Results from the Proof-of-Concept Phase 2 'SHINE' Study of CT1812 in Mild-to-Moderate Alzheimer's Disease

Focus on Pre-specified Lower p-tau217 Subgroup

Clinical Trials in Alzheimer's Disease (CTAD)
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Disclosures

Presenter Disclosures

- Professor Woodward has worked on Alzheimer's disease drug trials funded by pharmaceutical companies including AbbVie, Astra Zeneca, AZ Therapies, Biogen, Bristol Myers Squibb, Buck, Cognition Therapeutics, Eisai, INmune Bio, Janssen, Eli Lilly, Lundbeck, Merck/MSD, Novartis, Pfizer, Roche, Servier, Takeda, Tau Rx, vTv Therapeutics and Zinfandel
- He has also received honoraria for advisory and speaker activities by Roche, Eli Lilly, Eisai and Actinogen

Product Disclosure

- CT1812 is an investigational therapeutic that has not been approved for any use by the US Food and Drug Administration or other health authority

Tau Burden in Amyloid-related AD Clinical Trials

Baseline plasma p-tau217: predictive biomarker of response to therapy

- Plasma p-tau217 reflects brain amyloid and tau burden
- Prior data indicate that individuals with lower AD pathology at baseline, as reflected by lower levels of plasma p-tau217, have greater response to amyloid-based therapies, eg:
  - Donanemab TRAILBLAZER 2*
    - iADRS: 36% slowing in low tau tercile
    - iADRS: 21% slowing in high tau tercile
- Given CT1812's MoA of displacing Aβ oligomers, we hypothesized that larger treatment effect may be observed in participants with lower plasma p-tau217
- Prespecified subgroup analysis defined by median baseline plasma p-tau217 within study population

** Mintun MA et al. Predicting Efficacy in Donanemab-Treated Participants. slides presented at CTAD 2023*

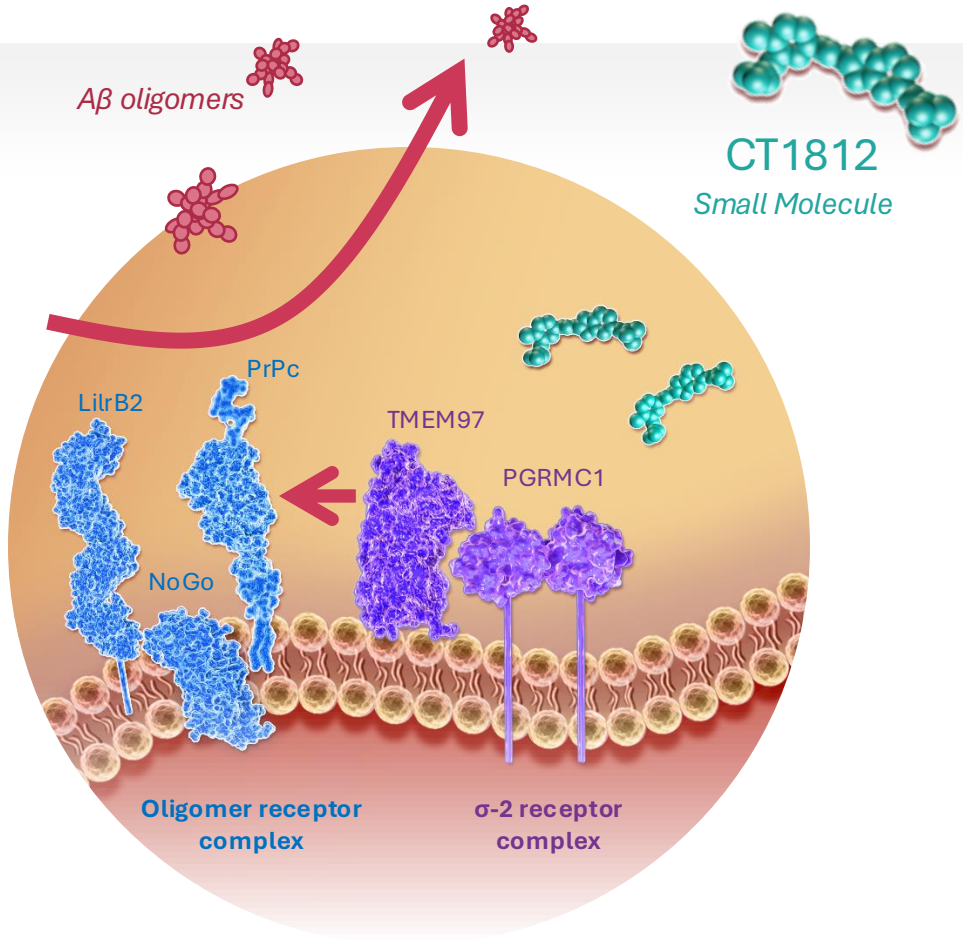
iARDS, Integrated Alzheimer's Disease Rating Scale

Cognition preserved in CT1812-treated participants with below median plasma p-tau217

CT1812 Mechanism of Action

Investigational, oral, small molecule oligomer antagonist

- First-in-class sigma-2 receptor modulator
- Preclinical and clinical evidence that CT1812 acts to displace Aβ oligomers from synapses, facilitating clearance of Aβ oligomers in the cerebrospinal fluid (CSF)
- Proposed *synaptoprotective* mechanism of action to slow further neuronal injury / loss
- MoA distinct from anti-amyloid immunotherapy



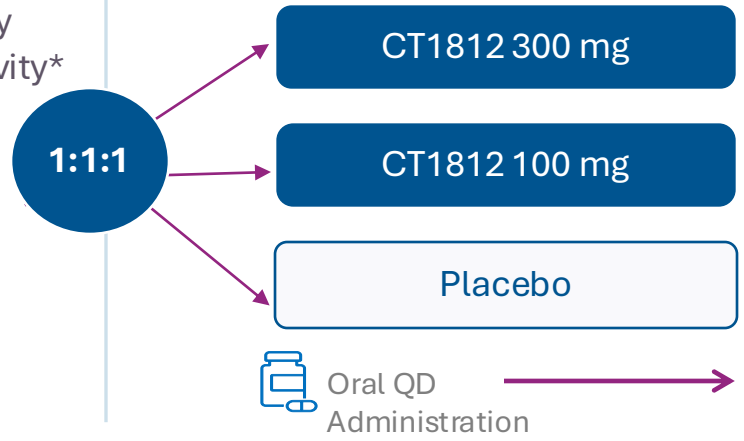
Phase 2 PoC Study in Mild-to-Moderate Alzheimer's Disease

Included prespecified analysis in participants with baseline plasma p-tau217 above and below median

Select Inclusion and Exclusion

- AD diagnosis confirmed by PET or CSF amyloid positivity*
- MMSE 18-26
- MRI w/o significant abnormality
- Stable regimen of AChEi or memantine permitted

Treatment Period
6 months



153 participants randomized in Australia, Netherlands, Spain, Czechia, and U.S.

Key Objectives

- Safety/tolerability
- Exploratory cognitive and functional: ADAS-Cog 11, MMSE, ADCS-ADL, ADCS-CGIC
- **Prespecified subgroups based on median plasma p-tau217 levels at baseline**
- Biomarkers

MMSE, mini-mental state examination; MRI, magnetic resonance imaging; AChEi, acetylcholinesterase inhibitor; QD, daily; ADAS-Cog, Alzheimer's disease assessment scale-cognitive subscale; ADCS, Alzheimer's disease cooperative study; ADL, activities of daily living; CGIC, clinical global impression of change

* Notes: independent of plasma p-tau217 levels, amyloid pathology (Aβ PET/CSF) was confirmed in all randomized participants. CSF cut-offs from Clinical Neurochemistry Lab at Sahlgrenska University Hospital in Gothenburg, Sweden or study protocol.

SHINE COG0201

SHINE COG0201 study (NCT03507790) partially funded by $31M NIA grant R01AG058660

Baseline Characteristics of Below/Above Median Plasma p-tau217 Groups

Reflects expected baseline characteristics based on mITT population

	mITT population (n=150)	Below median* p-tau217 Cohort (n=69)	Above or equal to median* p-tau217 Cohort (n=69)
Percent (%) female	60	59.4	58
Percent (%) white	96	94.2	97.1
Percent (%) non-Hispanic or Latino	92	89.9	97.1
ApoE4 Status: n (%) - Percent ApoE4 carriers - Percent ApoE4 non-carriers	 91 (61) 59 (39)	 42 (60.9) 27 (39.1)	 43 (62.3) 26 (37.7)
Percent (%) concomitant AChEi or NMDA use	62.7	55.1	68.1
Mean age (range)	72.7 (51-85)	72.6 (51-84)	72.8 (53-85)
MMSE at baseline mean (range)	21.37 (13-29)	21.94 (14-29)	20.83 (13-28)
Plasma p-tau217 mean (range) in pg/mL	1.10 (0.2-3.5)	0.66 (0.2 - 1.0)	1.53 (1.0-3.5)
CSF neurofilament light chain mean (range) in pg/mL	1217.67 (220.0-2850.0)	994.70 (220.0 - 1840.0)	1389.88 (513.0 - 2850.0)

* Median plasma p-tau217 was identified as 1.0pg/mL at baseline

Summary of SHINE Safety and Tolerability Findings

Full safety data presented at AAIC '24 showing favorable profile with most TEAEs mild or moderate

- CT1812 demonstrated a generally favorable safety and tolerability profile
- Most treatment emergent adverse events (TEAEs) were mild or moderate in severity
- Similar percentages of adverse events in pooled treated (76.5%) and placebo (78%) groups
- No discontinuations due to AEs in the 100mg dose group
- Most discontinuations were in 300mg dose group and all the reportable liver enzyme elevations were in 300mg dose group

Adverse Events	
CT1812	Placebo
76.5%	78%

Serious AEs	
CT1812	Placebo
4.9%	10%

Deaths	
CT1812	Placebo
0	1 (cancer)

Full safety results in *Vijverberg et al*. can be found at cogrx.com/publications

Impact of Plasma p-tau217 on Exploratory Outcomes:

Cognition and Function

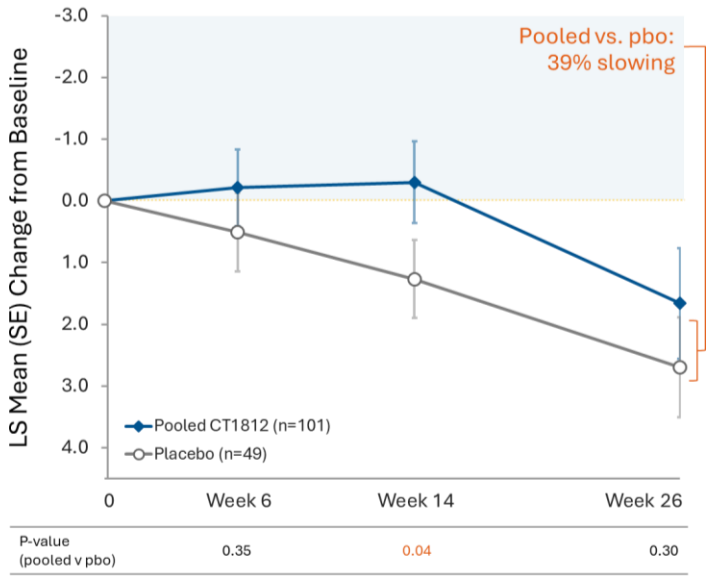
Simoa® ALZpath p-tau217 Advantage PLUS Assay

COGNITION™ Therapeutics

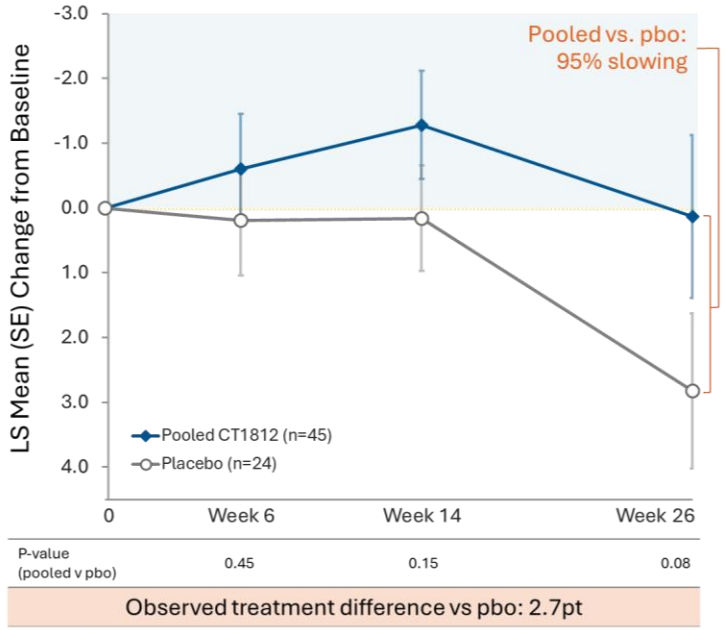
SHINE Cognitive Endpoints: *ADAS-Cog 11*

Preservation of ADAS-Cog 11 in participants below median plasma p-tau217†

mITT population* (n=150)

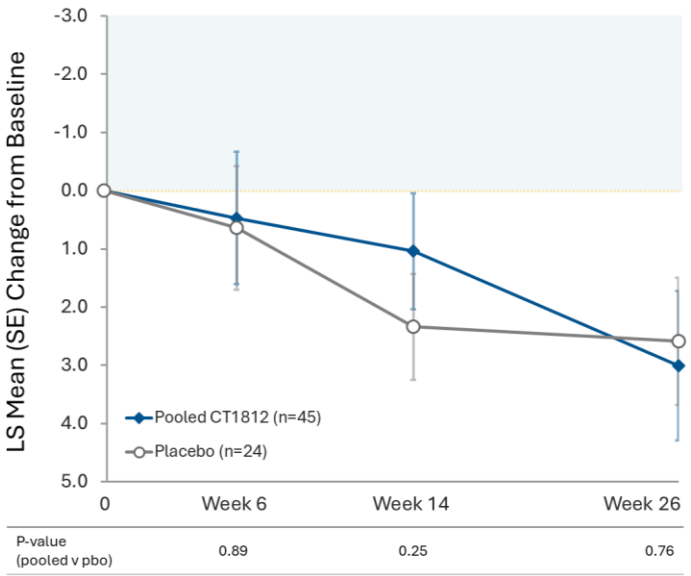


Below median p-tau217 (n=69)



Observed treatment difference vs pbo: 2.7pt

Above median p-tau217 (n=69)



WORSENING

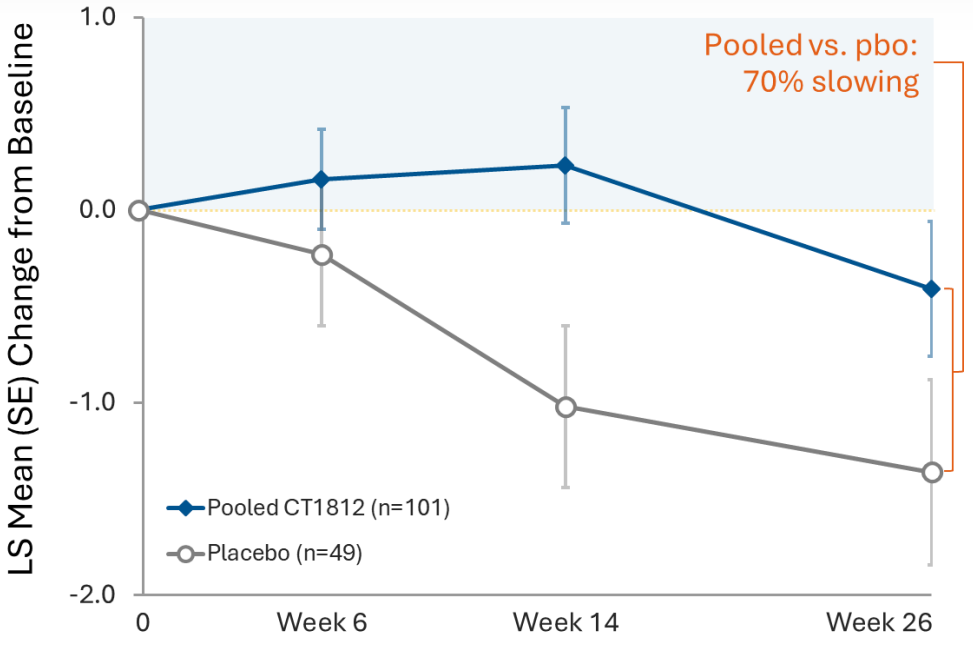
** ADAS-Cog 11 mITT in the pooled dose group vs placebo was the first of the ordered secondary efficacy endpoints*

† Median plasma p-tau217 level is 1.0pg/mL at baseline

SHINE Cognitive Endpoints: *MMSE*

*Preservation of MMSE in participants below median plasma p-tau217**

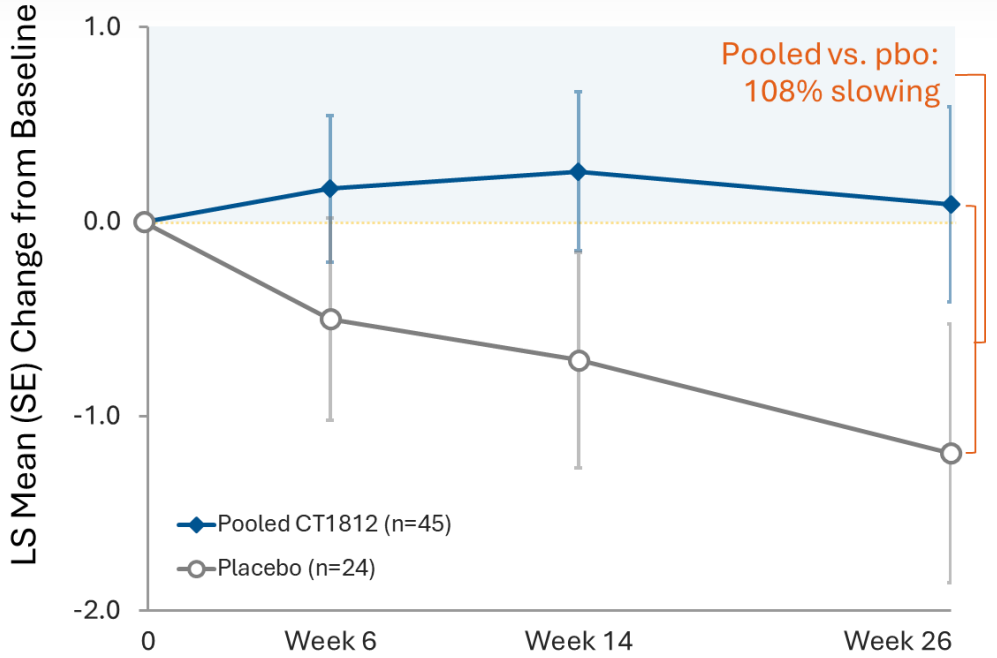
mITT population (n=150)



P-value (pooled v pbo)	0.40	0.02	0.11

Observed treatment difference vs pbo: 0.95 pt

Below median p-tau217 (n=69)



P-value (pooled v pbo)	0.29	0.16	0.13

Observed treatment difference vs pbo: 1.29 pt

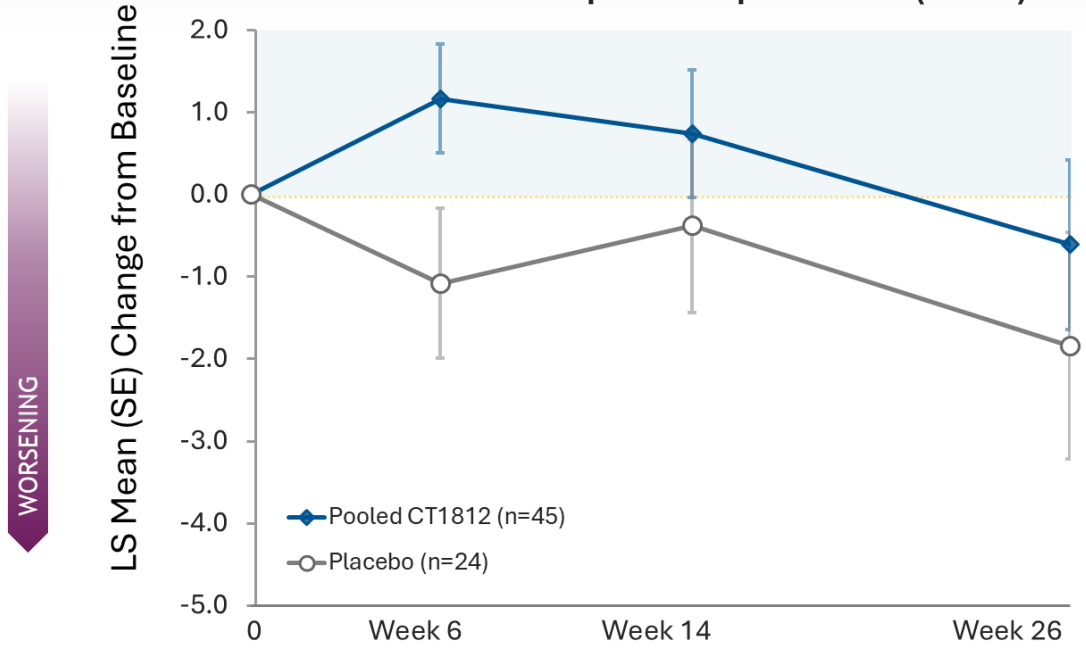
** Median plasma p-tau217 level is 1.0pg/mL at baseline*

SHINE Functional Endpoints: *ADCS-ADL and -CGIC*

*Function and global impression preserved in participants below median plasma p-tau217**

ADCS-ADL

Below median plasma p-tau217 (n=69)

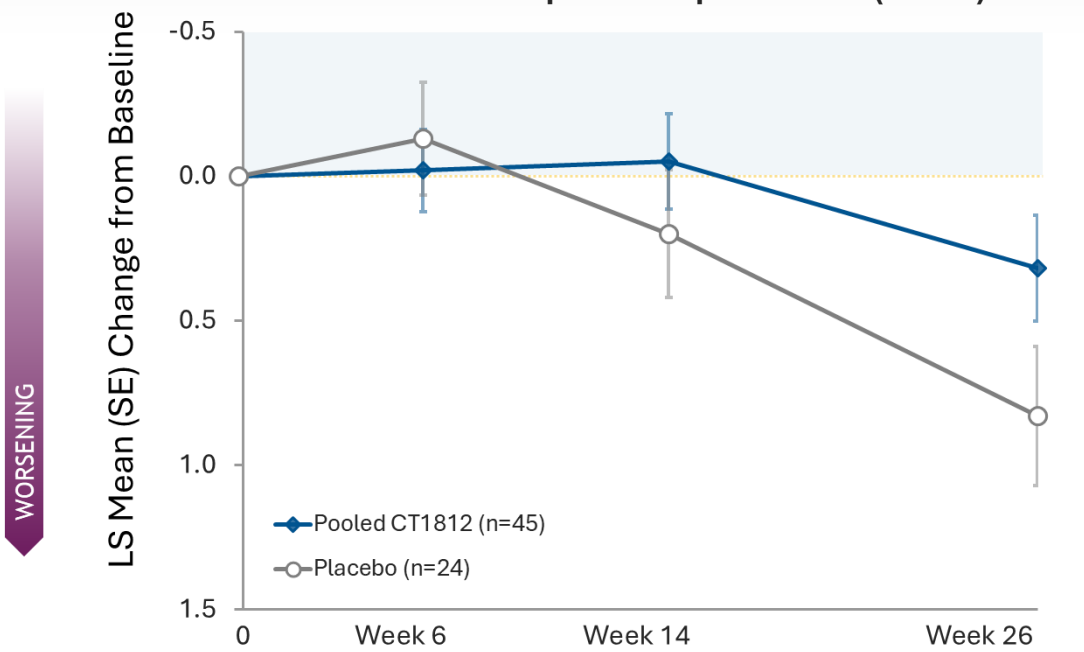


P-value (pooled v pbo)	0.05	0.40	0.47

Observed treatment difference vs pbo: 1.24 pt

ADCS-CGIC

Below median plasma p-tau217 (n=69)



P-value (pooled v pbo)	0.65	0.37	0.09

Observed treatment difference vs pbo: 0.51 pt

** Median plasma p-tau217 level is 1.0pg/mL at baseline*

CT1812 SHINE Study: Summary and Conclusions

Baseline plasma p-tau217 biomarker identifies strong CT1812-treatment responder group

- CT1812 generally safe and well tolerated
- mITT showed favorable trends in CT1812-treated participants
- Optimal dose range identified

- Large cognitive impact observed in pre-specified below-median plasma p-tau217 subgroup
- Limitations: small sample size; exploratory outcomes need to be confirmed in larger studies
- Will assess optimal plasma p-tau217 cut-point for future studies

SHINE trial supports advancing CT1812 to Phase 3 in mild-to-moderate Alzheimer's disease in population defined by plasma p-tau217

Additional SHINE data:

Results from COG0201
Vijverberg et al. AAIC 2024

Topline CSF Biomarker Outcomes:
Di Caro et al. AAIC 2024

Exploratory CSF Proteomics Biomarker Outcomes
Di Caro et al. AAIC 2024

cogrx.com/publications

Cognition preserved in CT1812-treated participants with below median plasma p-tau217

Thank You

Science & Clinical Medicine Advance
Through the Work of Many

Investigators

National Institute of Aging

SHINE participants, care
partners and family members