Zervimesine (CT1812) Treatment Benefits Patients with Lower Baseline Plasma p-tau217 Across the Mild-to-Moderate AD Spectrum

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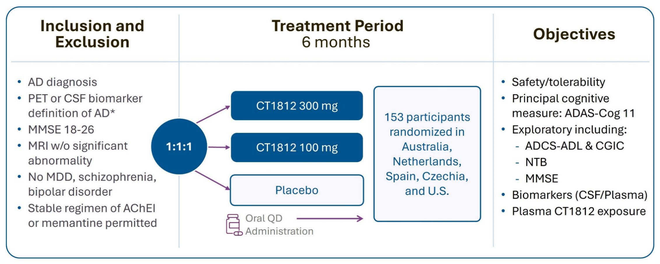
Results from COG0201 (SHINE) define a patient population likely to benefit from CT1812 treatment

Background

- CT1812 is an oral small molecule allosteric Aβ oligomer antagonist in clinical development for Alzheimer's disease (AD) and dementia with Lewy bodies (DLB)
- CT1812 is a sigma-2 receptor ligand that reduces the binding affinity of toxic Aβ oligomers[1,2]
- Topline mITT and prespecified p-tau217 subgroup analyses from the Phase 2 COG0201 'SHINE' Study were presented at the AAIC 2024 and CTAD 2024, respectively[3,4]



* *Cut-offs from Clinical Neurochemistry Lab at Sahlgrenska University Hospital in Gothenburg, Sweden or study protocol*

Rationale:

- There is a range of brain AD pathology burden across the mild-to-moderate clinical severity spectrum that is measurable by p-tau217 levels
- Individuals with lower AD pathology at baseline as reflected by lower levels of p-tau217 have a greater response to amyloid-lowering therapies[5]. The same may be true for treatment responsiveness to CT1812
- In COG0201, the median plasma p-tau217 of study participants (1.0 pg/mL) defines the lower and higher p-tau217 groups

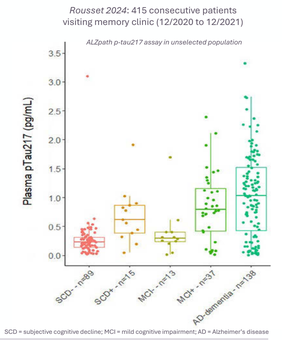
Methods

Cognitive, Functional and Biomarker Outcomes:

- Cognitive and functional assessments were performed at baseline and on study days 42, 98, 182
- Plasma p-tau217 was assessed at baseline using the Quanterix assay with Alzpath p-tau217 antibody
- The median plasma p-tau217 of study participants (1.0 pg/mL) defines the lower and higher p-tau217 groups
- Cut-point is consistent with median observed in an AD dementia cohort in a real-world clinical setting (Rousset 2024,right)[6]

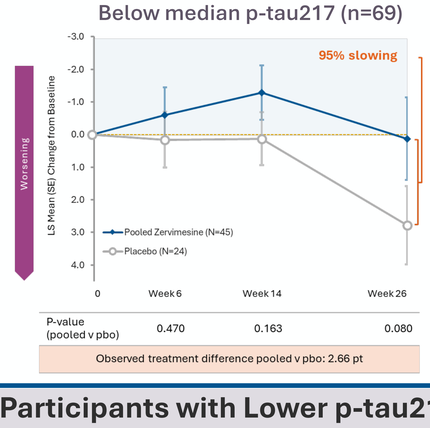
Statistical Analysis:

- Mean change from baseline was analyzed using a mixed-model for repeated measures (MMRM) with treatment as the main effect, visit, baseline score, and APOE ε4 (+ or -) status as covariates; and treatment by visit as an interaction term



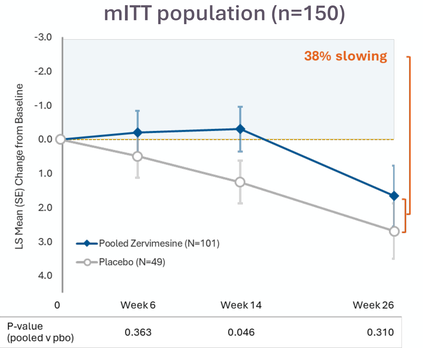
SCD = subjective cognitive decline; MCI = mild cognitive impairment; AD = Alzheimer's disease

ADAS-Cog11: Robust Effect in Participants with Lower p-tau217 (left)

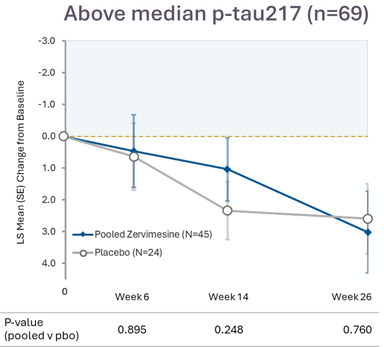


P-value (pooled v pbo)	0.470	0.163	0.080

Observed treatment difference pooled v pbo: 2.66 pt

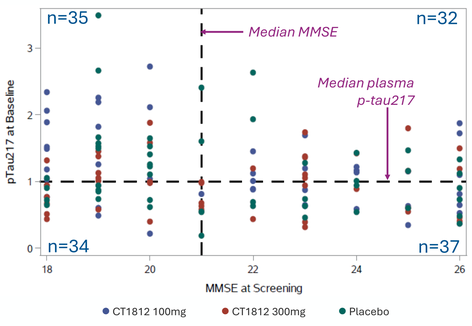


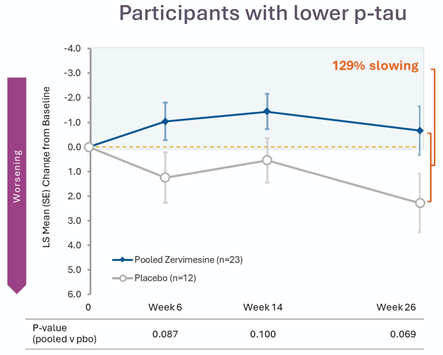
P-value (pooled v pbo)	0.363	0.046	0.310



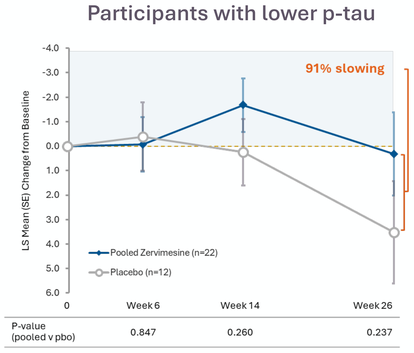
P-value (pooled v pbo)	0.895	0.248	0.760

ADAS-Cog11: Treatment Effect in Participants with Lower p-tau217 Observed Across MMSE Spectrum

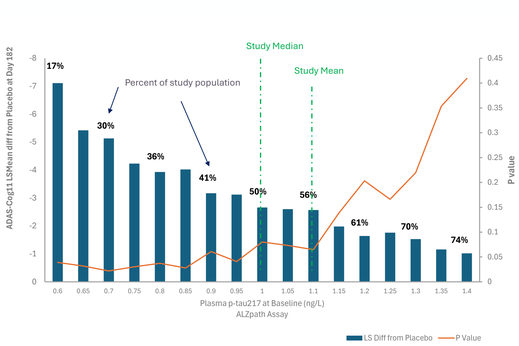




P-value (pooled v pbo)	0.087	0.100	0.069



P-value (pooled v pbo)	0.847	0.260	0.237



Consistently Better Outcome in Below Median Baseline p-tau217

Outcome Measure	Below median p-tau217	Above median p-tau217
	LS Mean Difference from Placebo (95%CI) p value	
ADAS-Cog11	-2.66 (-5.66, 0.33) 0.080	0.42 (-2.31, 3.14) 0.760
MMSE	1.29 (-0.37, 2.94) 0.126	0.83 (-0.88, 2.53) 0.336
ADCS-CGIC	-0.51 (-1.12, 0.09) 0.093	0.09 (-0.46, 0.65) 0.732
ADCS-ADL	1.27 (-2.17, 4.71) 0.463	-0.23 (-3.40, 2.93) 0.883

Demographics & Baseline Characteristics

	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)

Adverse Events

- CT1812 demonstrated a generally favorable safety and tolerability profile
- See Vijverberg EGB, et al (AAIC 2024) for full safety findings[4]

Summary

- CT1812 Treatment effect was particularly robust in participants with plasma p-tau217 less than 1.0 pg/mL
- A cut-point of approximately 1.0 pg/mL is consistent with the literature for a median value in the mild-to-moderate AD population (Rousset et al., 2024[6])
- Future study plans will include an enriched study population with lower levels of plasma p-tau217
  - Limit exposure to those individuals most likely to receive benefit
  - Reduce study size and cost
- Limitations of the study include small group numbers and 6-months exposure

Acknowledgements

Cognition Therapeutics thanks the participants and their caregivers, as well as the study site investigators and staff. We also thank NIH / NIA for continued support of CT1812 development.

Conclusions

- This study provides evidence that CT1812 may slow cognitive decline in people with mild-to-moderate AD
- Plasma p-tau217 may define a treatment-responsive population for future studies
- Early AD population is being studied in the ongoing 18-month COG0203 'START' study in 540 patients (NCT05531656)

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- SHINE COG0201 study (NCT03507790) partially funded by $31M NIA grant (R01AG058660)
- CT1812 is an investigational therapeutic that has not been approved for use by the US Food and Drug Administration (FDA)
- The USAN Council has adopted zervimesine as the United States Adopted Name (USAN) for CT1812

References:
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2. LaBarbera, K.M., Sheline, Y.I., Izzo, N.J. et al. *Transl Neurodegener* 2023, 12(24)
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6. Rousset et al. *Alzheimer's Dement.* 2024, 16, e70003