COGNITION™ Therapeutics

CT1812 for Alzheimer's Disease

Focusing on the Lower p-tau217 Subgroup

October 30, 2024

Forward-looking Statements

FORWARD-LOOKING STATEMENTS

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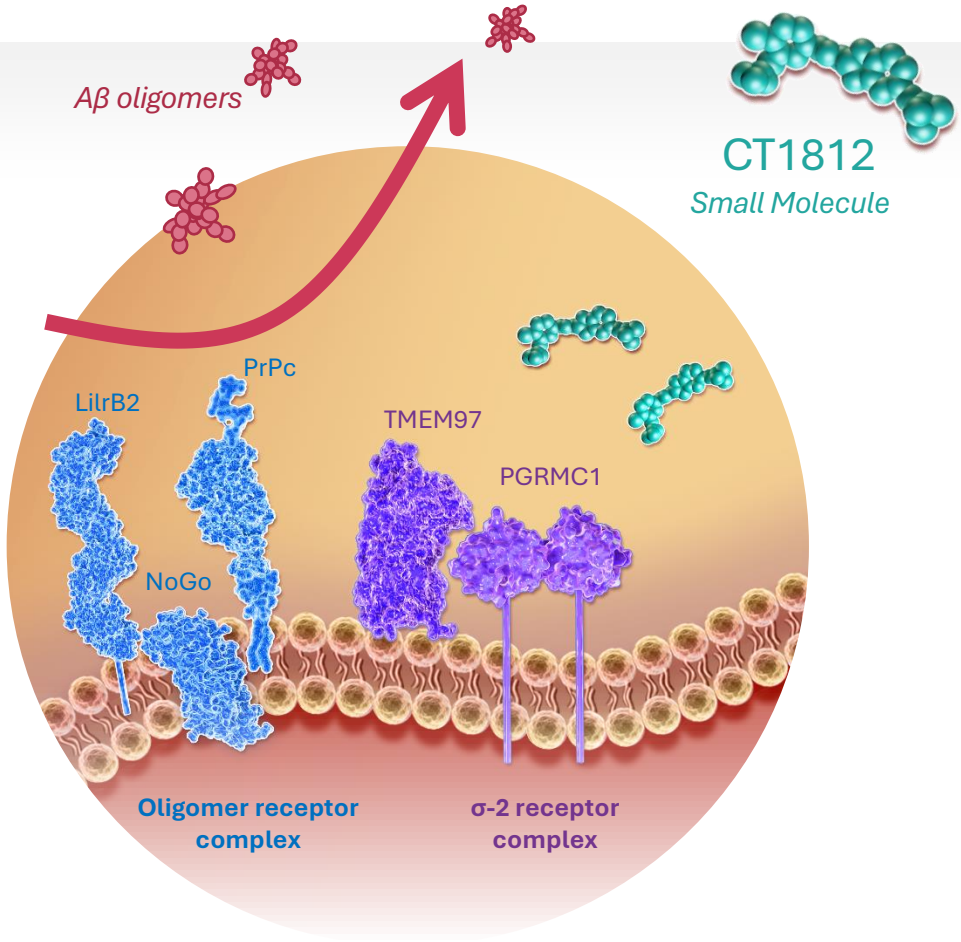
CT1812 Mechanism of Action

Investigational, oral, small molecule oligomer antagonist

- 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



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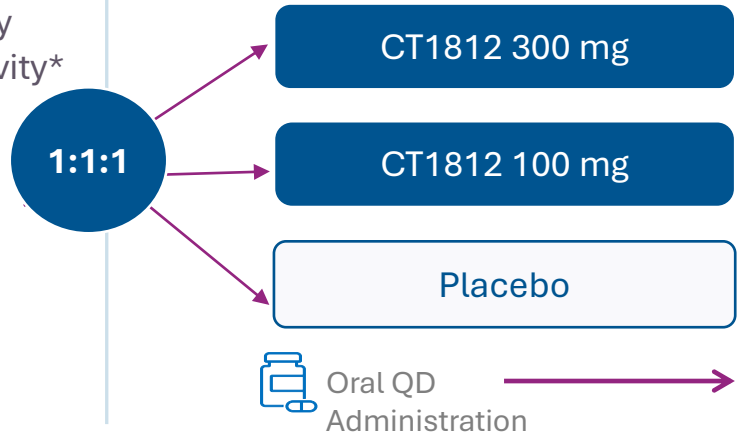
Phase 2 PoC Study in Mild-to-Moderate Alzheimer's Disease

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

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Tau Burden in Amyloid-related AD Clinical Trials

Plasma p-tau217: prognostic biomarker of response to therapy

- Plasma p-tau217 reflects brain amyloid and tau burden
- Prior data indicate that individuals with lower AD pathology, as reflected by lower 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 MoA of displacing Aβ oligomers, hypothesized that larger treatment effect may be observed in participants with lower plasma p-tau217
- Prespecified subgroup analysis defined by median plasma p-tau217 within study population

Baseline Characteristics of Below/Above median p-tau217

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	1.07 (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

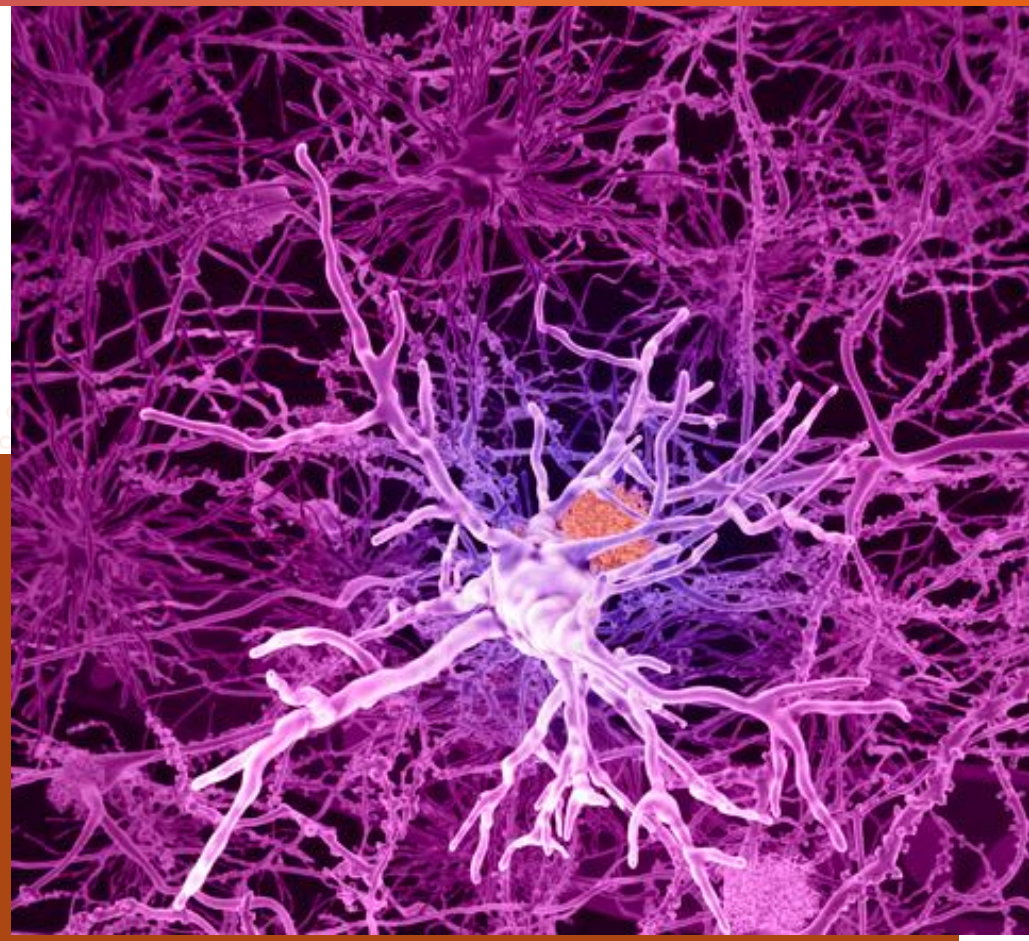
Adverse Events	
CT1812	Placebo
76.5%	78%

Serious AEs	
CT1812	Placebo
4.9%	10%

Deaths	
CT1812	Placebo
0	1 (cancer)

Impact of Plasma p-tau217

Cognition and Function



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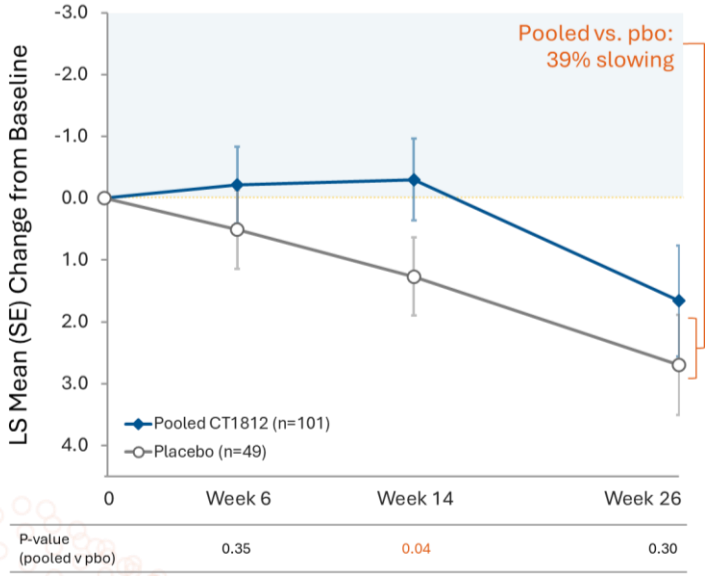
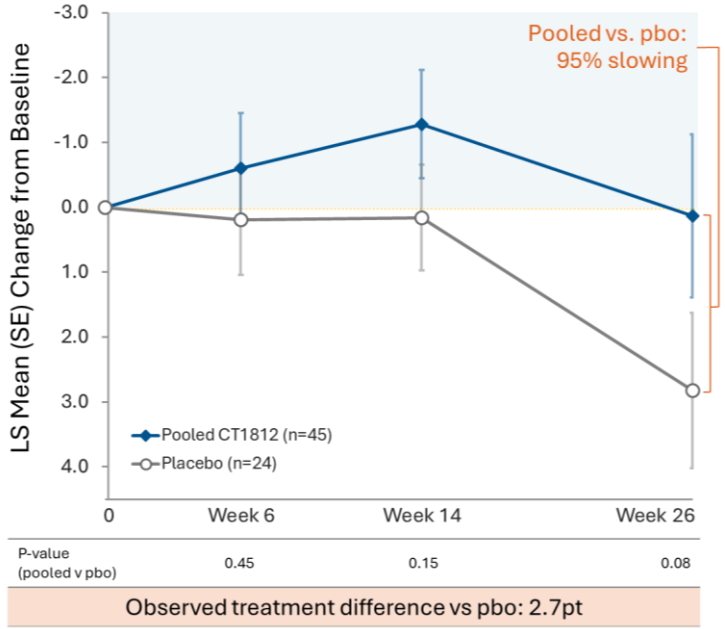
SHINE Cognitive Endpoints: *ADAS-Cog 11*

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

mITT population* (n=150)

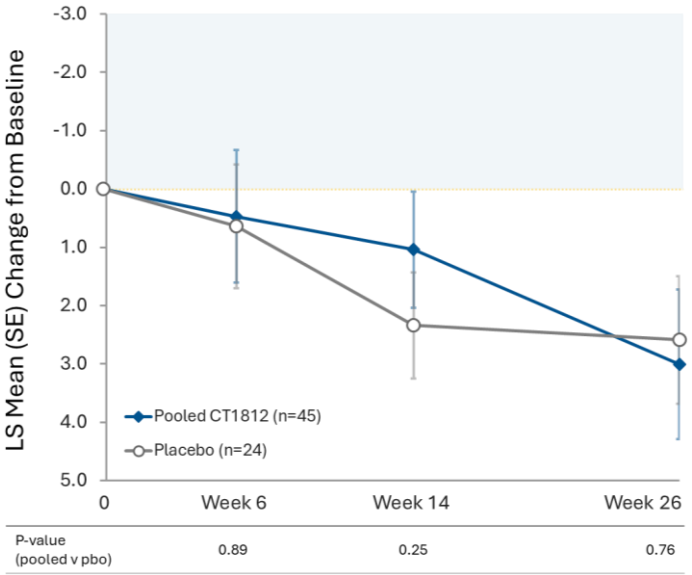


Below median p-tau217 (n=69)



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

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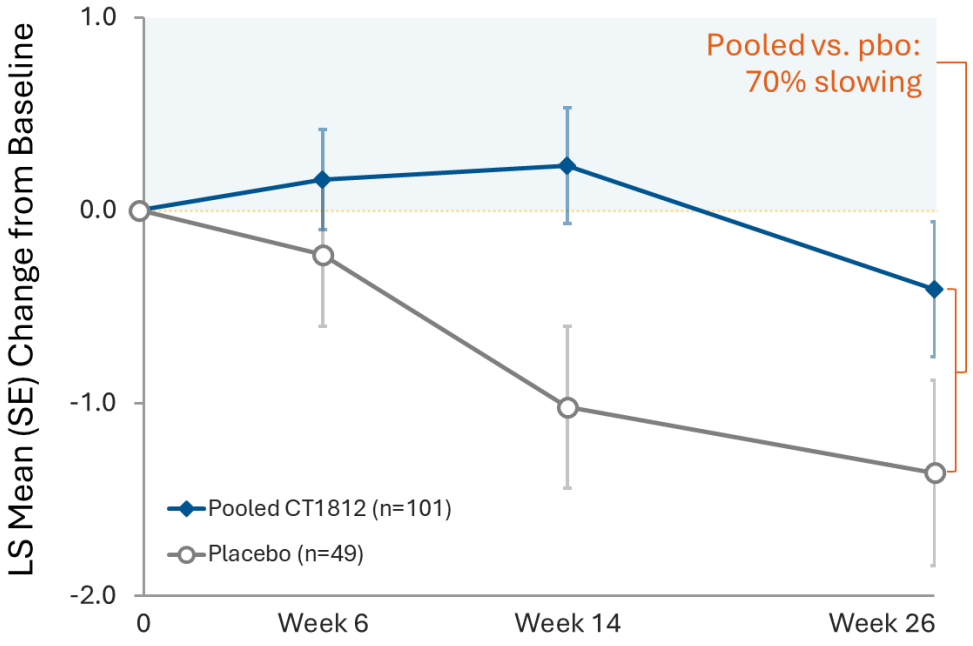
SHINE Cognitive Endpoints: *MMSE*

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

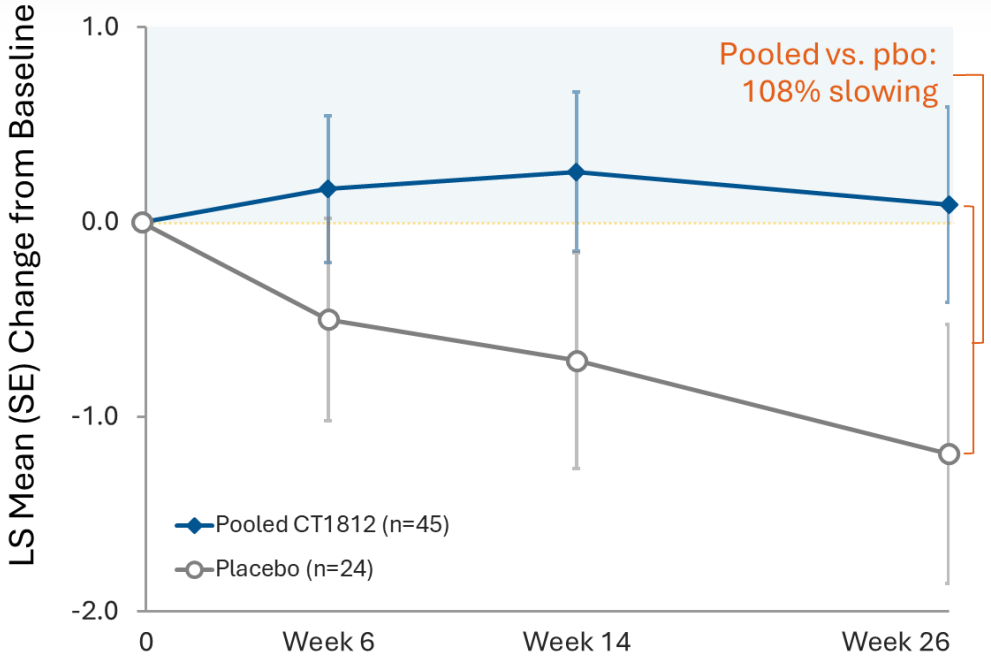
mITT population (n=150)



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*

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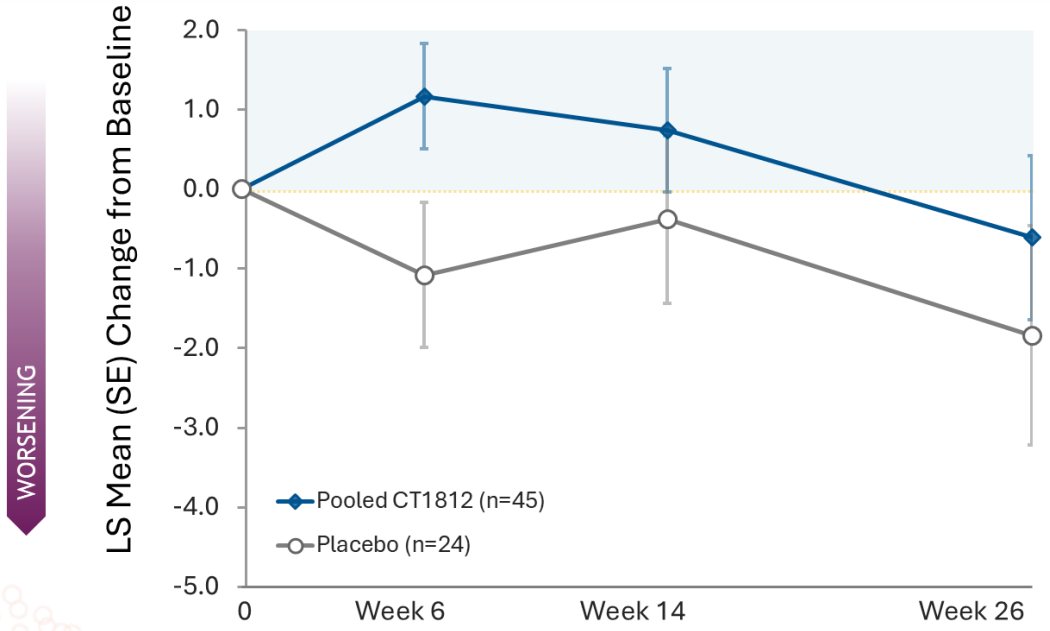
SHINE Functional Endpoints: *ADCS-ADL and -CGIC*

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

ADCS-ADL

Below median plasma p-tau217 (n=69)

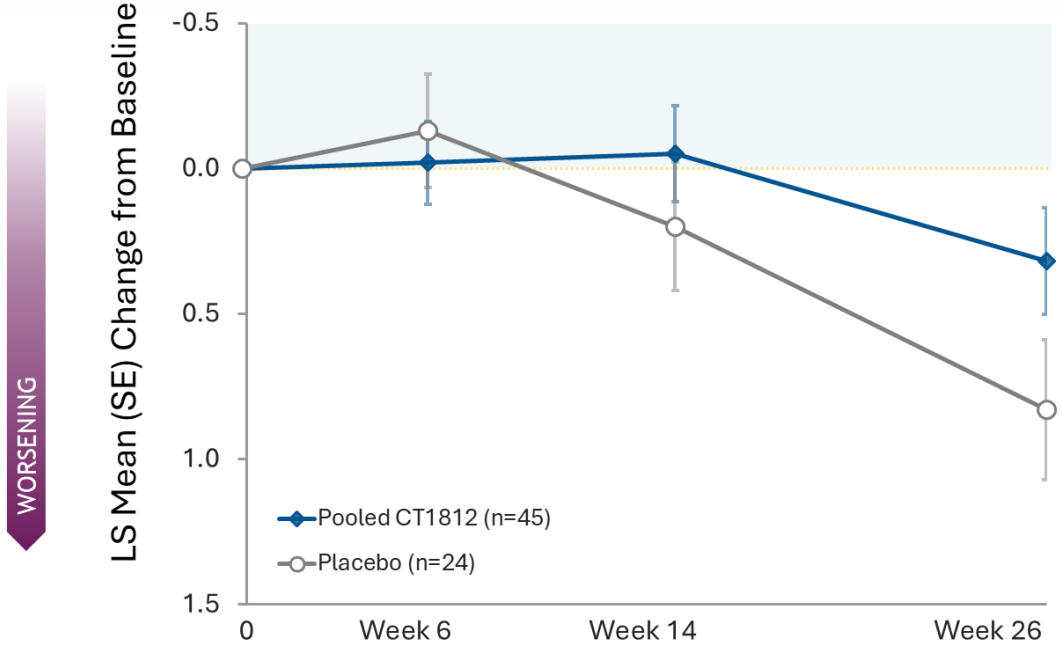


P-value (pooled v pbo)	0.05	0.40	0.47

Observed treatment difference vs pbo: 1.24 pt

ADCS-CGIC

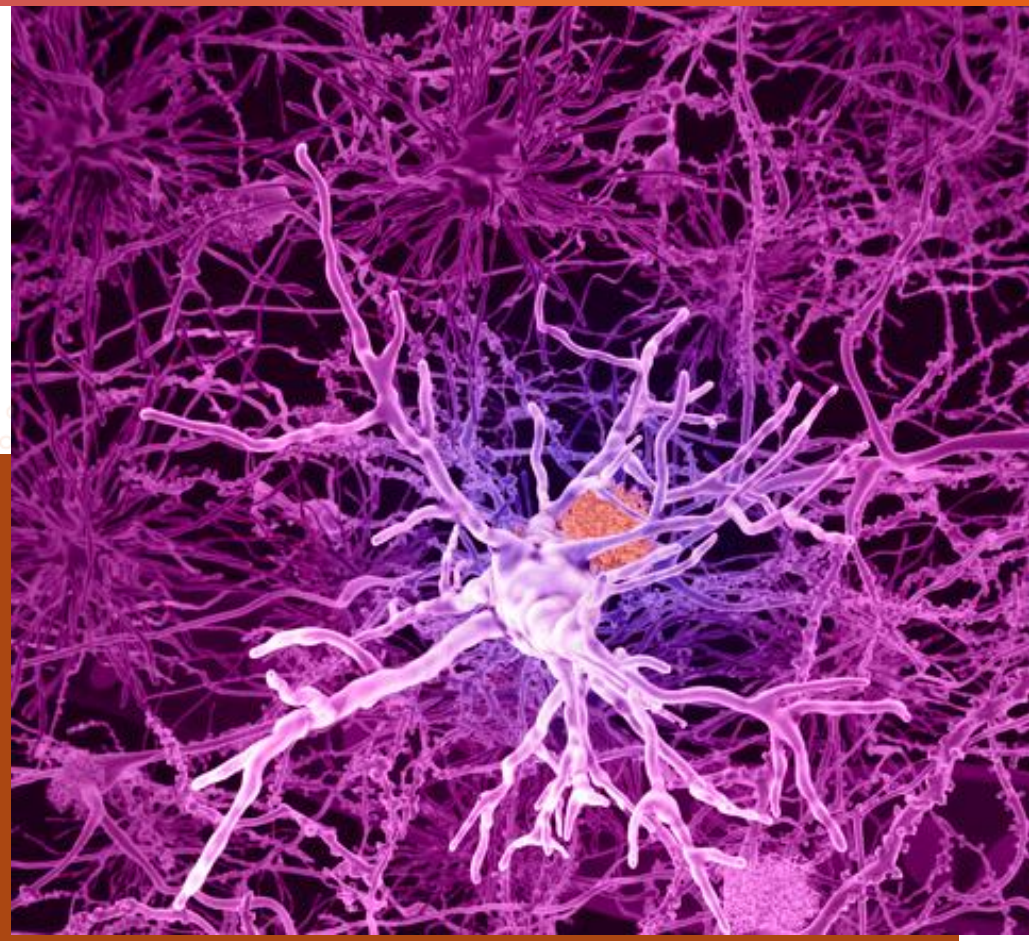
Below median plasma p-tau217 (n=69)



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*



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CT1812 SHINE Study: Summary and Conclusions

Plasma p-tau217 biomarker identifies strong CT1812-treatment responder group

- CT1812 generally safe and well tolerated
- mITT showed favorable trends in CT1812-treated participants

- 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 Snapshot

Successful Phase 2 AD trial read out plus signal-finding studies ongoing in other indications

Alzheimer's Disease

- Pursuing 2 populations: mild-to-moderate; and early / MCI
  - ✓ Achieved goals of Phase 2 SHINE study in mild-moderate AD
  - Phase 2 START ongoing in early AD with ACTC
- Oral QD drug with no added ARIA-risk, important differentiator
- Extensive preclinical/clinical foundation supports oligomer antagonism approach

Dementia with Lewy Bodies (DLB)

- Phase 2 signal-finding SHIMMER study in mild-to-moderate DLB completed enrollment; data ETA YE
  - Will determine CT1812's impact on constellation of symptoms
- No approved d-m treatments
- CT1812 protects against oligomers of both amyloid beta (Aβ) and alpha-synuclein (α-syn)

Geographic Atrophy Secondary to dry AMD

- Phase 2 signal-finding MAGNIFY study in geographic atrophy (GA) ongoing
  - Will determine to what extent CT1812 protection of RPE cells preserves vision
- Oral QD drug important differentiator from IVT therapies

Thank You

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