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Positive Impact of CT1812 (Zervimesine) Treatment on Plasma Biomarkers in Lower p-tau217 Subgroup Aligns with Clinical Benefits in Mild-to-Moderate AD Patients

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Disclosures

Presenter Disclosures:

- Mary Hamby, PhD is an employee of Cognition Therapeutics

Product Disclosure:

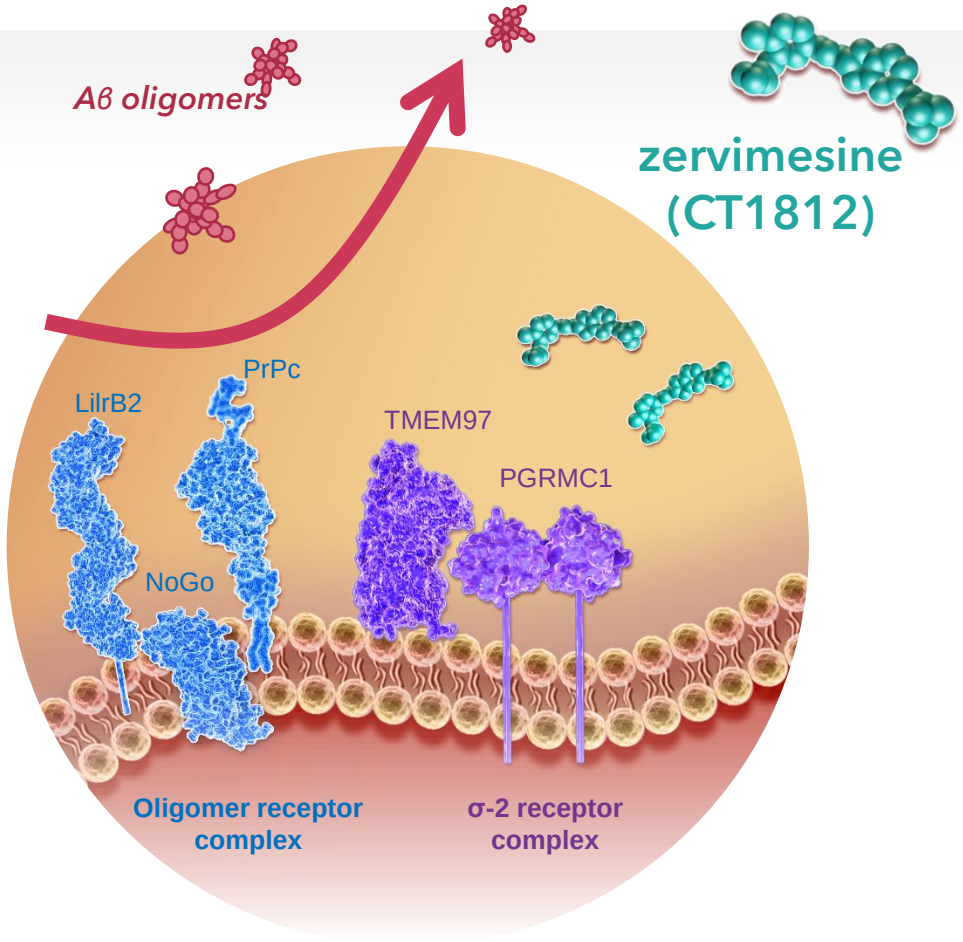
- CT1812 (zervimesine*) is an investigational therapeutic that has not been approved for any use by the US Food and Drug Administration or any other health authority
- Plans for subsequent clinical trials have not yet been reviewed by FDA or EMA

*CT1812 assigned USAN name: zervimesine

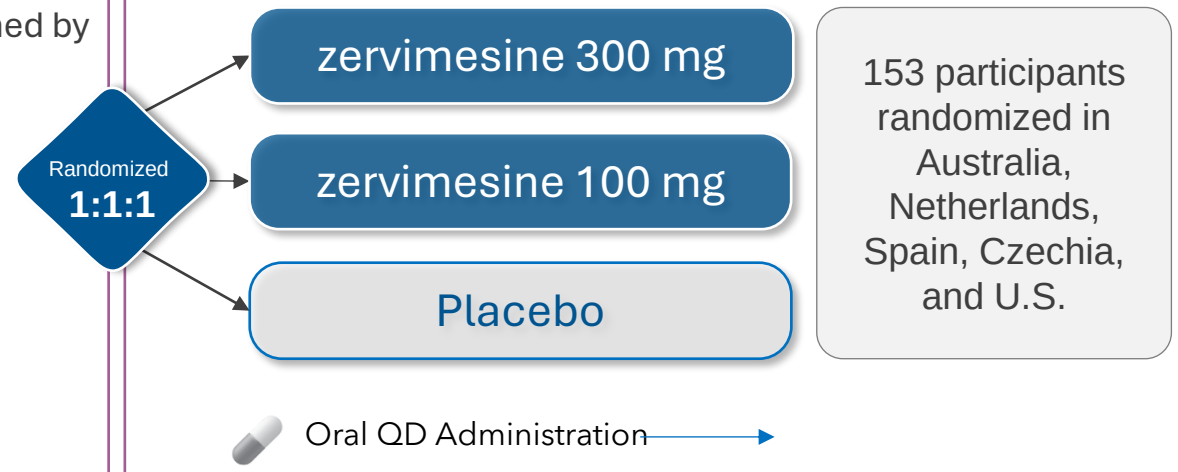
Zervimesine (CT1812) Mechanism of Action

Investigational, oral, small molecule oligomer antagonist

- Preclinical and clinical evidence that zervimesine 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 immunotherapies



Phase 2 Safety and Efficacy Study in Adults with Mild-to-moderate Alzheimer's Disease

Enrollment Criteria	Treatment Period 6 months	Assessments
- AD diagnosis confirmed by PET or CSF amyloid positivity* - MMSE 18-26 - MRI w/o significant abnormality - Stable regimen of AChEi or memantine permitted	 153 participants randomized in Australia, Netherlands, Spain, Czechia, and U.S.	- 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

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

Full safety and tolerability data are available in presentations from CTAD / AAIC on our website

SHINE COG0201

* 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.

Summary of SHINE Safety and Tolerability findings

Favorable safety profile vs placebo, AEs well balanced between arms, no ARIA

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

Adverse Events

Zervimesine	76.5%
Placebo	78.0%

Serious AEs

Zervimesine	4.9%
Placebo	10.0%

Deaths†

Zervimesine	0
Placebo	1 (cancer)

* occurring in a zervimesine treatment group at a rate >10% and at a rate >2X the placebo rate
† not considered treatment related

Plasma p-tau217 Reflects Brain Amyloid and Tau Burden

- Plasma p-tau217 is a blood-based biomarker representing AD pathology (amyloid plaques and tau)[1]
  - The degree of AD brain pathology can be indirectly assessed by measuring levels of plasma p-tau217[1]
- Given zervimesine MoA, we hypothesized that a larger treatment effect may be observed in participants with less AD pathology / lower tau
- SHINE included a prespecified subgroup analysis defined by median plasma p-tau217 (AlzPath, 1 pg/ml) at baseline

- Prior data indicate that individuals with lower AD pathology 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

1) Salvadó et al. 2023

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

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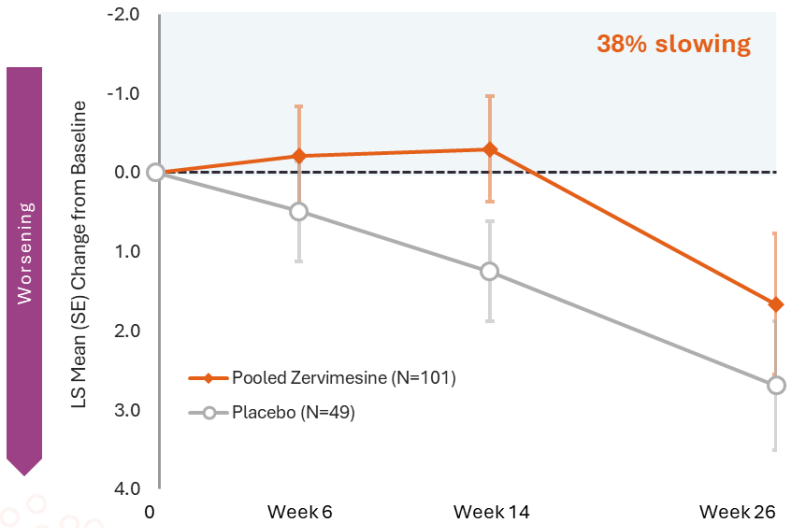
SHINE Cognitive Endpoints: *ADAS-Cog 11*

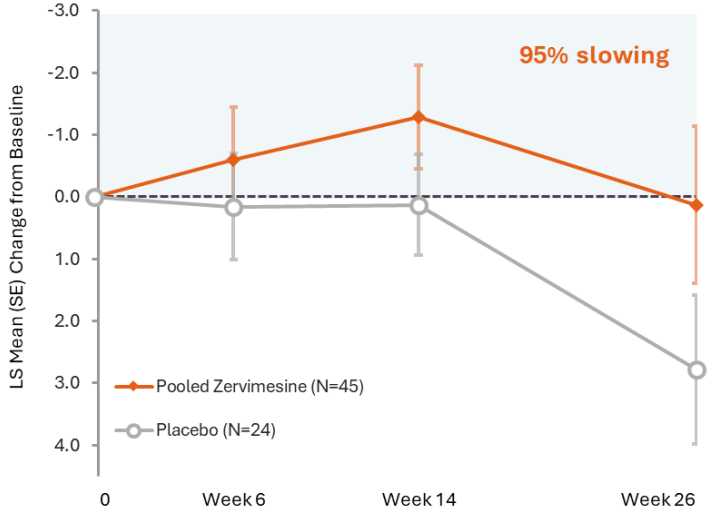
Preservation of cognition in participants in below-median plasma p-tau217† subgroup

mITT population* (n=150)



P-value (pooled v pbo)	Week 6	Week 14	Week 26
	0.363	0.046	0.310

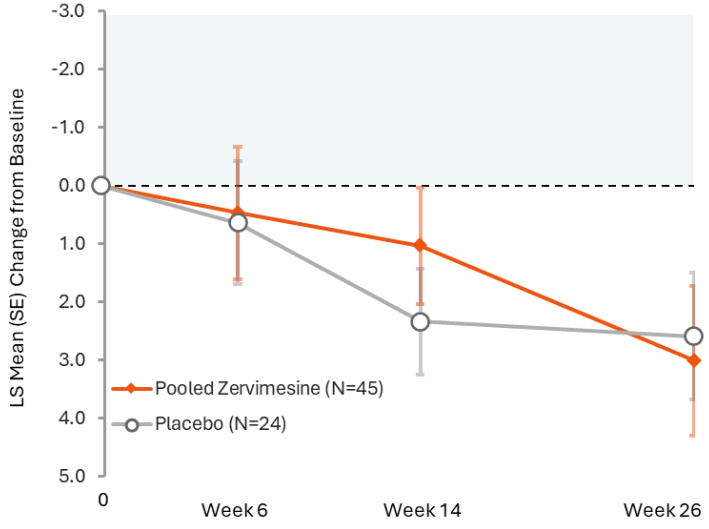
Below median p-tau217 (N=69)



P-value (pooled v pbo)	Week 6	Week 14	Week 26
	0.470	0.163	0.080

Observed treatment difference pooled v pbo: 2.66 pt

Above median p-tau217 (N=69)



P-value (pooled v pbo)	Week 6	Week 14	Week 26
	0.895	0.248	0.760

** 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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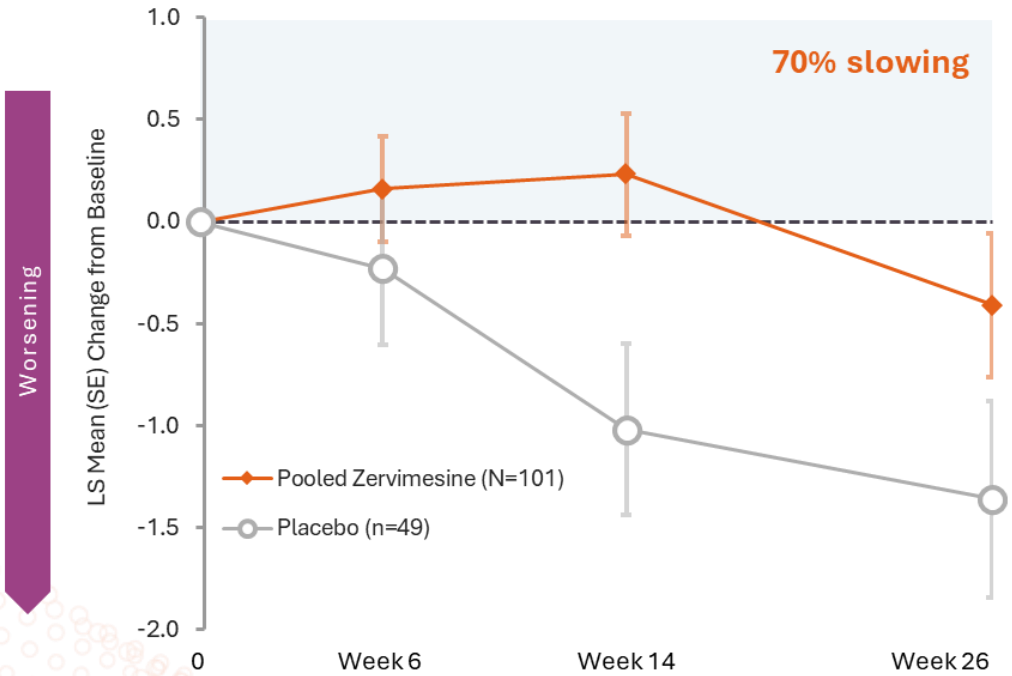
SHINE Cognitive Endpoints: *MMSE*

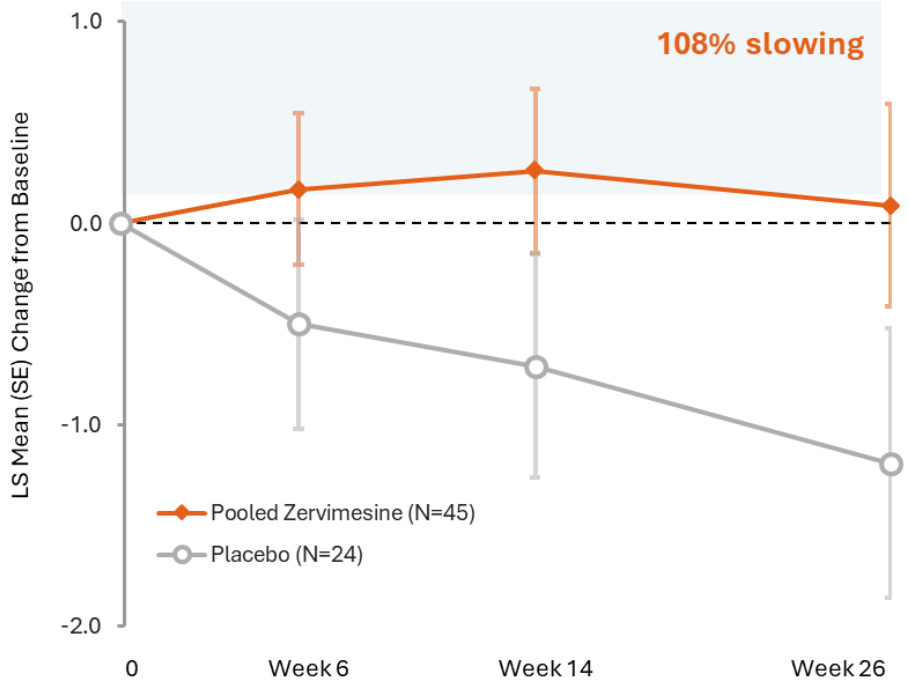
Preservation of MMSE in participants in below-median plasma p-tau217* subgroup

mITT population (n=150)



	Week 6	Week 14	Week 26
P-value (pooled v pbo)	0.396	0.016	0.111

Below median p-tau217 (n=69)



	Week 6	Week 14	Week 26
P-value (pooled v pbo)	0.292	0.159	0.126

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

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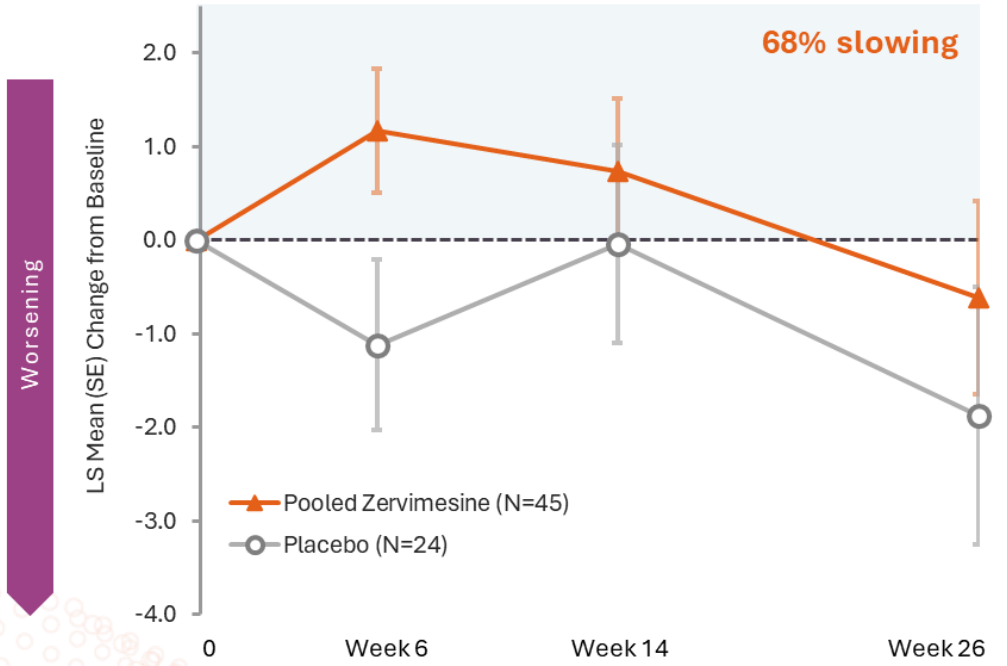
SHINE Functional Endpoints: *ADCS-ADL and -CGIC*

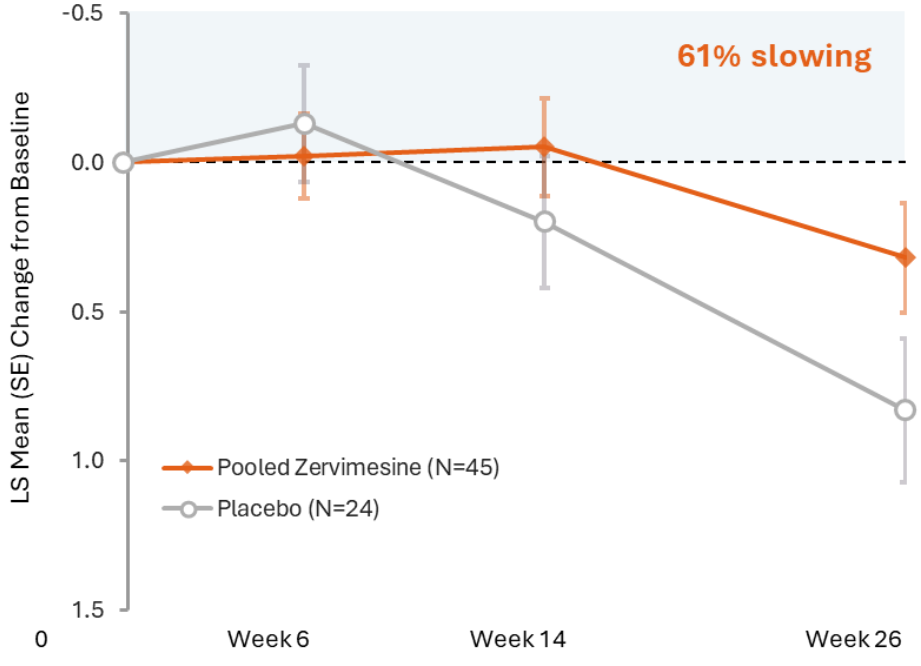
Function and global impression preserved in below-median plasma p-tau217* subgroup

ADCS-ADL
Below median plasma p-tau217 (n=69)



P-value (pooled v pbo)	0.046	0.383	0.463

ADCS-CGIC
Below median plasma p-tau217 (n=69)



P-value (pooled v pbo)	0.649	0.365	0.093

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

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Larger Biomarker Effect Observed in Below Median p-tau217 Group vs mITT

Plasma biomarker (ng/L)		mITT (N=150)	< median p-tau217 (N=69)	> median p-tau217 (N=69)
Aβ42	*LS mean (SE)*	-0.188 (0.2393)	-0.64 (0.326)	0.24 (0.322)
	95% CI	(-0.66, 0.29)	(-1.289, 0.018)	(-0.400, 0.885)
	p-value	0.4343	0.0565	0.4539
Aβ40	*LS mean (SE)*	-8.272 (5.0557)	-12.27 (7.296)	-1.07 (6.793)
	95% CI	(-18.28, 1.74)	(-26.869, 2.334)	(-14.653, 12.523)
	p-value	0.1044	0.0980	0.8759
GFAP	*LS mean (SE)*	-3.2 (10.53)	-28.35 (11.687)	23.07 (16.789)
	95% CI	(-24, 18)	(-51.769, -4.933)	(-10.544, 56.679)
	p-value	0.7593	**0.0186**	0.1748
NFL	*LS mean (SE)*	-1.44 (1.130)	-2.67 (1.503)	-0.22 (1.707)
	95% CI	(-3.7, 0.8)	(-5.681, 0.339)	(-3.637, 3.200)
	p-value	0.2057	0.0809	0.8987
p-Tau217	*LS mean (SE)*	-0.053 (0.0569)	-0.10 (0.079)	0.02 (0.089)
	95% CI	(-0.17, 0.06)	(-0.264, 0.056)	(-0.154, 0.203)
	p-value	0.3581	0.1976	0.7884
Brain-derived tau	*LS mean (SE)*	-0.168 (0.0987)	-0.11 (0.089)	-0.19 (0.149)
	95% CI	(-0.36, 0.03)	(-0.293, 0.070)	(-0.491, 0.104)
	p-value	0.0907	0.2208	0.1987

More robust effect sizes observed across biomarkers measured in below median p-tau217 subgroup, save for brain-derived tau

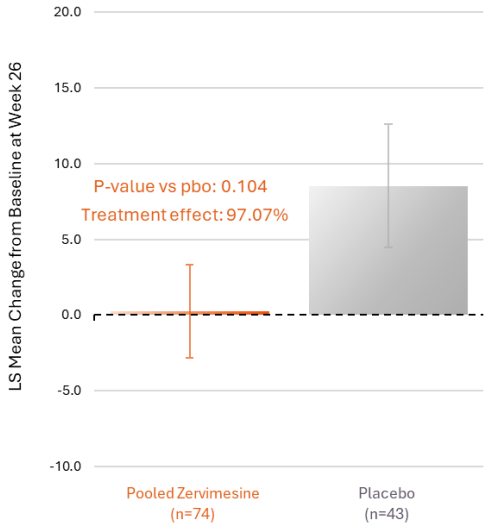
Trend p≤0.10
Significant p≤0.05

** N= size of population included in trial (mITT) or subgroup*

Biomarker Impact on Amyloid: Plasma Aβ42 and Aβ40

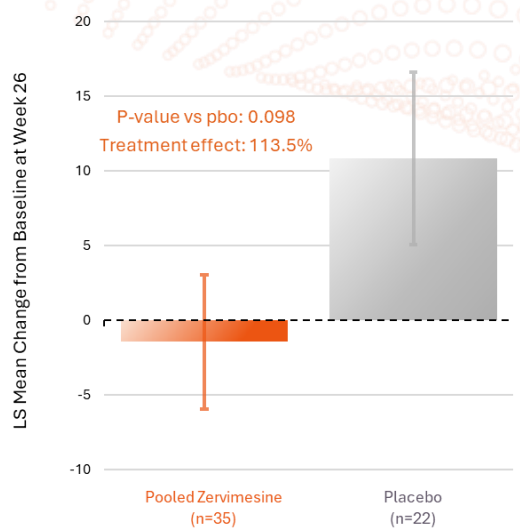
Aβ40

mITT (N=117)



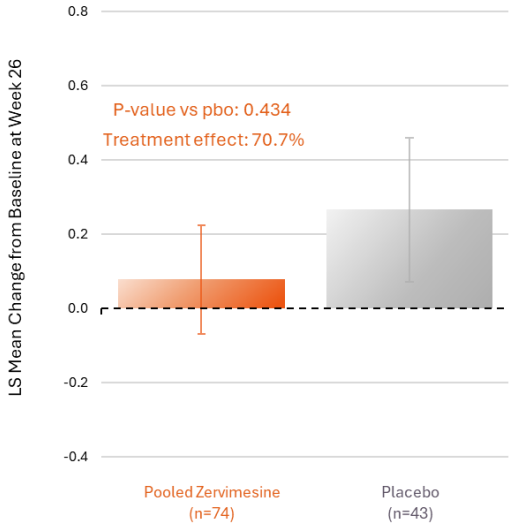
	Pooled Zervimesine (n=74)	Placebo (n=43)
Baseline mean pg/mL (SD)	111.56 (30.5941)	107.392 (25.8103)

below median p-tau217 (N=57)

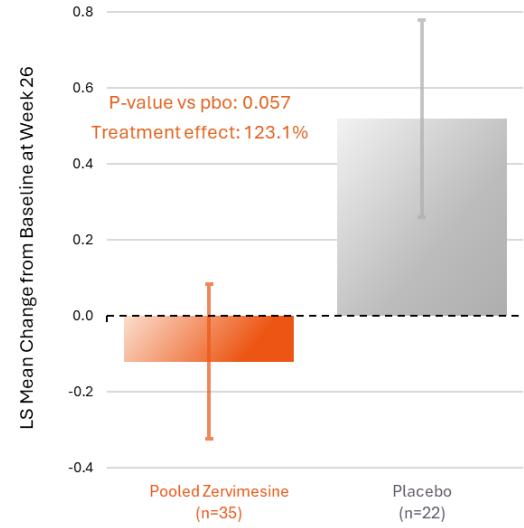


	Pooled Zervimesine (n=35)	Placebo (n=22)
Baseline mean pg/mL (SD)	112.162 (37.773)	101.892 (27.406)

Aβ42



	Pooled Zervimesine (n=74)	Placebo (n=43)
Baseline mean pg/mL (SD)	5.832 (1.6768)	5.581 (1.2994)



	Pooled Zervimesine (n=35)	Placebo (n=22)
Baseline mean pg/mL (SD)	5.915 (2.111)	5.748 (1.439)

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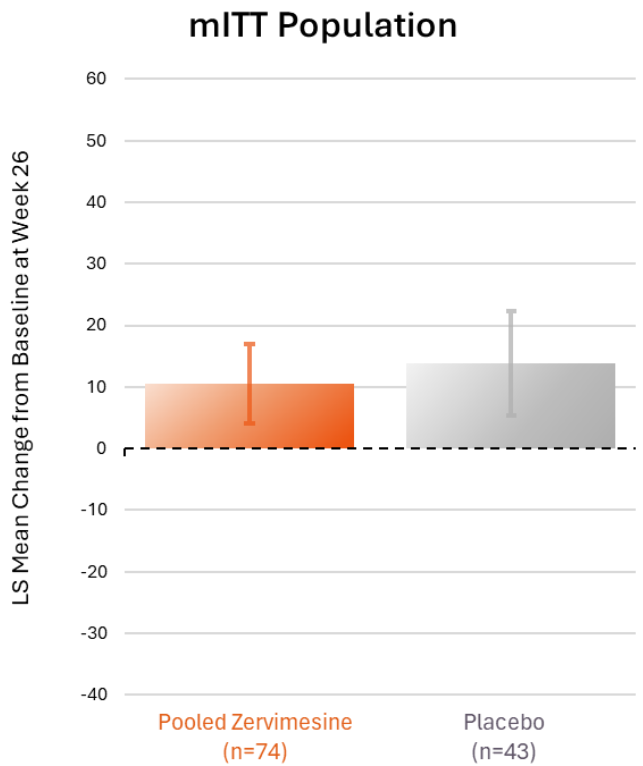
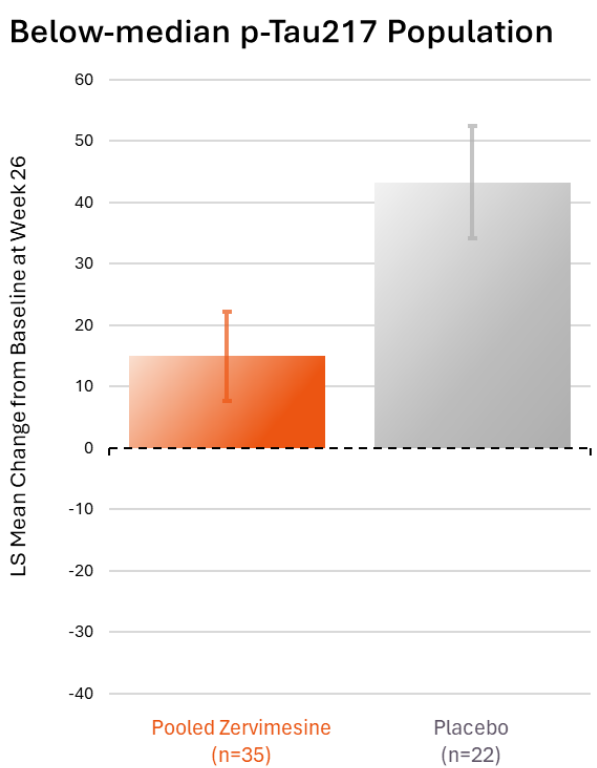
Biomarker impact on neuroinflammation: Plasma GFAP

Significant impact ($p<0.05$) observed in population with lower plasma p-tau217 at baseline



	Pooled Zervimesine (n=74)	Placebo (n=43)
Baseline mean pg/mL (SD)	205.3 (87.12)	210.3 (103.49)
P-value vs pbo	0.759	



	Pooled Zervimesine (n=35)	Placebo (n=22)
Baseline mean pg/mL (SD)	175.000 (82.605)	146.125 (64.625)
P-value vs pbo	0.019	

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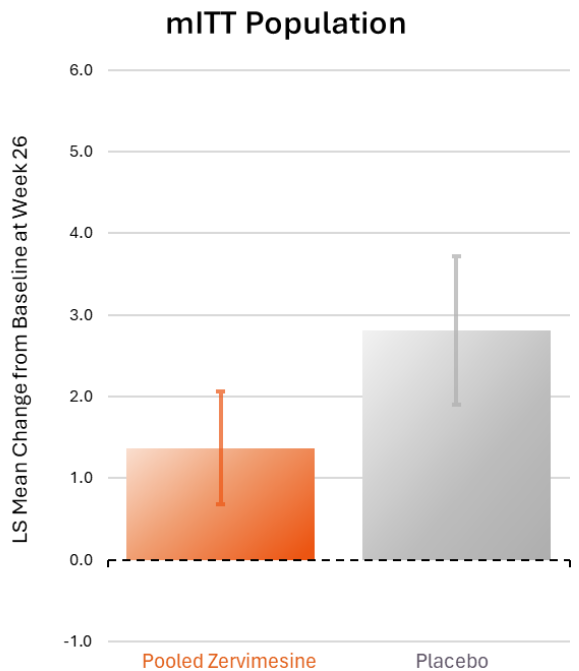
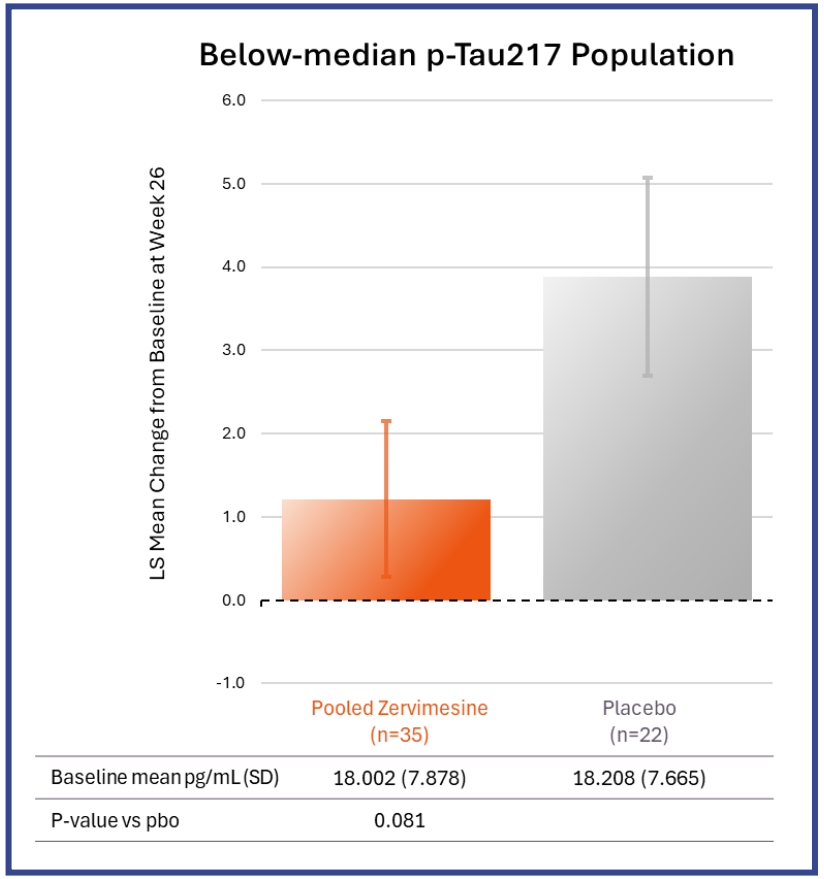
Biomarker Impact on Neurodegeneration: Plasma NfL

Noticeable trend in dampening neurodegeneration



Baseline mean pg/mL (SD)	20.81 (8.098)	22.26 (9.558)
P-value vs pbo	0.206	



Baseline mean pg/mL (SD)	18.002 (7.878)	18.208 (7.665)
P-value vs pbo	0.081	

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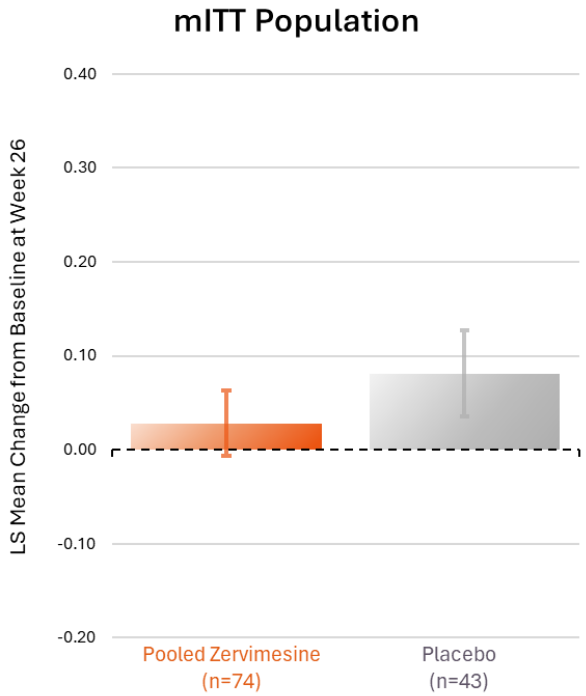
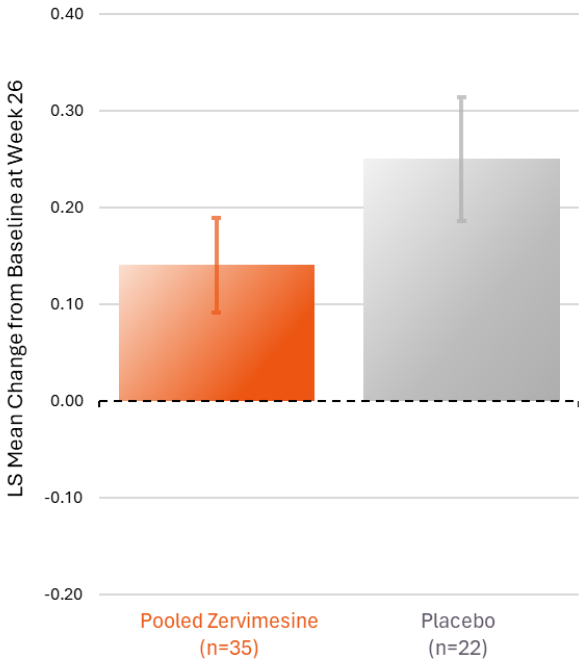
Trend Towards Change in p-Tau217 May Suggest Slowing of AD Progression



Baseline mean pg/mL (SD)	1.068 (0.5263)	1.146 (0.6556)
P-value vs pbo	0.358	



Baseline mean pg/mL (SD)	0.660 (0.211)	0.667 (0.187)
P-value vs pbo	0.198	

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Up to 123% Percent Slowing on Assessments

Biomarker findings align with strong, consistent efficacy signals across measures

Zervimesine Pooled (100/300mg)

	Cognition			Function		Biology		
	ADAS-Cog 11	ADAS-Cog 13	MMSE	ADCS-ADL	ADCS-CGIC	Plasma GFAP	Plasma NfL	Plasma Aβ 40 & 42
mITT	38%	39%	70%	26%	28%	23%	51%	71-97%
⇩ median p-tau217	95%	103%	108%	67%	61%	65%	69%	113-123%

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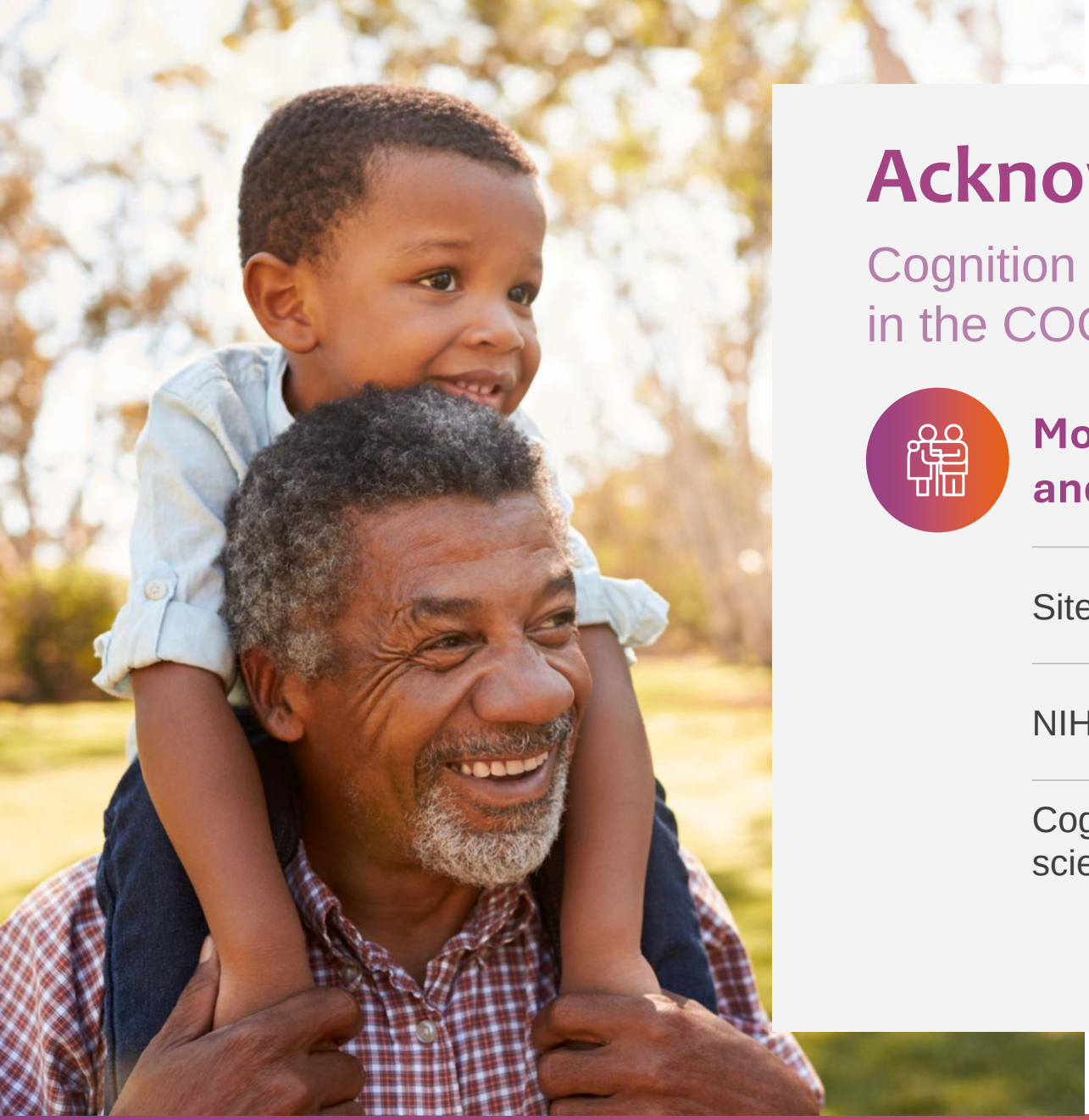
SHINE Study: Summary and Conclusions

Baseline plasma p-tau217 biomarker identified strong zervimesine-treatment responder group

- Zervimesine was found to be generally safe and well-tolerated
- Robust cognitive and functional impact observed in the pre-specified below-median plasma p-tau217 subgroup
- Prominent effects on recognized biomarkers of neuroinflammation (GFAP), neurodegeneration (NfL) and amyloid biology (Aβ42) consistent with favorable clinical outcomes
- This study enabled dose selection and a biomarker-defined responder population (low plasma pTau217) to be identified for Ph3

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



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Most importantly – each study participant and their care partners

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