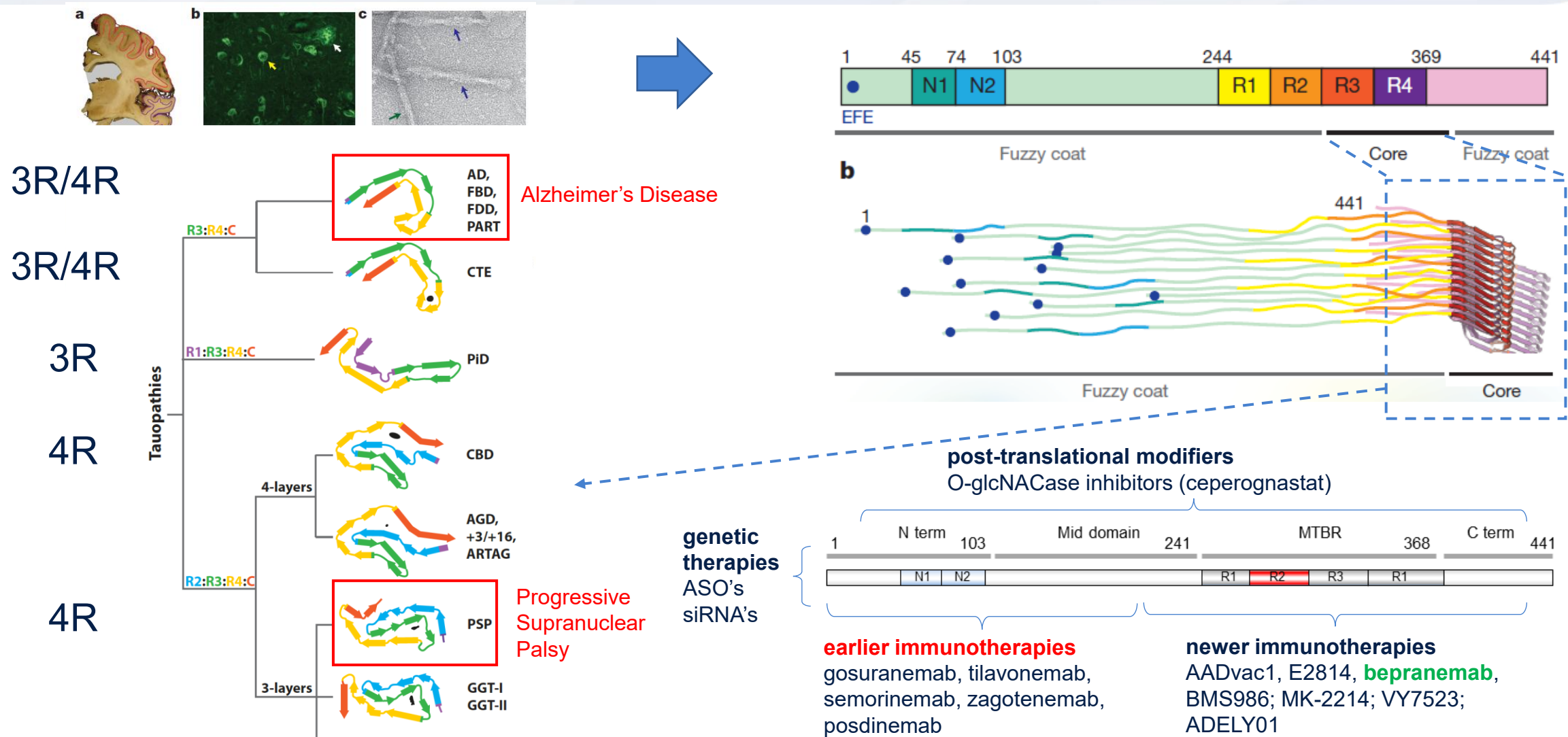


- Reduced cognitive decline
- No effect on functional decline
- Lowest dose most effective
- Dose-related side effects: confusion & falls (~1 week post injection)

Tau PET (SUVR)



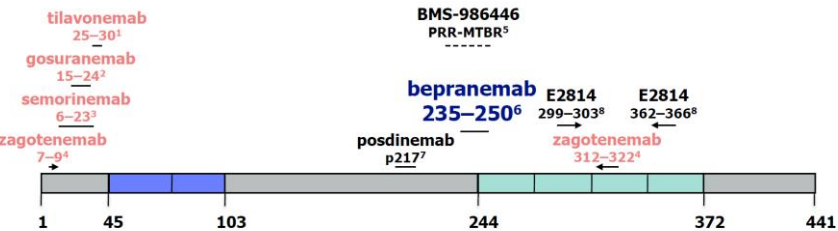
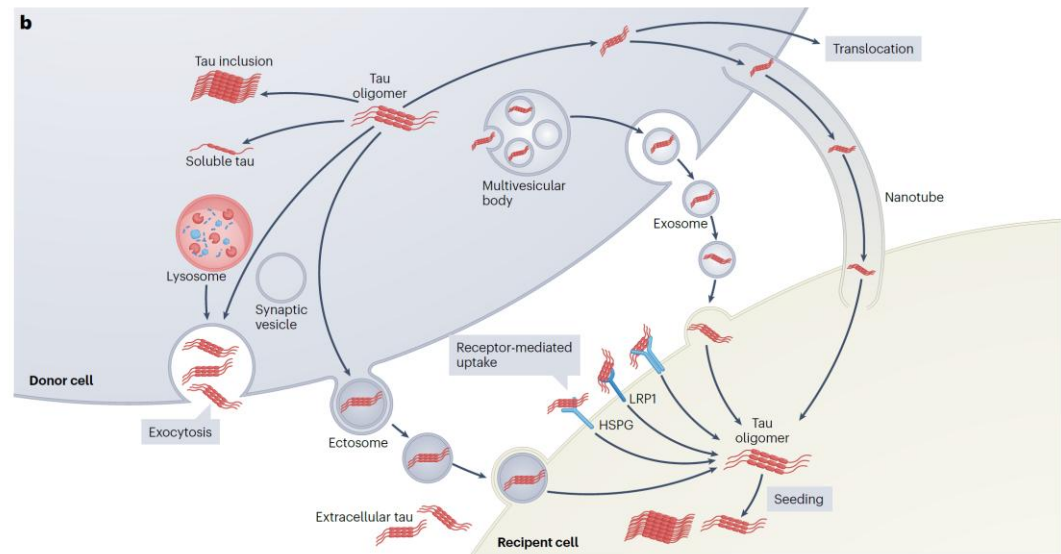
Disease specific tau aggregate structures: impact on treatments?



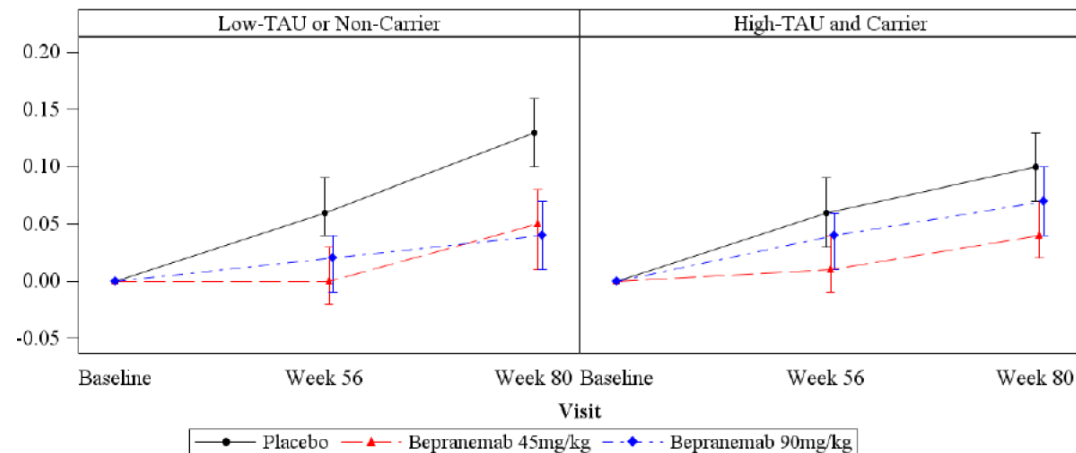
Fitzpatrick, *Nature*, 2017; Falcon, *Nature*, 2018; Shi, *Nature*, 2022; Horie, *Brain*, 2021; Samudra, *J. Clin Invest*, 2023; Lane-Donovan & Boxer, *Neurotherapeutics*, 2024

MTBR targeted mAb shows potential benefits in early AD

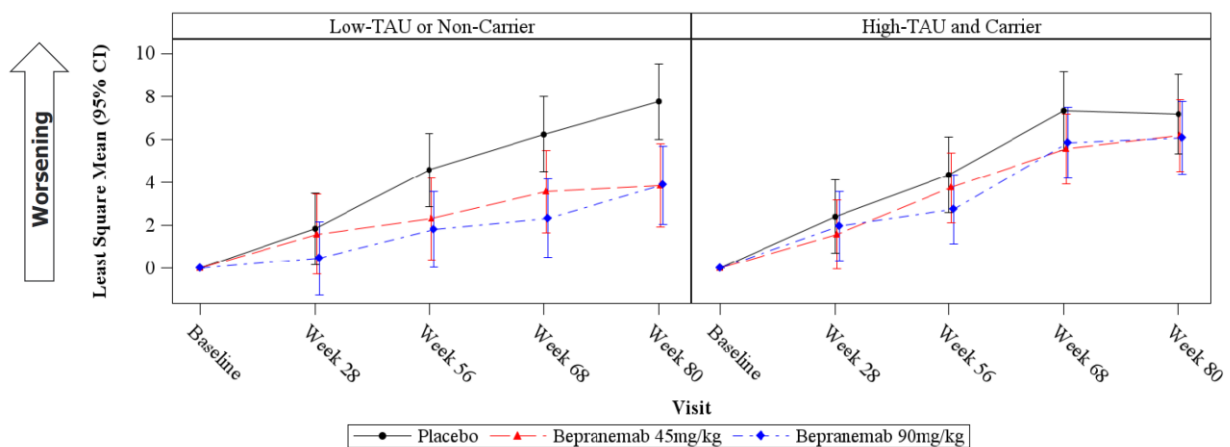
Transcellular spread of toxic tau?
Relevant for human disease?



Insoluble tau in brain (PET)

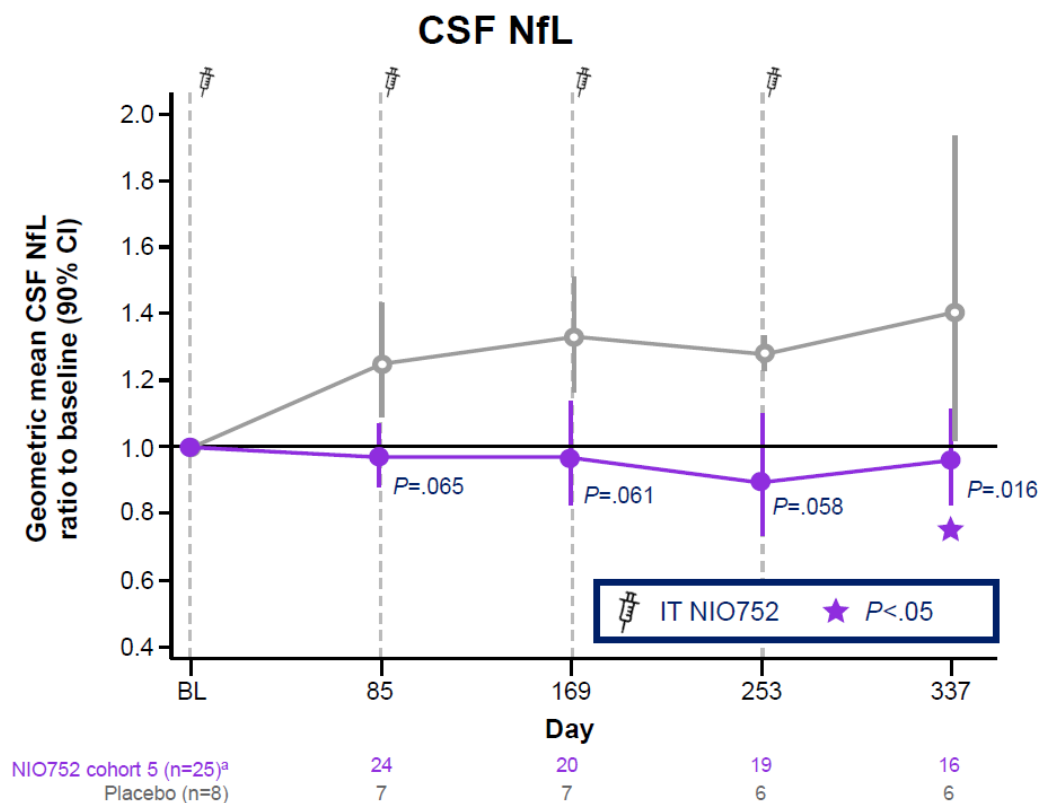
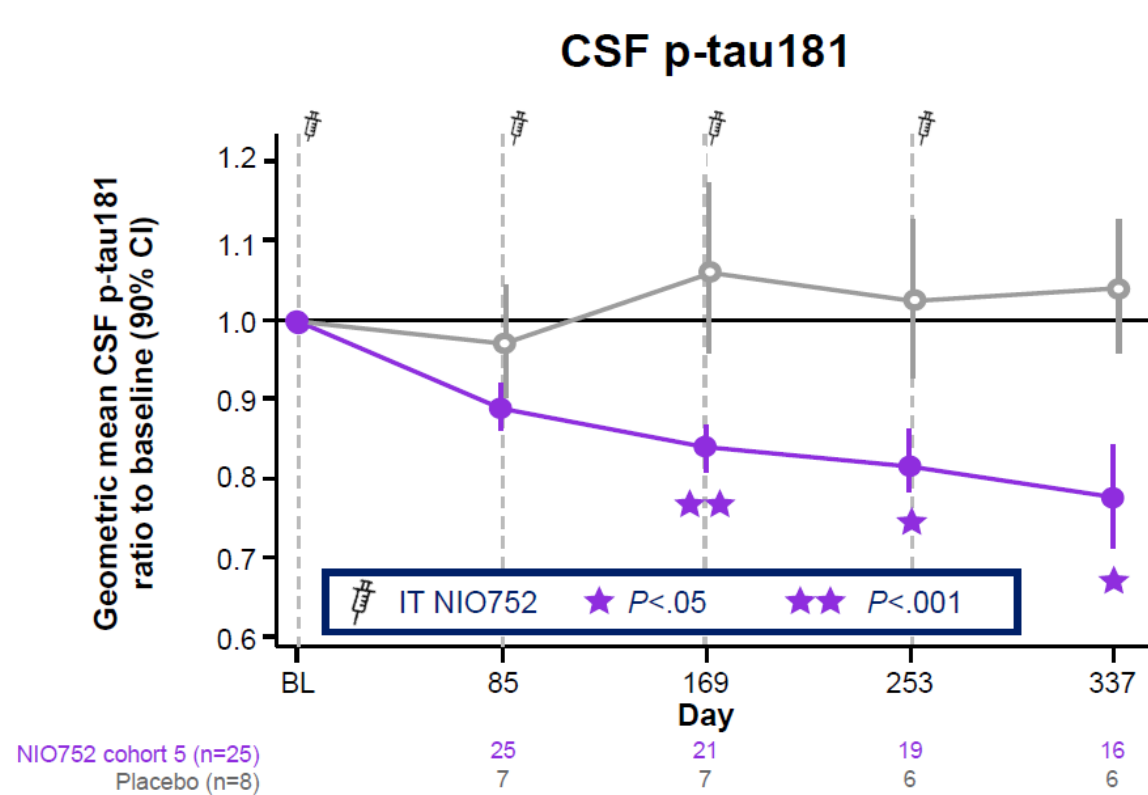


Cognitive status (ADAS-cog)



Parra Bravo et al. Nature Reviews Molecular Cell Biology 2024
Bepranemab data presented at CTAD 2024

Tau reduction stabilizes neurodegeneration in PSP (tau ASO Ph1)



Hoglinger et al, presented at AD/PD2026

Phase 3 trial: NCT07498426

Summary

- Targeting tau reflects close clinico-pathologic correlation
- Reduced production and targeting all forms of tau – pragmatic solution
- Exciting early results with gene silencing
- Global unmet need for AD and Primary Tauopathies
- Rationale for expansion beyond Alzheimer's disease

ARO-MAPT Phase 1/2a Study Clinical Data Update

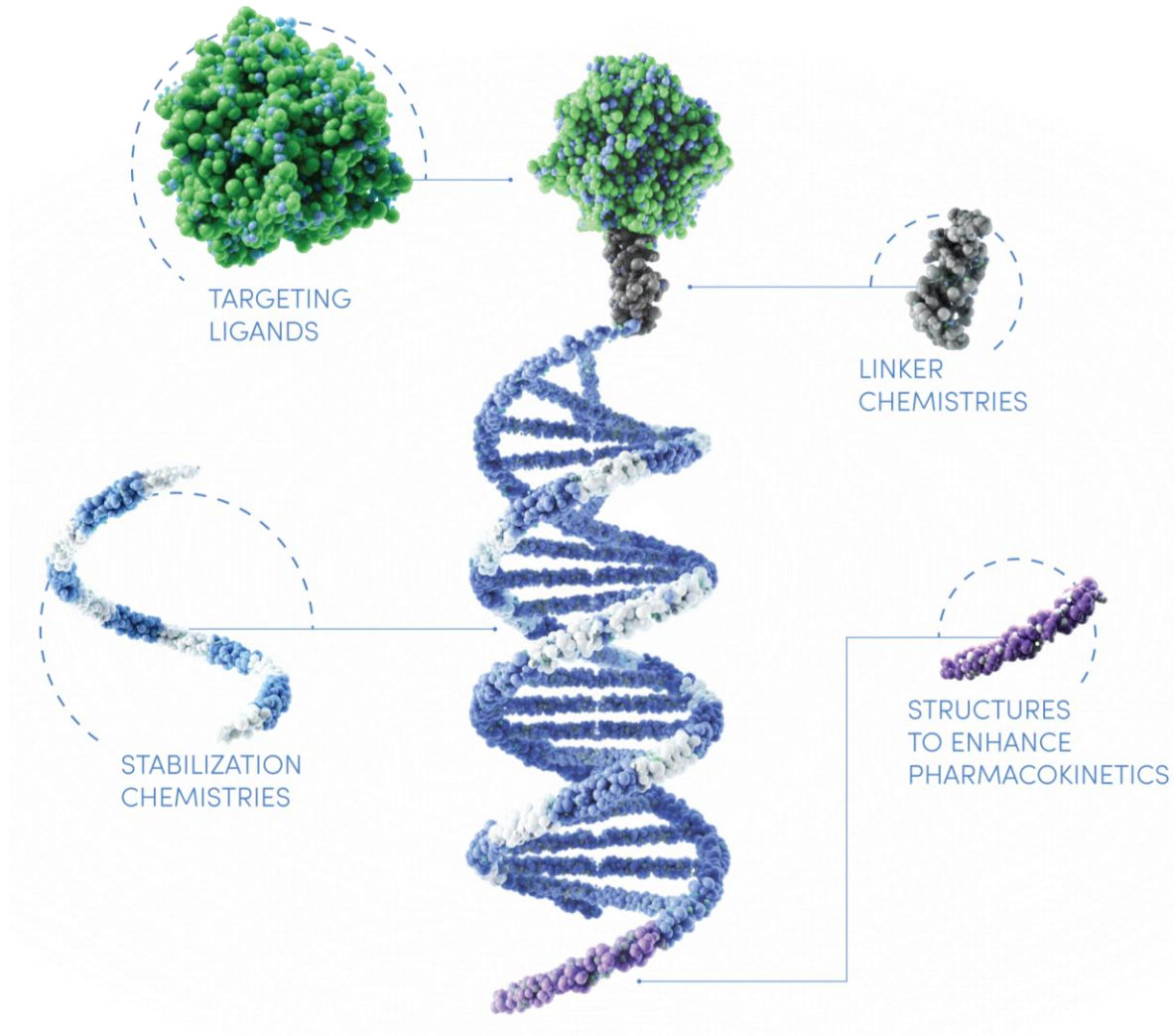
TRiM™ CNS-SC Platform & Overview of ARO-MAPT

James Hamilton MD, MBA

Chief Medical Officer and Head of R&D



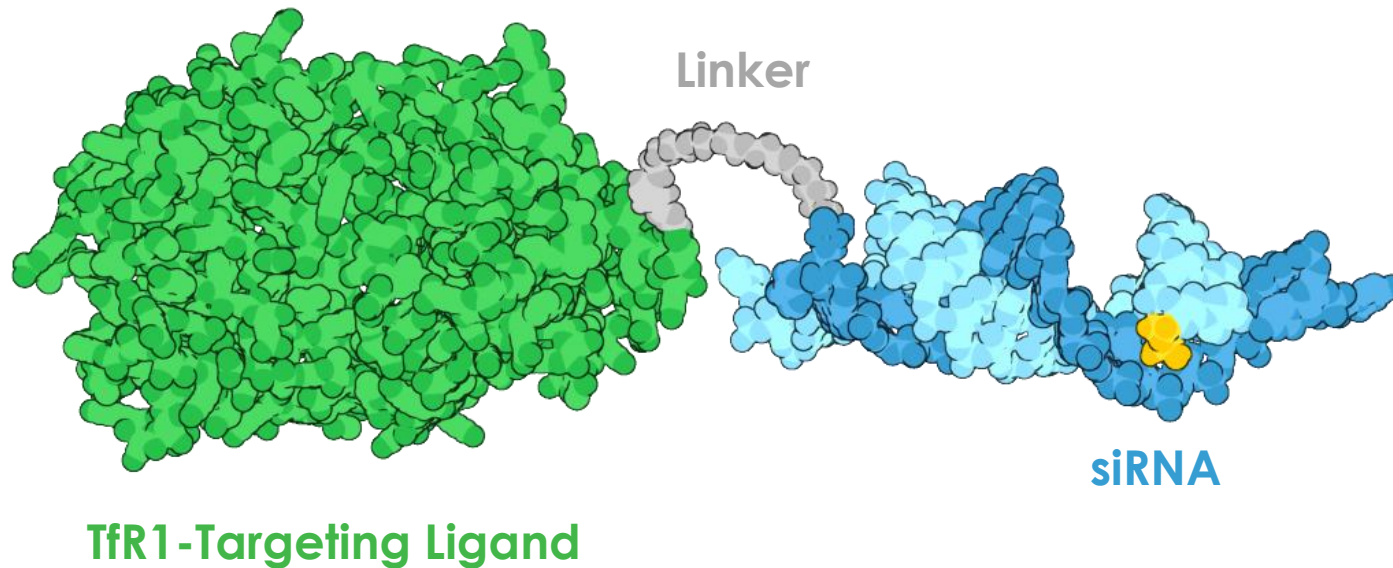
TRiM™ Platform: Targeted RNAi Molecule



TRiM is a Modular, Structurally Simple Platform to:

- 1 Optimize siRNA sequence selection
- 2 Address multiple cell types
- 3 Provide reproducibility of GLP tox and manufacturing
- 4 Move rapidly from idea to the clinic

Delivering siRNA Across the Blood Brain Barrier: CNS-Targeting TRiM™ Platform via Subcutaneous Administration



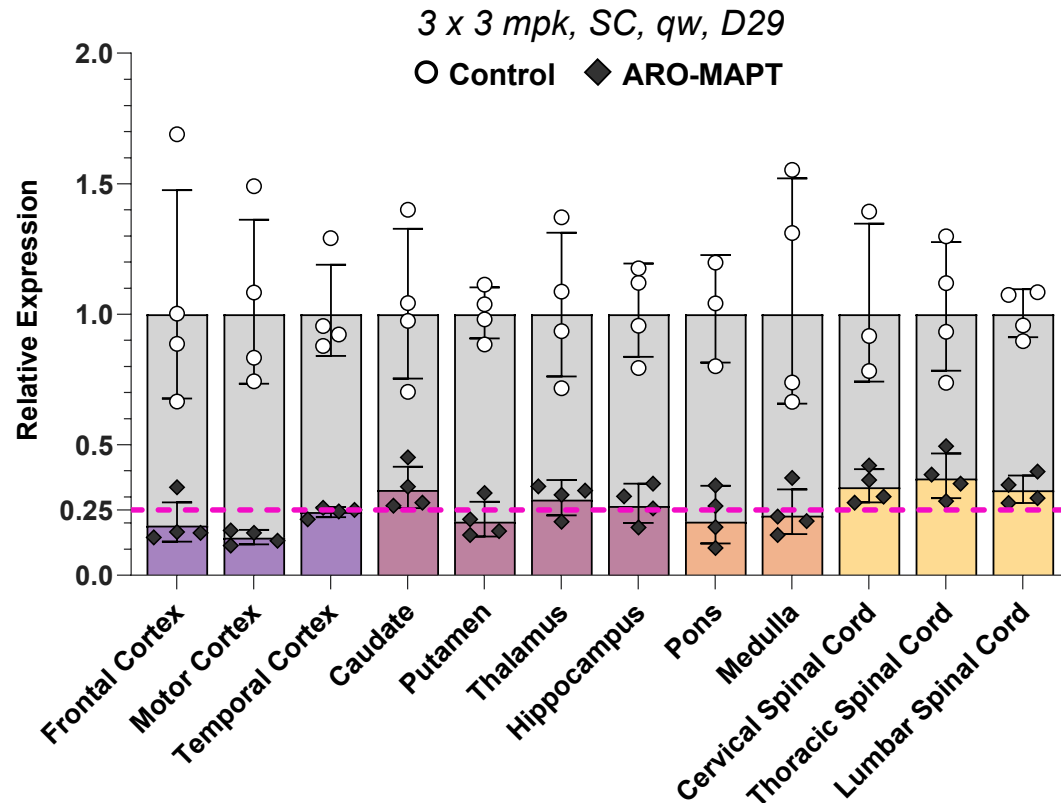
Systemic Delivery Platform Targeting the CNS

- **Ligand-driven** delivery
- **Effective and durable** reduction in expression levels
- **Convenient** subcutaneous (SC) administration (quarterly dosing)
- **Favorable** safety profile (rodent and NHP >10x margin over efficacious dose)

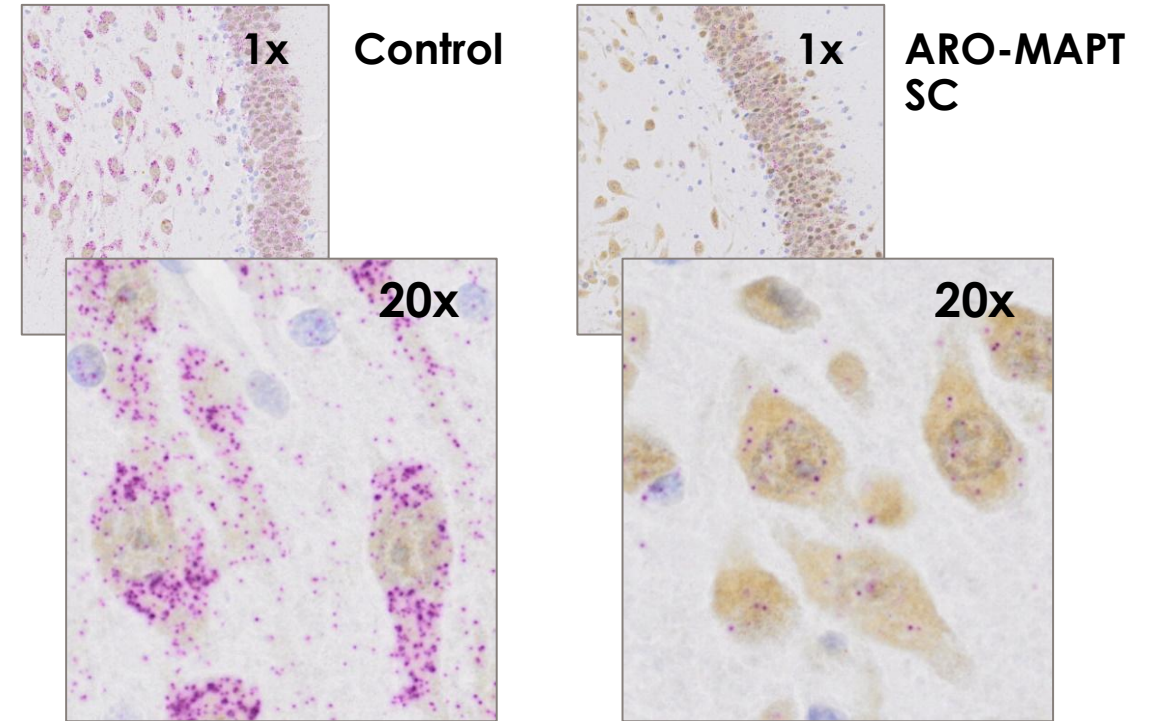
ARO-MAPT Achieves Deep Knockdown of MAPT mRNA Throughout the CNS with Subcutaneous Administration in Cyno



MAPT mRNA Reduction in NHP CNS Regions



MAPT mRNA Depletion in Hippocampus



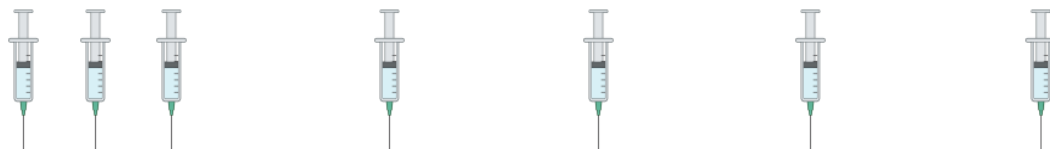
MAPT mRNA shown in purple

mRNA Knockdown Corroborated by RNAscope

Tau Protein Reduction in Cerebrospinal Fluid in Monkeys

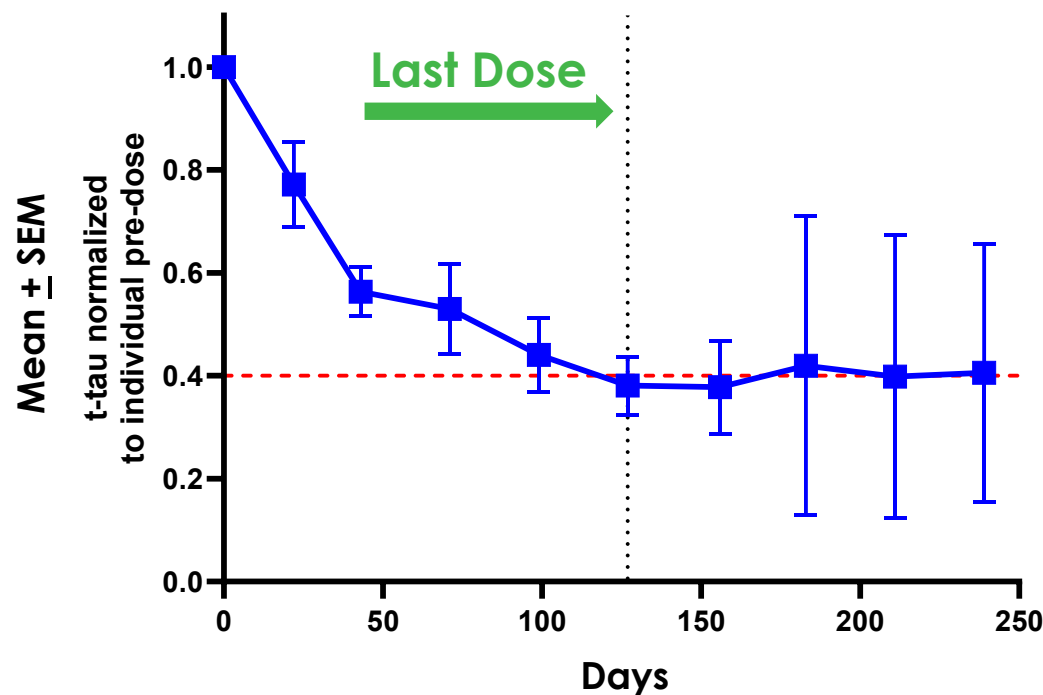


7x3 mg MAPT siRNA/kg SC: 3 Weekly Loading Doses + 4 Monthly Maintenance Doses



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

CSF T-Tau Levels

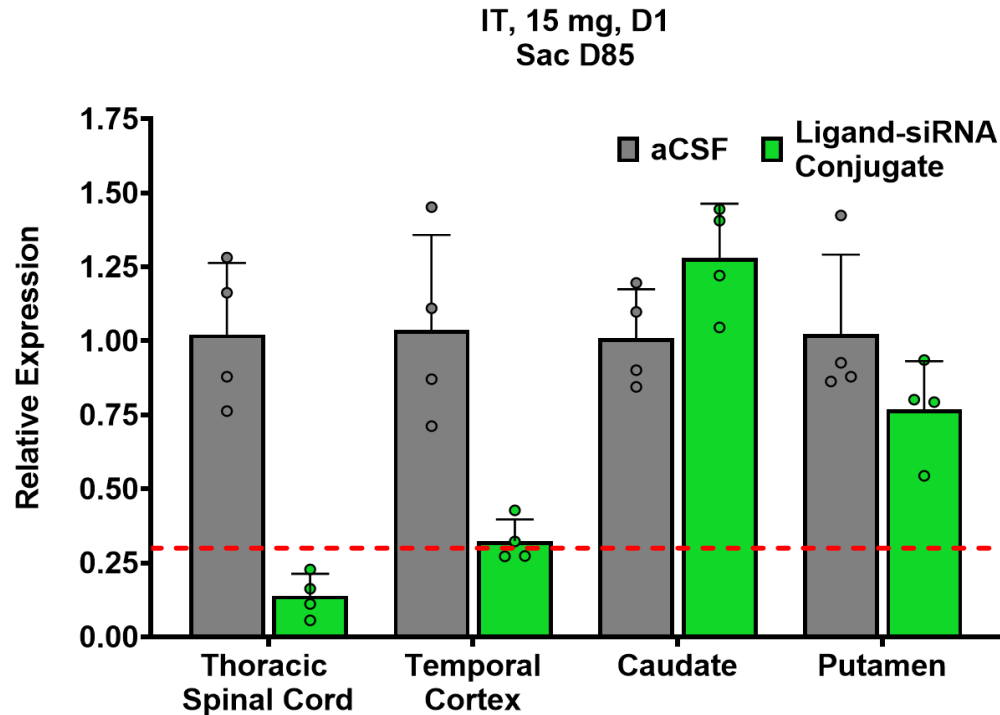


Tau Protein Reduction Maintained at 50–60% Up to 4 Months After Last Dose.

BBB Platform Achieves Uniform Reduction Across the Brain



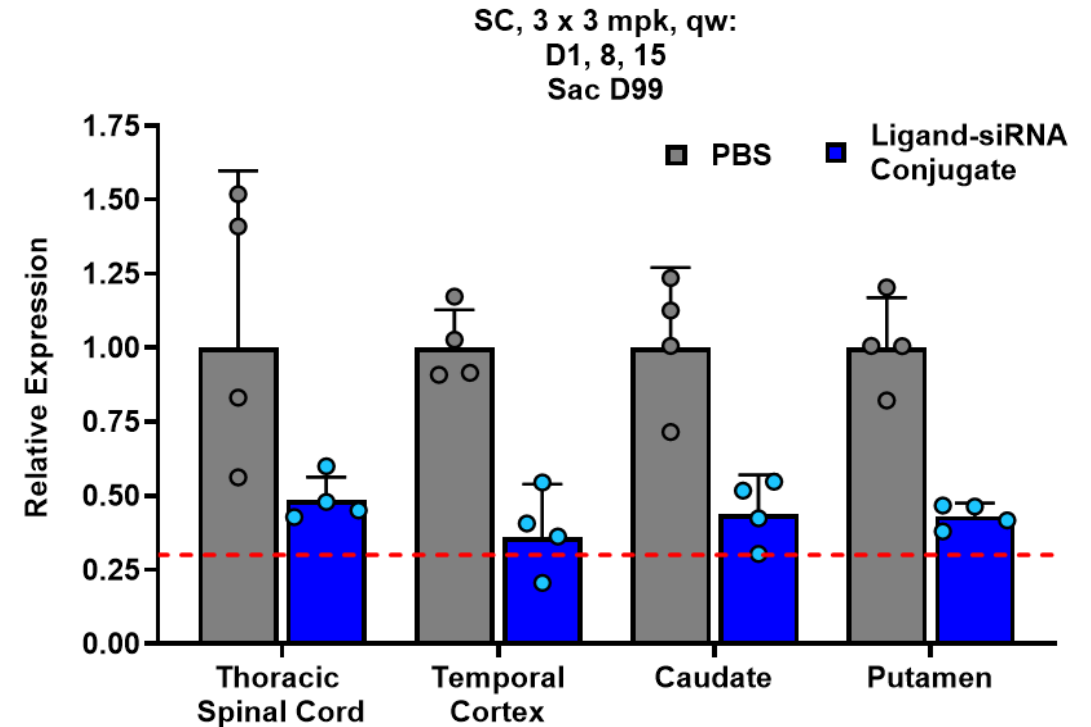
MAPT mRNA Reduction in NHP Brain Regions by IT



Intrathecal Administration:

- Minimal mRNA reduction in deep brain regions.

MAPT mRNA Reduction in NHP Brain Regions by SC

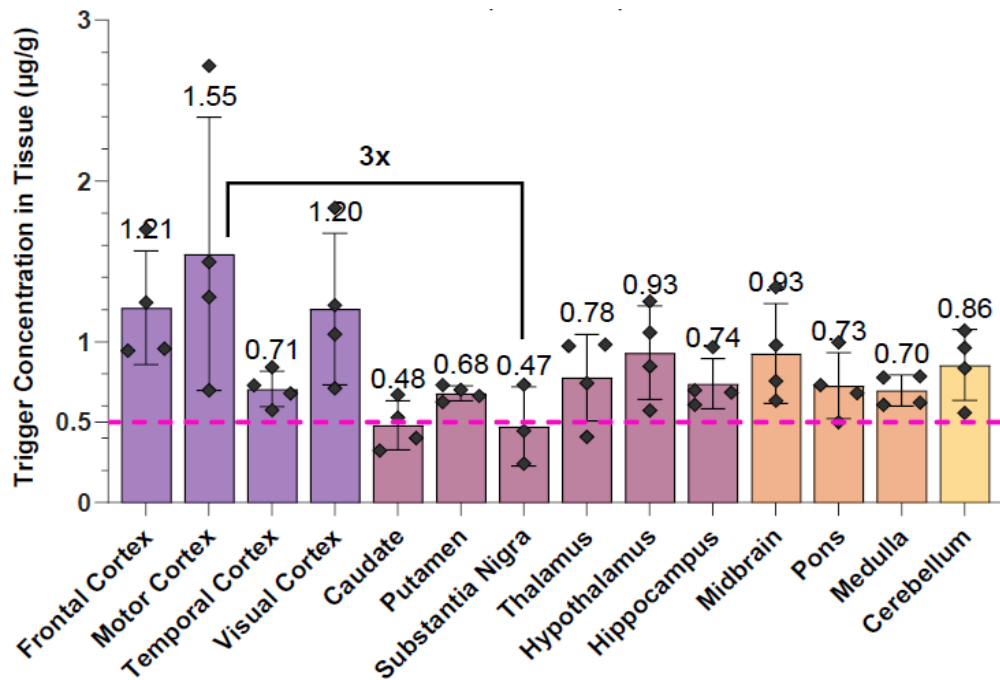


Subcutaneous Administration:

- Even mRNA reduction across brain regions, including deep brain.

TfR1 BBB siRNA Delivery Platform Improves Homogeneity of Brain Distribution versus IT Administered ASO (without a lumbar puncture)

TfR1-ligand Conjugated siRNA – NHPs



Administration:
IV/SC

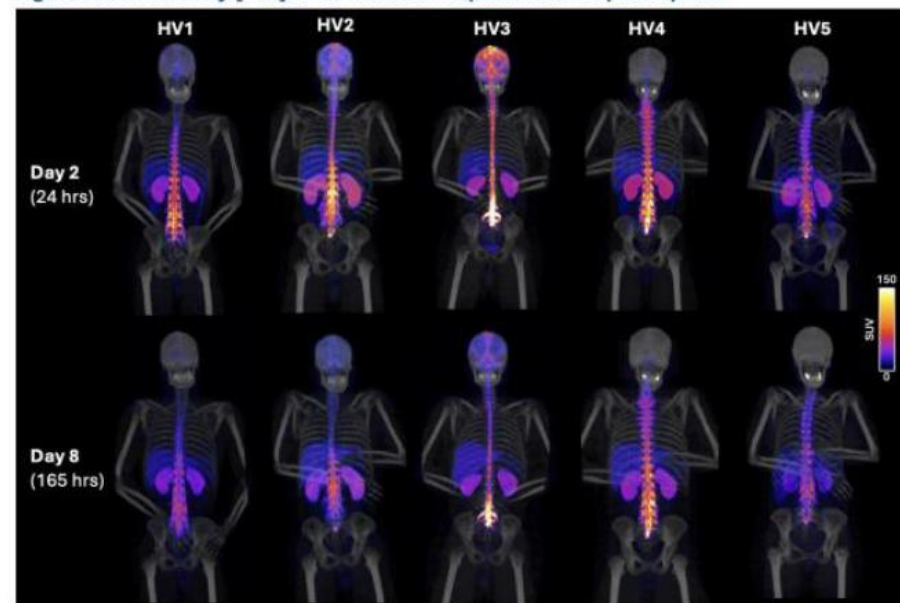
Distribution: Capillary Network

- Homogenous delivery (location, location, location)
- Broad pharmacodynamic effect
- Greater exposure

Collins et al. CTAD 2025.

Non-shuttled ASO – Humans

Figure 3. Whole body [⁸⁹Zr]Zr-DFO-BIIB080 uptake across participants



Whole body SUVs were calculated at 24 hrs and Day 8 and projected onto subjects' CT scans. SUV colorscale ranges from 0 to 150

Administration:
LP

Distribution: CSF Flow

- Heterogenous delivery
- Lesser exposure

ARO-MAPT Phase 1/2a Study Clinical Data Update

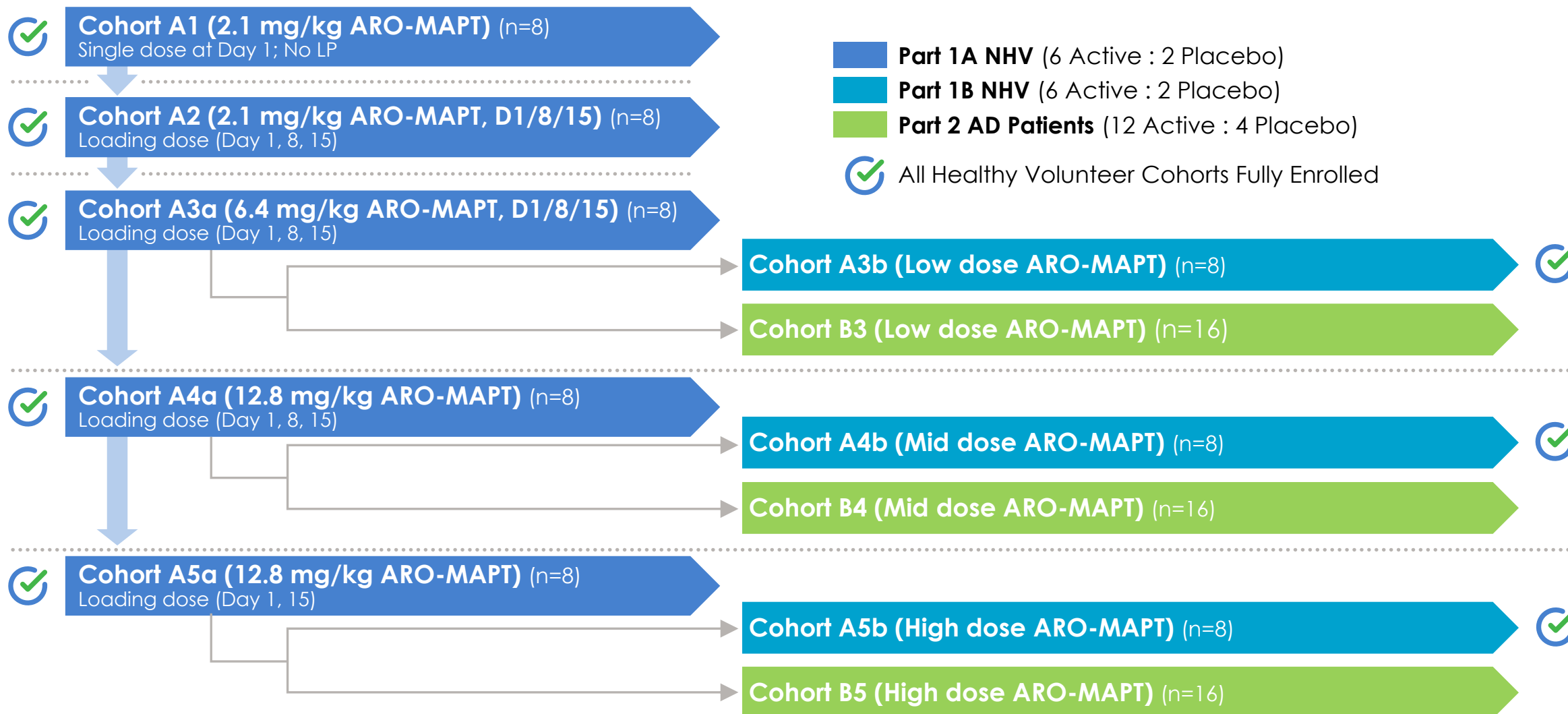
Clinical Study Update from AROMAPT-SC-1001

James Hamilton MD, MBA

Chief Medical Officer and Head of R&D



AROMAPT-SC-1001: Phase 1 Study in Healthy Volunteers and Patients with Alzheimer's Disease (AD)



*dose represents total conjugate dose

AD Cohort Patient Population

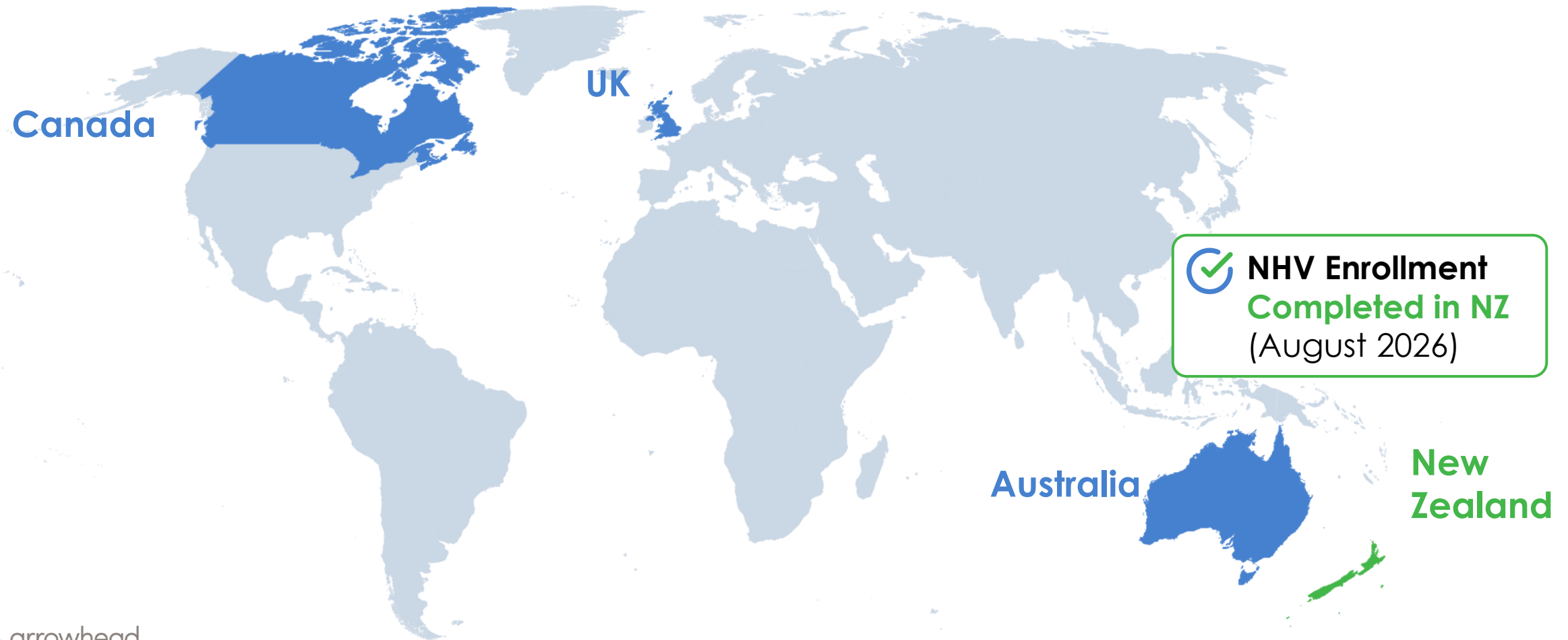
Key Inclusion Criteria:

- Age 50-80
- Early Alzheimer's Disease as defined by CDR and MMSE cutoffs
- Presence of at least one biomarker (CSF, Plasma or PET) consistent with Alzheimer's
- Not using or planning to use AD disease modifying therapies (including anti-amyloid monoclonal antibodies)

AROMAPT-SC-1001: Sites Open in UK, Canada, AU, and NZ

NHV (Part 1a and Part 1b)

Early Alzheimer's Disease (Part 2)



Key Endpoints

1^o Safety

2^o Pharmacokinetics



Exploratory



NHVs

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

AD Subjects:

- 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

Baseline NHV Characteristics

Characteristic	AROMAPT-SC-1001	
	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.

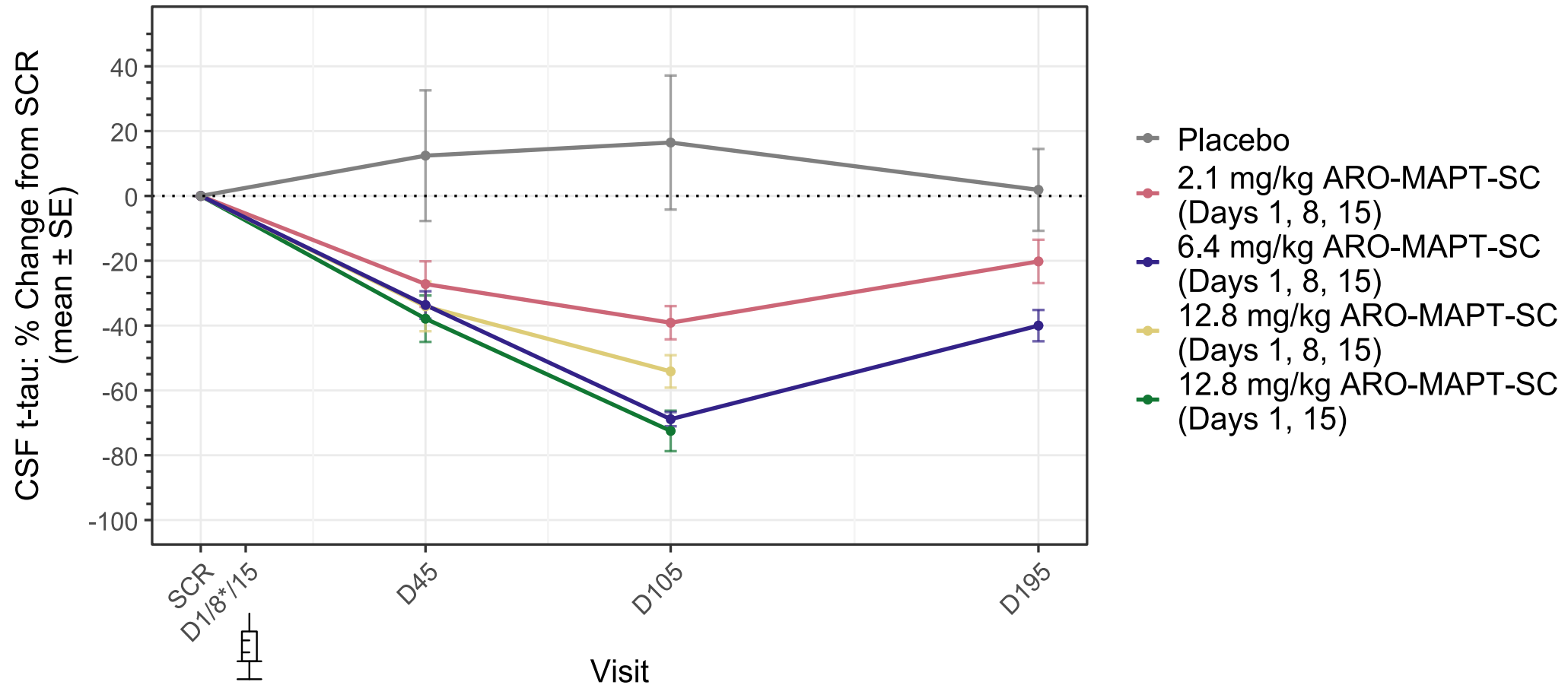
1. High SD due to single healthy volunteer with elevated CSF tau at baseline; when excluded, mean (SD) = 51.4 (34.2) pg/mL.

2. Data cutoff: 25aug26, prior to full enrollment of Part 1b

Loading Dose of ARO-MAPT Achieved Individual CSF tau reduction of Up to **85%** with Mean Reduction of Up to **73%** at Day 105, Duration Supports Dosing Every 3 Months

CSF t-tau: Part 1A, Loading Dose Only

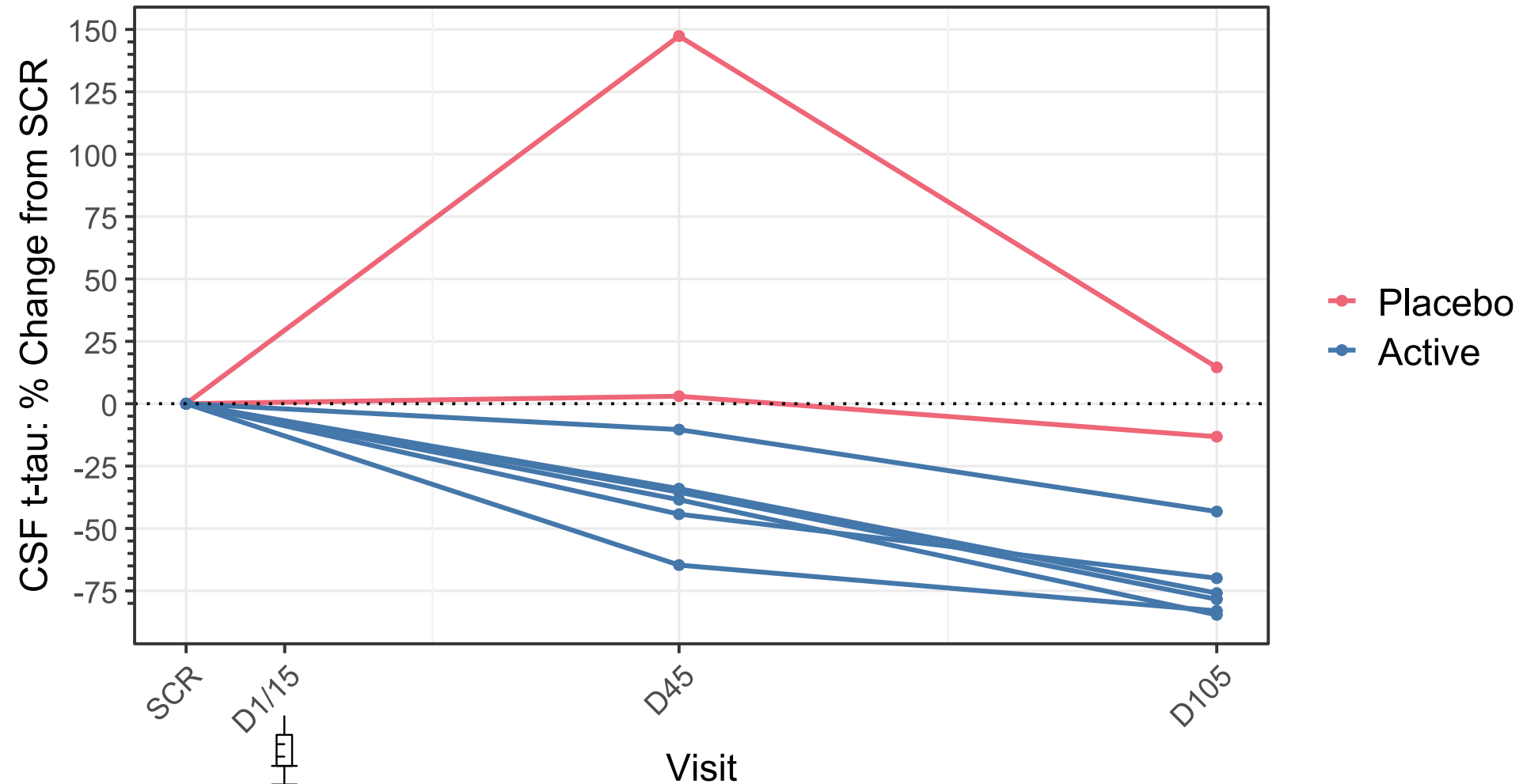
CSF Tau — Part 1a (all subjects)



*Cohort A5a is not dosed on Day 8.

Consistent individual response to ARO-MAPT, maximal individual response of **85%**

CSF Tau — A5a individual trajectories



ARO-MAPT Demonstrates a Favorable Safety Profile

N of 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)

✔ 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 persistent anemia or neurobehavioral AEs.

Next Steps

- ✔ Finish dosing in MAD NHV cohorts (data update in 2027)
- ✔ Enrollment in early AD Cohorts (data update in 2027)
- ✔ Engage with FDA in anticipation of Phase 2 studies in MAPT-FTD and PSP

Conclusions

- ✓ Arrowhead's subcutaneous CNS siRNA delivery platform has been well tolerated to date in NHVs and AD patients
- ✓ Subcutaneous administration of ARO-MAPT in NHVs demonstrated deep, dose-dependent, and durable knockdown of CSF t-tau with potential for more homogenous brain distribution
- ✓ These data represent initial clinical validation of ARO-MAPT and importantly of the TRiM™ CNS platform which is an important milestone for Arrowhead and for our partners using this platform
- ✓ In addition to ARO-MAPT, Arrowhead has multiple wholly owned CNS targeted brain shuttle delivered preclinical development programs including two planned CTAs for YE 2026 or early 2027

ARO-MAPT Phase 1/2a Study Clinical Data Update

Key Takeaways

Chris Anzalone, Ph.D.

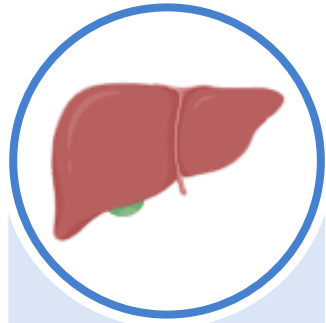
President and CEO



Key Takeaways

-  **A major scientific breakthrough:** Clinically validated delivery across the blood-brain barrier that overcomes central obstacles of CNS siRNA medicines
-  **Simple treatment:** Subcutaneous administration eliminates the need for spinal injections, making treatment more practical for large patient populations
-  **A platform with expansive potential:** The technology could support an entire pipeline targeting neurodegenerative diseases, psychiatric conditions, sleep disorders, migraine, obesity, and other neurological conditions
-  **ARO-MAPT is a candidate with substantial potential:** Tau reduction could be an important treatment for Alzheimer's disease and, nearer-term, a powerful treatment for multiple primary tauopathies

TRiM™ Platforms Drive Robust Pipeline for Multiple Tissue Types



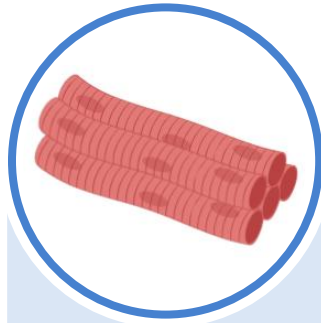
Liver

Strong
clinical
validation



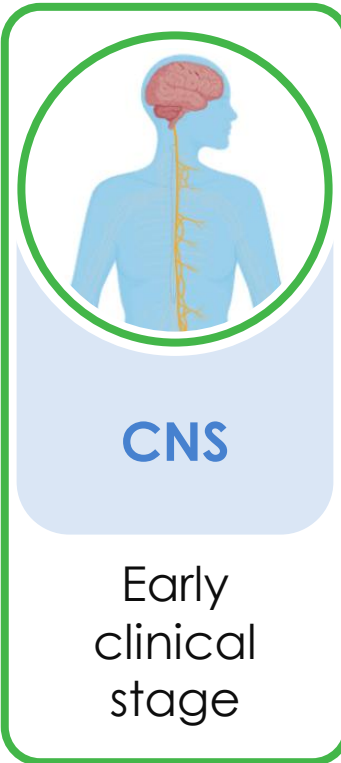
Lung

Deep lung
clinical
validation



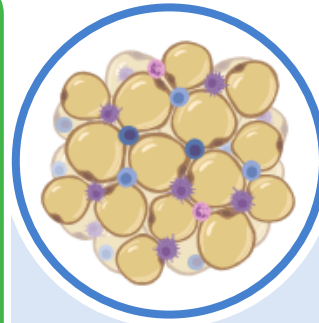
Skeletal
Muscle

Mid clinical
stage



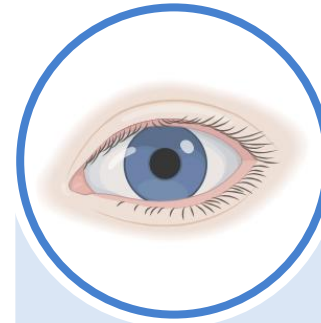
CNS

Early
clinical
stage



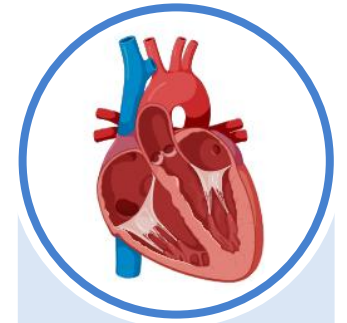
Adipose

Early
clinical
stage



Ocular

Preclinical
stage



Cardio-
myocyte

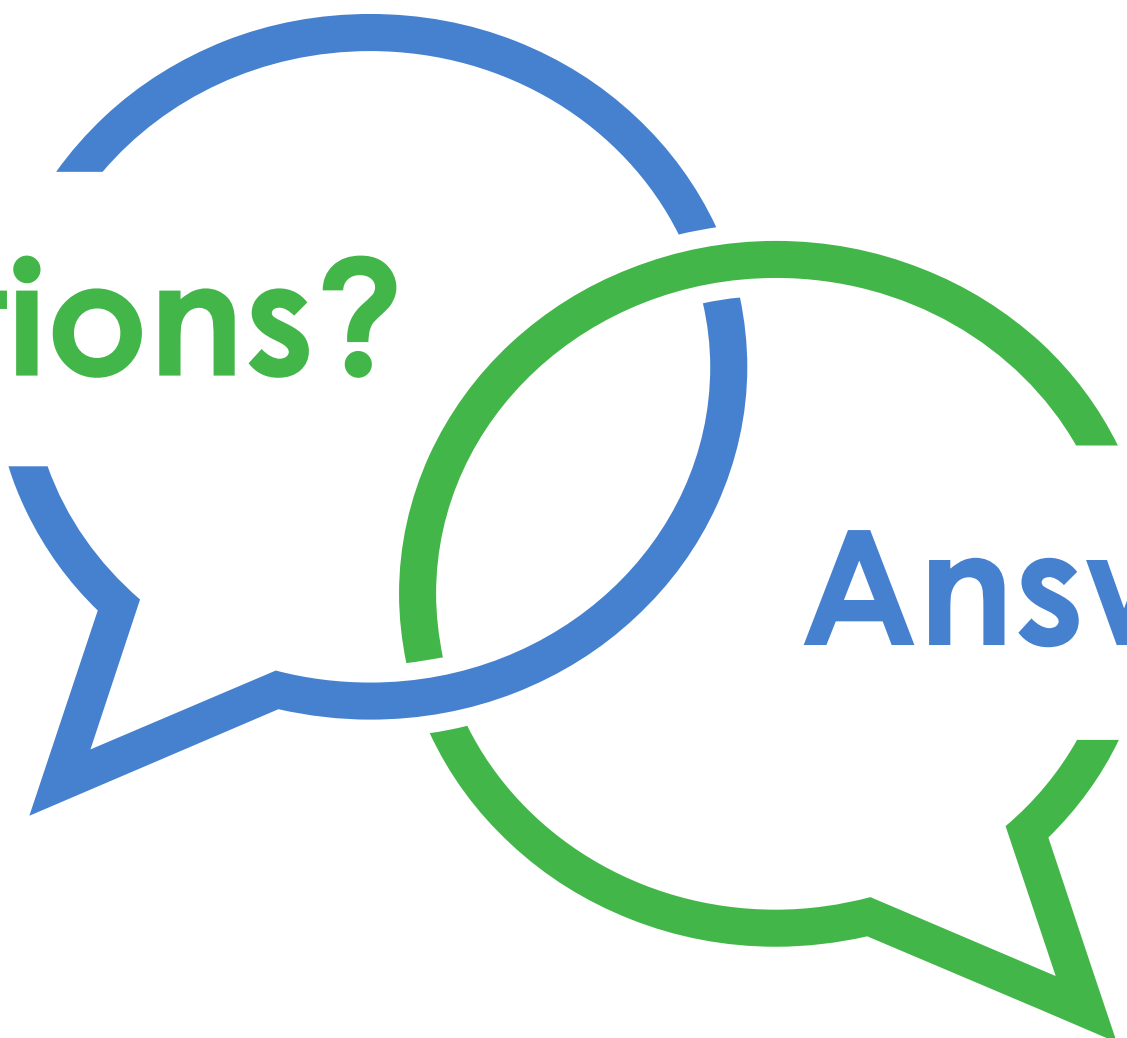
Preclinical
stage

Arrowhead now has **clinical** proof of concept for delivery to and knockdown in a 5th organ system

Multiple “firsts” in 2026

In less than 12 months, Arrowhead further solidified its position as the leading RNAi innovator with the following “firsts”

- 1 Clinical PoC for brain delivery of siRNA after subcutaneous injection
- 2 Clinical PoC for silencing two genes with a single RNAi molecule
- 3 Clinical PoC for deep and durable knockdown of an adipocyte expressed gene



Questions?

Answers.