COGNITION™ Therapeutics

Targeting Pathogenic Oligomers:

A Disruptive Approach to the Treatment of Neurodegenerative Diseases

January 2025

Forward-looking Statements

FORWARD-LOOKING STATEMENTS

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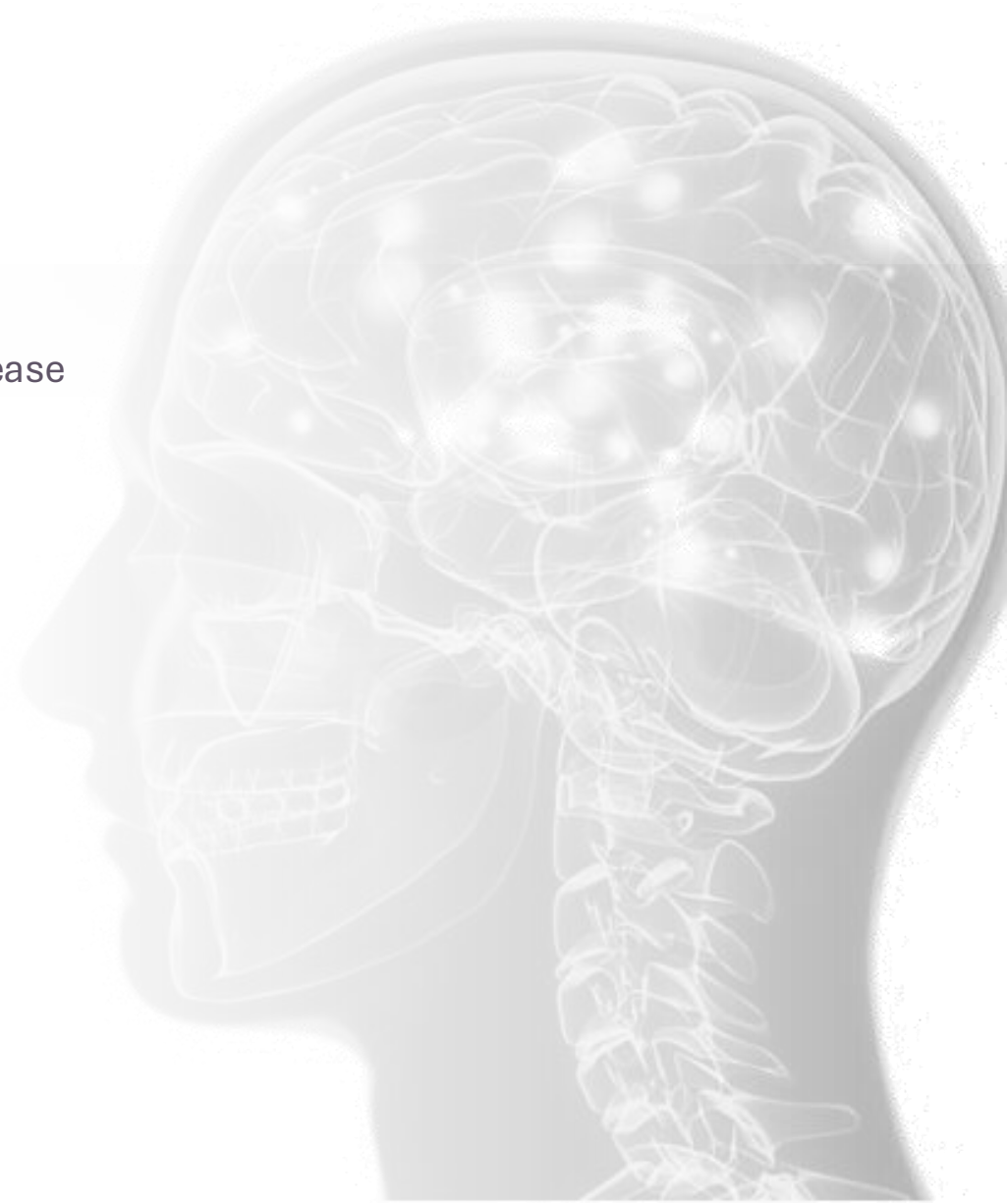
Executive Summary

First-in-class oligomer antagonist with compelling efficacy data



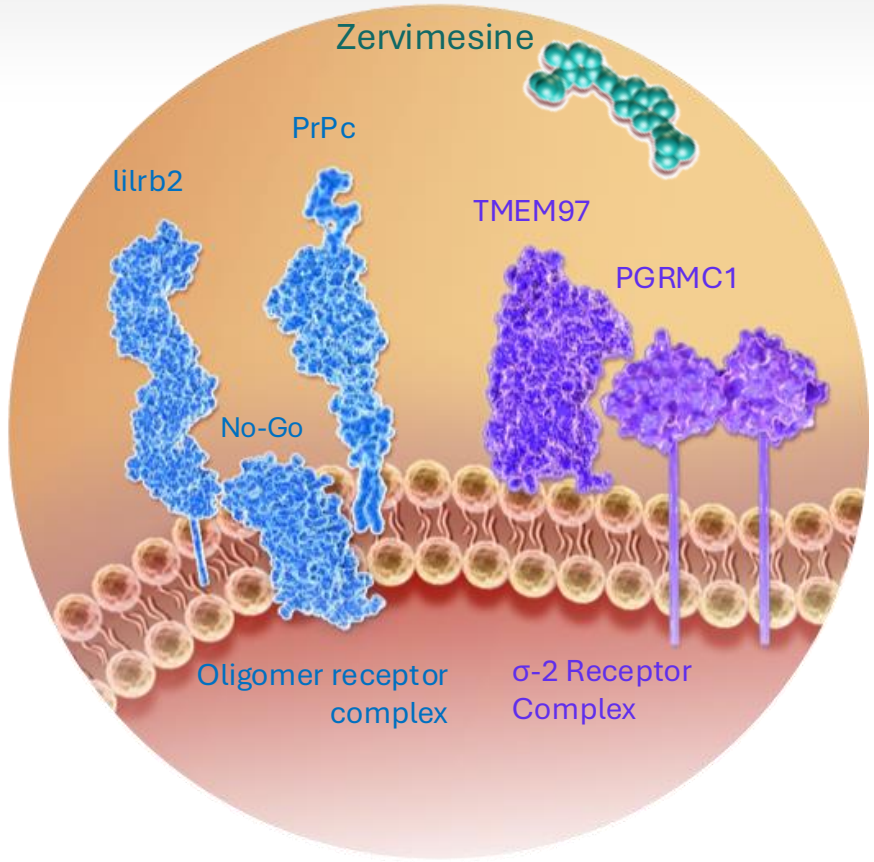
- **Consistent efficacy** in Alzheimer's disease and DLB studies
  - One of few compounds effective in *both* mild & moderate Alzheimer's disease
- **Well tolerated safety** profile
  - ARIA unexpected based on MoA
  - Modest side effect profile for use in aging population
- **Oral QD** administration
  - No need for IV therapy or imaging surveillance
- **Potential first-to-market for dementia with Lewy bodies (DLB)**
  - Strong responses across behavioral, functional, cognitive, and movement measures in Phase 2 SHIMMER study
- **Robust intellectual property** covering platform & compounds, including zervimesine (CT1812) through 2040 with PTE

ARIA: amyloid-related imaging abnormalities; MOA: mechanism of action; PTE: patent term extension

Zervimesine (CT1812) – Lead Product Candidate

Extensive comp of matter IP on zervimesine and other candidates developed from foundational platform

- BBB-penetrant small molecule oligomer antagonist
- Distinct MoA: ligand of TMEM97 (sigma-2) receptor
- Oral, once-daily dosing, favorable safety data
- Fast Track granted for Alzheimer's disease
- Phase 2 PoC efficacy across cognitive measures in mild-to-moderate Alzheimer's disease
- Phase 2 PoC efficacy across four key symptom categories in mild-to-moderate DLB

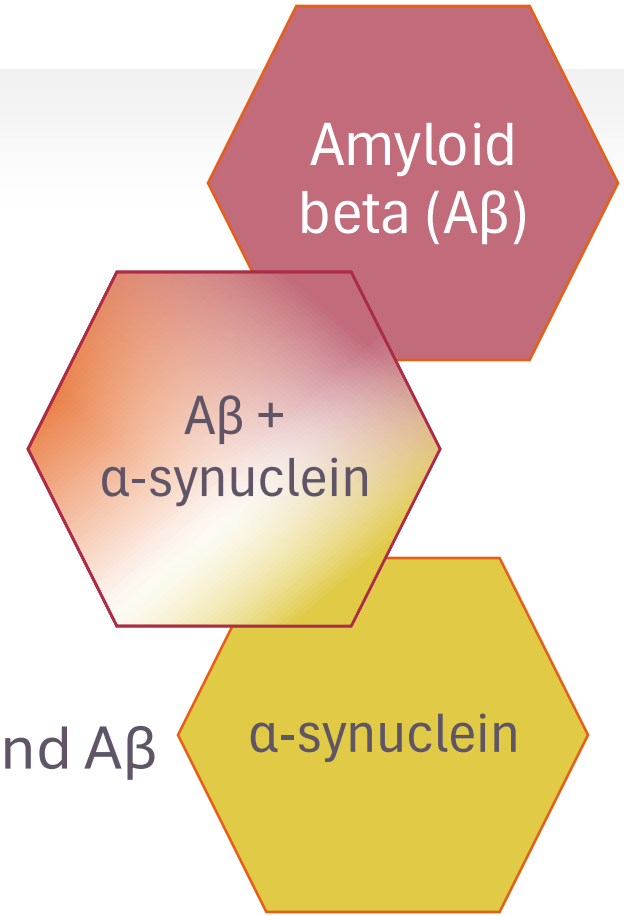


BBB: blood brain barrier; PoC: proof of concept

AD and DLB: 2 Diseases with Overlapping Pathology

Primary treatment goal – slow the progression of cognitive decline

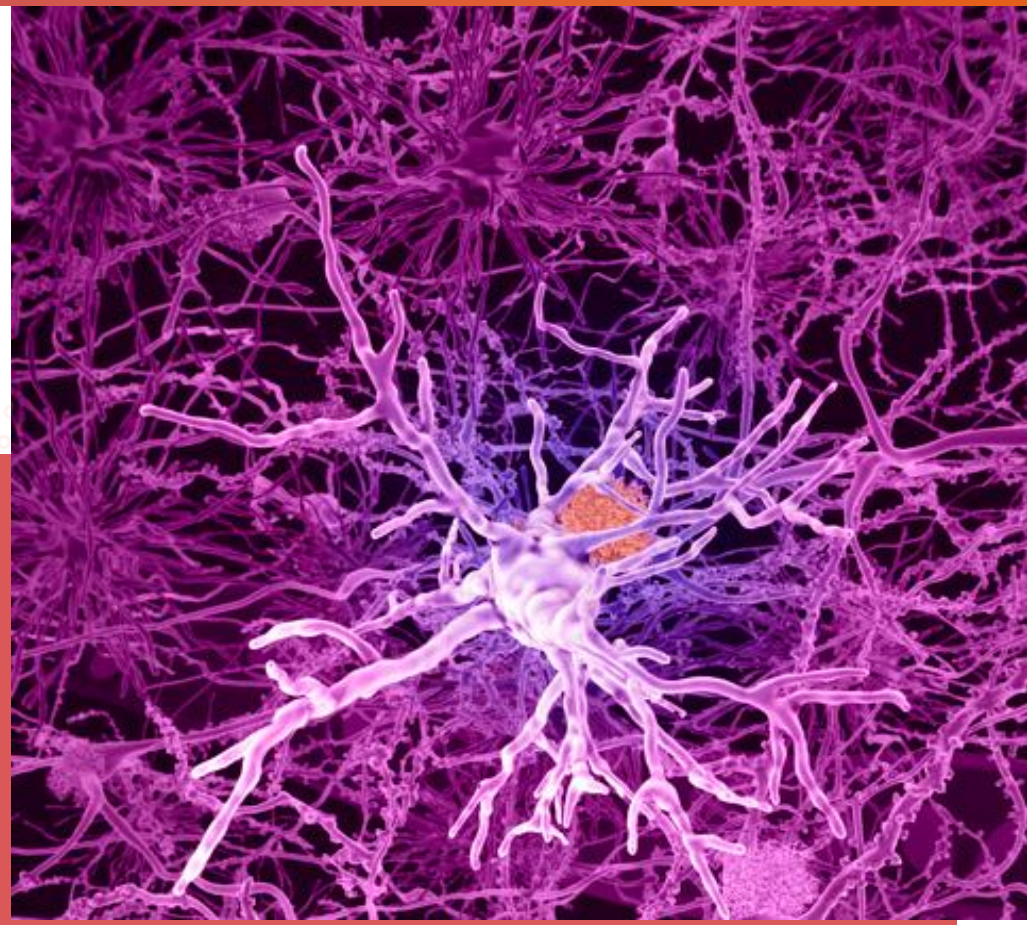
- Aβ: closely associated with Alzheimer's pathogenesis
- α-synuclein: closely associated with Lewy body dementias
- Co-pathology is common
  - Up to 80% of DLB patients have BOTH α-synuclein and Amyloid beta (Aβ)[1]
  - Appx 50% of Alzheimer's patients have BOTH Aβ and α-synuclein[2]
- Zervimesine has shown protective function against α-synuclein and Aβ



1. NIH Requests for Application RFA-NS-25-010 accessed 12/09/2024 https://tinyurl.com/26d6ertd
2. Bassil F et al. Neuron. 2019 Nov 20;105(2):260–275.e6. https://doi.org/10.1016/j.neuron.2019.10.010

Dementia with Lewy Bodies (DLB)

Strong clinical signals across four major symptom domains in Phase 2 SHIMMER Study



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Dementia with Lewy Bodies (DLB)

- 2nd most common cause of dementia after Alzheimer's disease
- Patients may have faster decline than Alzheimer's
- Characterized by cognitive impairment that precedes development of motor symptoms
- Patients often require several physician visits over 18 months before being correctly diagnosed
- More common in men

Core Symptoms of DLB

- Fluctuating cognition and alertness
- Neuropsychiatric symptoms such as visual hallucinations, anxiety, depression and delusions
- Decline in cognition, attention, executive function
- Spontaneous parkinsonism
- REM sleep behavior disorder

SHIMMER Study in Dementia with Lewy Bodies

Conducted in collaboration with experts at LBDA and University of Miami

Enrollment Criteria	Treatment Period 6 months	Assessments	Program Objectives

- Age 50-85
- DLB diagnosis
- MRI
- MMSE: 18-27
	Randomized 1:1:1
	Zervimesine 300 mg
	Zervimesine 100 mg
	Placebo
	Oral QD Administration
	130 participants randomized from 31 sites across U.S. , including LBDA centers of excellence
		- Safety/tolerability
		- Global CGIC
		- Cognition
		  - MoCA, MMSE, CDR
		- Function
		  - UPDRS III
		  - ADL
		- Behavior
		  - Epworth Sleep
		  - Fluctuations
		- Biomarkers
			✓ Identify efficacy signal(s)
			✓ Confirm safety and tolerability profile
			✓ Identify dose(s) for Phase 3
			✓ Explore impact on behavioral symptoms of sleep and fluctuations

SHIMMER COG1201 study (NCT05225415) partially funded by $30M NIA grant R01AG071643

DLB, Dementia with Lewy Bodies; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; QD, daily; NIA, National Institute on Aging; LBDA, Lewy Body Dementia Association

Summary of SHIMMER Safety and Tolerability findings

Favorable safety profile vs placebo, AEs well balanced between arms

- Total AE frequency was similar in zervimesine and placebo
- Most AEs were mild or moderate
- Fewer Serious AE occurred in the zervimesine treated group compared to placebo treated
- There were no deaths related to study drug

- Study Discontinuations due to AEs not related to LFTs:
  - Placebo – 4.8%
  - 100mg zervimesine – 4.5%
  - 300 mg zervimesine – 9.3%
- Participants with LFT elevations ≥ 3x ULN
  - 100mg zervimesine – 3
  - 300mg zervimesine – 6
  - Placebo – 0
- Most common AEs* (other than increased LFTs) in the zervimesine group were diarrhea and abdominal discomfort

Adverse Events

Zervimesine	94.3%
Placebo	88.1%

Serious AEs

Zervimesine	10.3%
Placebo	19.0%

Deaths†

Zervimesine	2 (2.2%)
Placebo	1 (2.4%)

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

Four Symptom Domains Drive Lewy Body Disease Burden

"A multifactorial disease with a buffet of symptoms"

	Behavior	Cognition	Function	Movement
Patient symptom	Hallucinations, anxiety, delusions	Memory and problem solving	Bathing, toileting, shopping, meal preparation	Standing, maintaining balance
Assessment tool	Neuropsychiatric Inventory (NPI) Care Partner's NPI of "Distress"	Cognitive Drug Research (CDR) System Montreal Cognitive Assessment (MoCA) Clinician Assessment of Fluctuation (CAF)	ADCS-Activities of Daily Living (ADL)	MDS-Unified Parkinson's Disease Rating Scale (UPDRS)

Up to 91% Percent Slowing on Assessments

Strong clinical signals across major DLB symptoms relative to placebo

	Behavior		Cognition			Function	Movement
	NPI (total)	NPI (distress)	CDR (episodic memory)	MoCA	CAF	ADCS-ADL	UPDRS
Zervimesine Pooled (100/300mg)	**82%**	**114%***	**85%**	**60%**	**91%**	**52%**	**62%**

* Measure of the distress experienced by the care partners of SHIMMER participants

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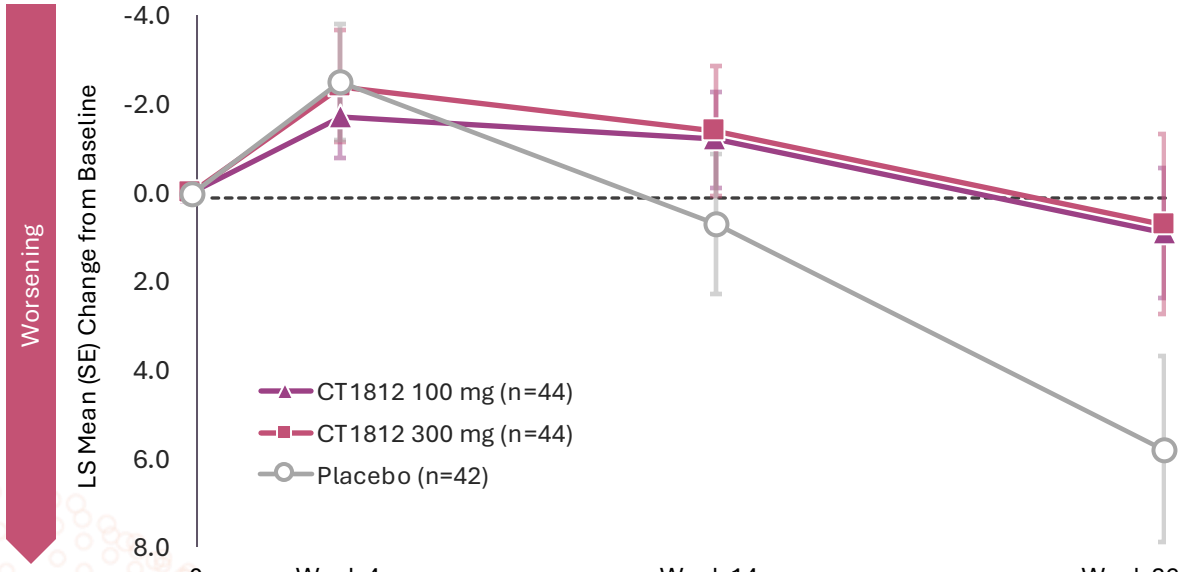
Zervimesine Showed Dramatic 82% Impact on Neuropsychiatric Measures

NPI captures a variety of patient disturbances, including hallucinations, anxiety, and delusions

NPI A-L

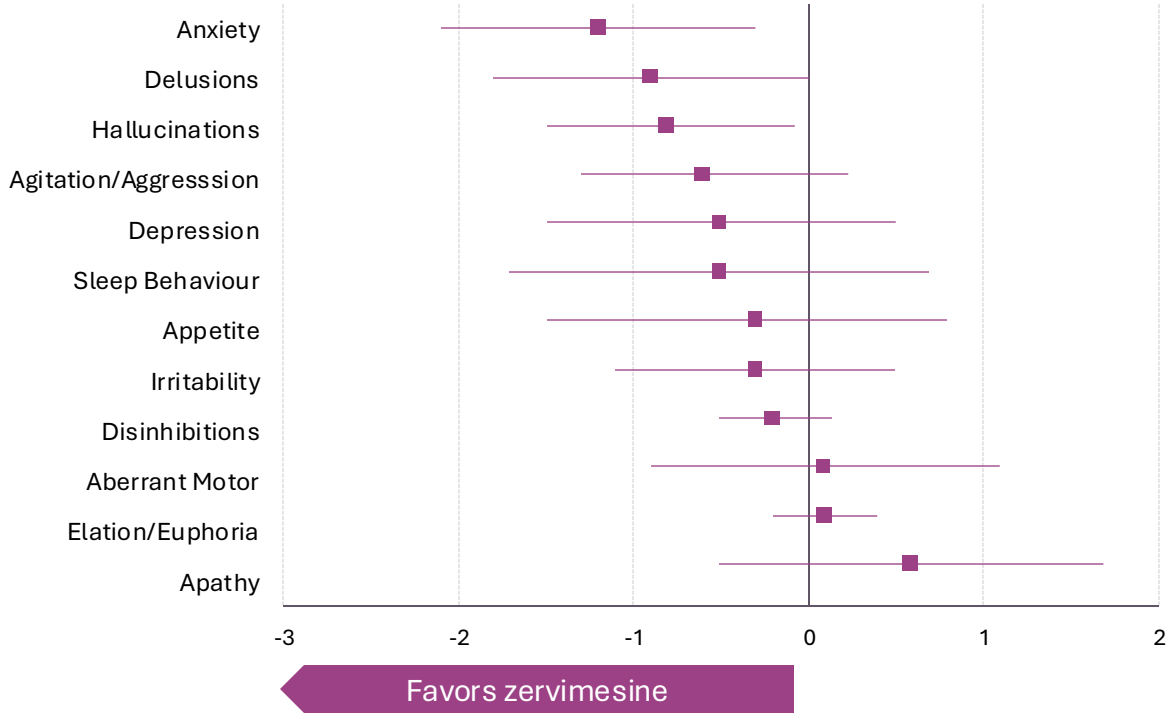
NPI Total Score (A-L)



	Week 4	Week 14	Week 26
P-value (pooled v pbo)	0.745	0.277	0.054

NPI favor Treatment with Zervimesine

LS Mean Difference from Placebo 95% CI



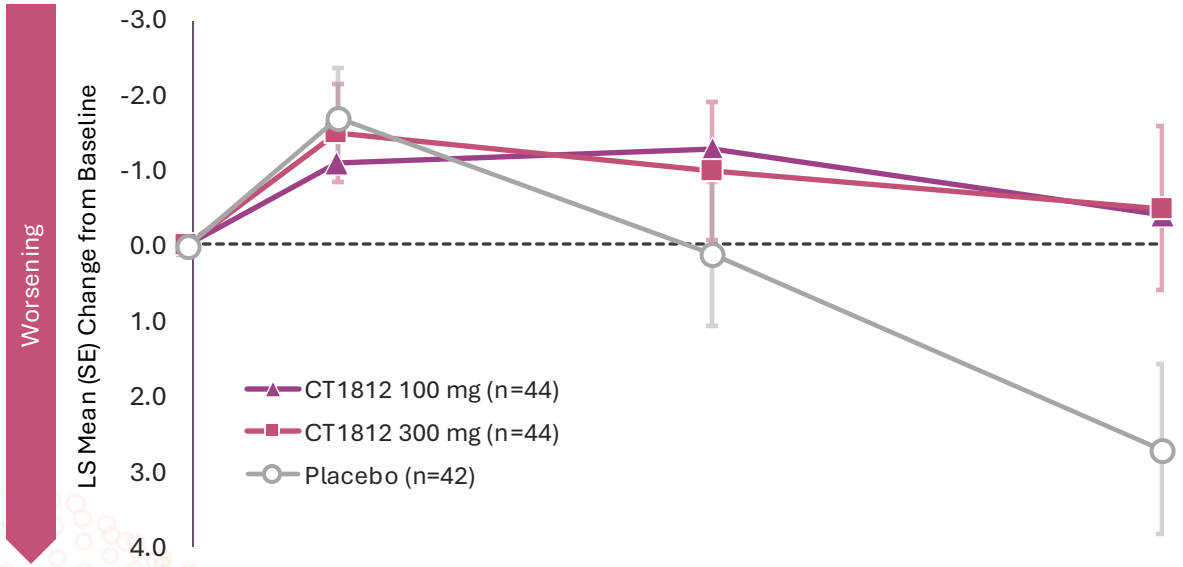
NPI: Neuropsychiatric inventory

Because Participants Improved in Hallucinations, Delusions & Anxiety, Caregivers were Notably Better

New tool created to measure caregiver burden in DLB

NPI A-J Distress

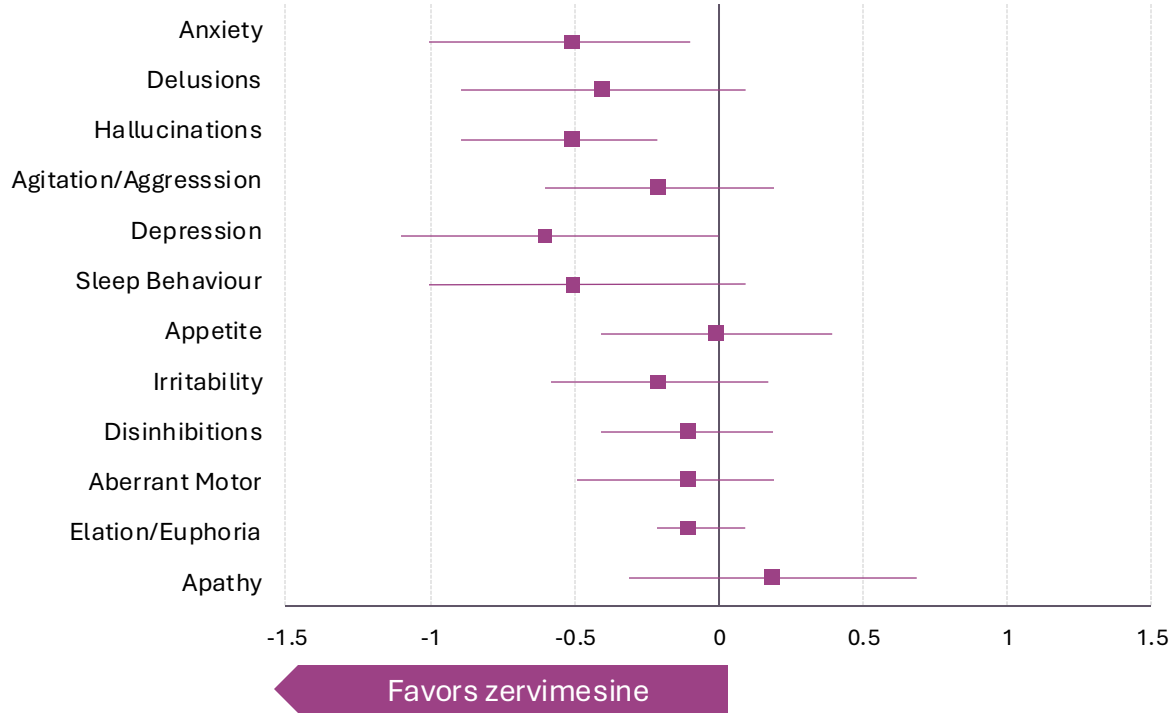
NPI Total Score (A-J) Caregiver Distress



P-value (pooled v pbo)	0.598	0.288	0. 025

NPI Distress favors Treatment with Zervimesine

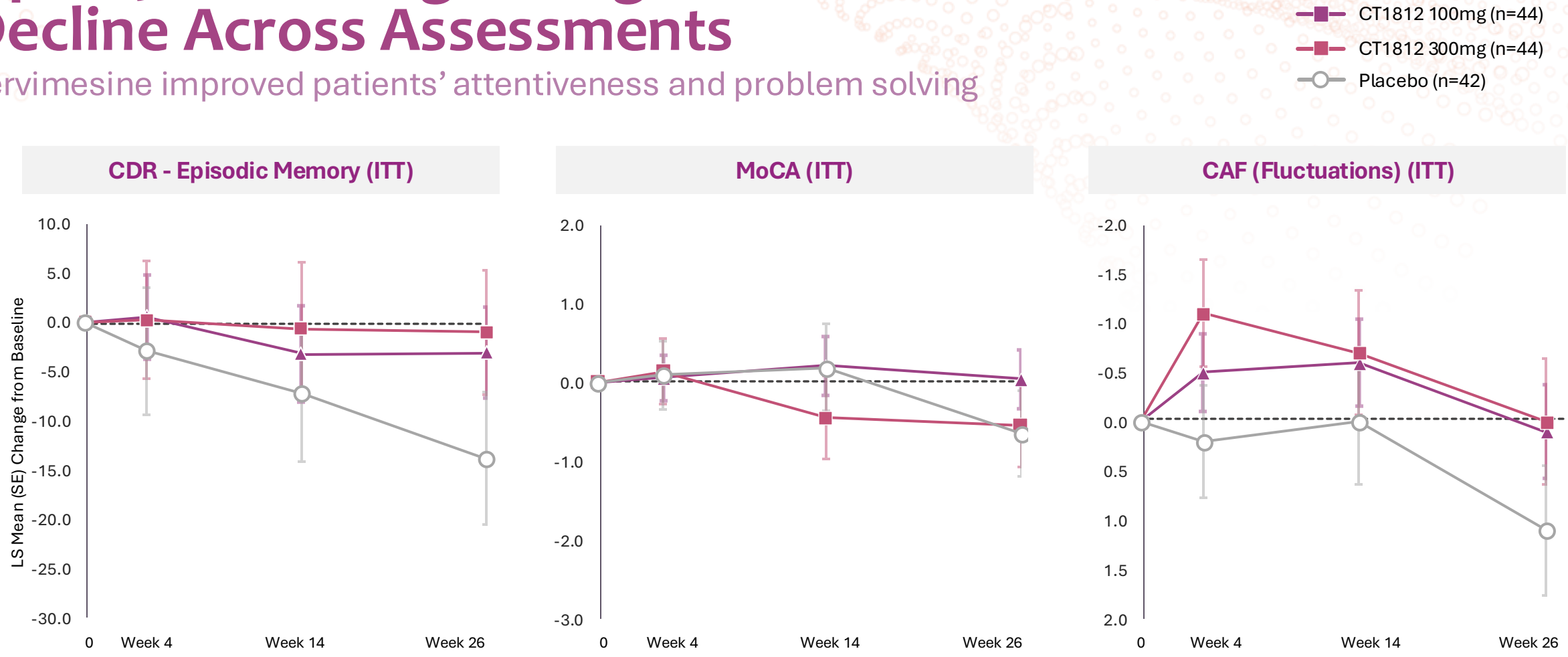
LS Mean Difference from Placebo 95% CI



NPI Distress: Neuropsychiatric inventory (Care Partner Distress)

Up to 91% Slowing of Cognitive Decline Across Assessments

Zervimesine improved patients' attentiveness and problem solving



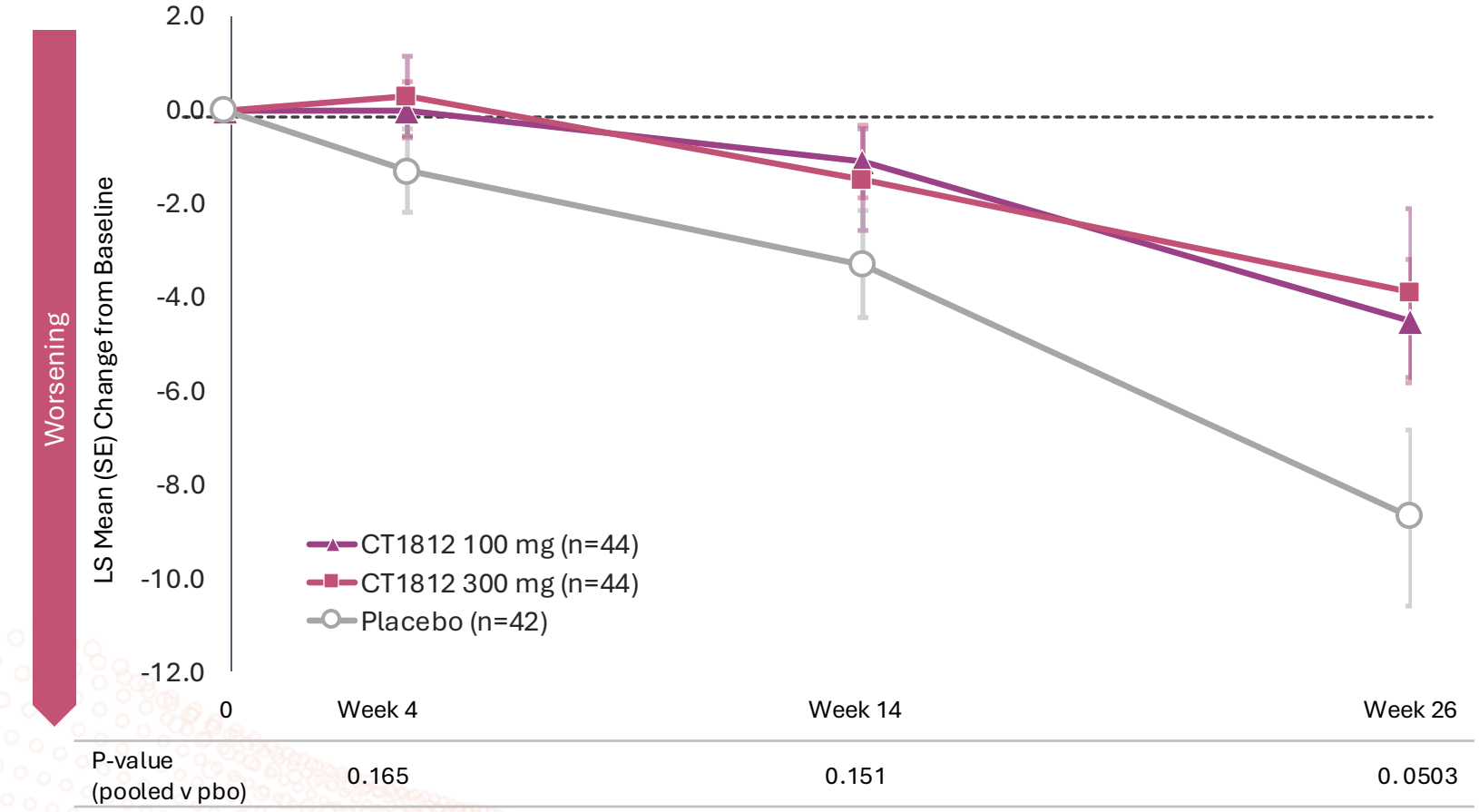
	Week 4	Week 14	Week 26
P-value (pooled v pbo)	0.674	0.539	0.152
	0.979	0.643	0.550
	0.137	0.429	0.2097

CDR: Cognitive Drug Research (CDR) Battery; MoCA: Montreal Cognitive Assessment; CAF: Clinician Assessment of Fluctuation

People on Zervimesine Maintained Self-care

52% preservation in activities of daily living (ADL) measures

ADCS-ADL



	Week 4	Week 14	Week 26
P-value (pooled v pbo)	0.165	0.151	0.0503

Components of ADL Score

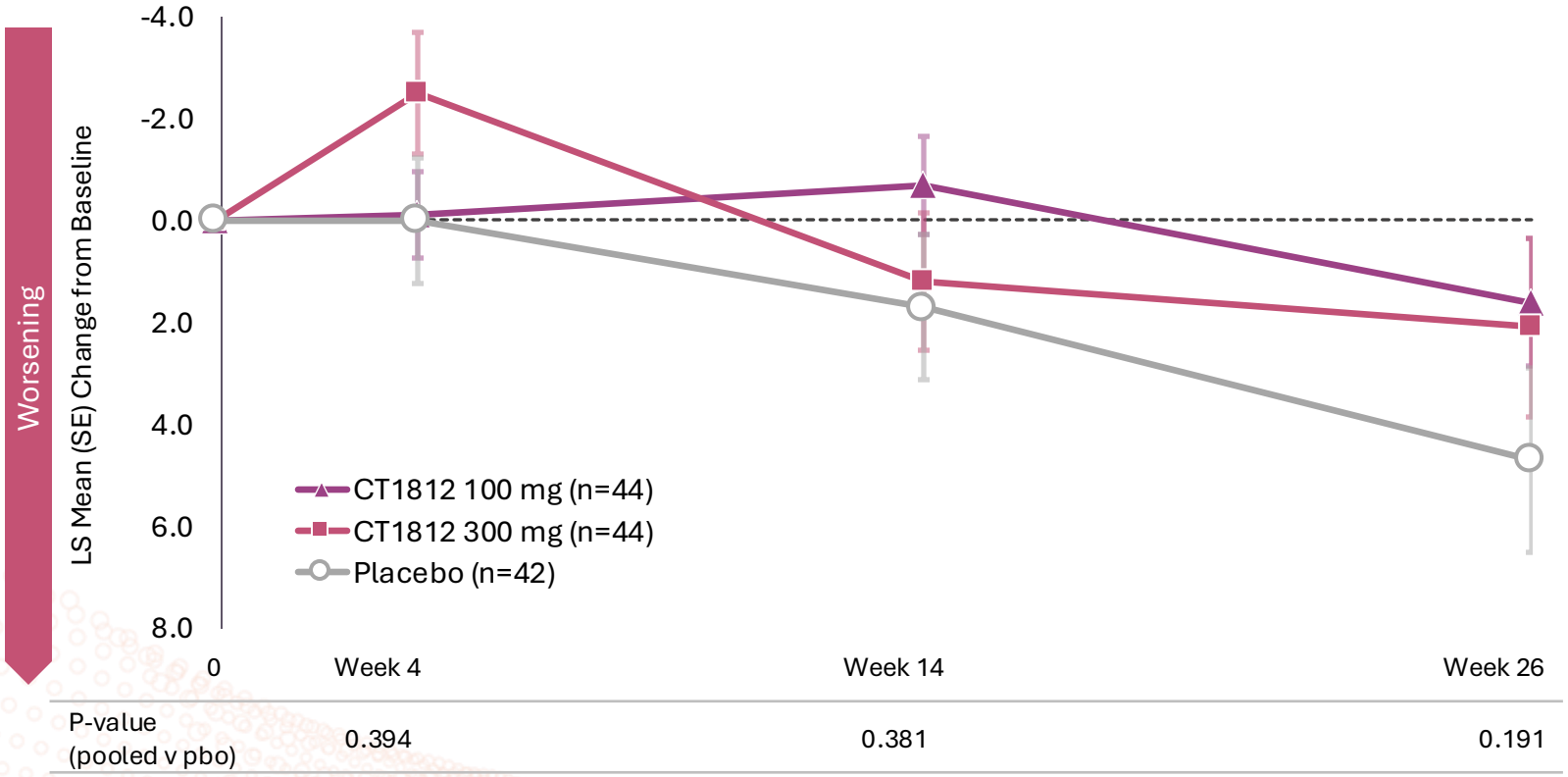
- Bathing
- Toileting
- Dressing
- Conversing
- Grooming
- Shopping
- Feeding
- Writing

ADCS-ADL: Activities of Daily Living

People Treated with Zervimesine Maintained Motor Function

62% preservation in measures of movement

MDS-UPDRS3



	Week 4	Week 14	Week 26
P-value (pooled v pbo)	0.394	0.381	0.191

Components of UPDRS:

- Balance
- Speech
- Rigidity
- Tremor
- Gait
- Facial expression

ADCS-ADL: Activities of Daily Living

SHIMMER Met and Exceeded Objectives and Expectations

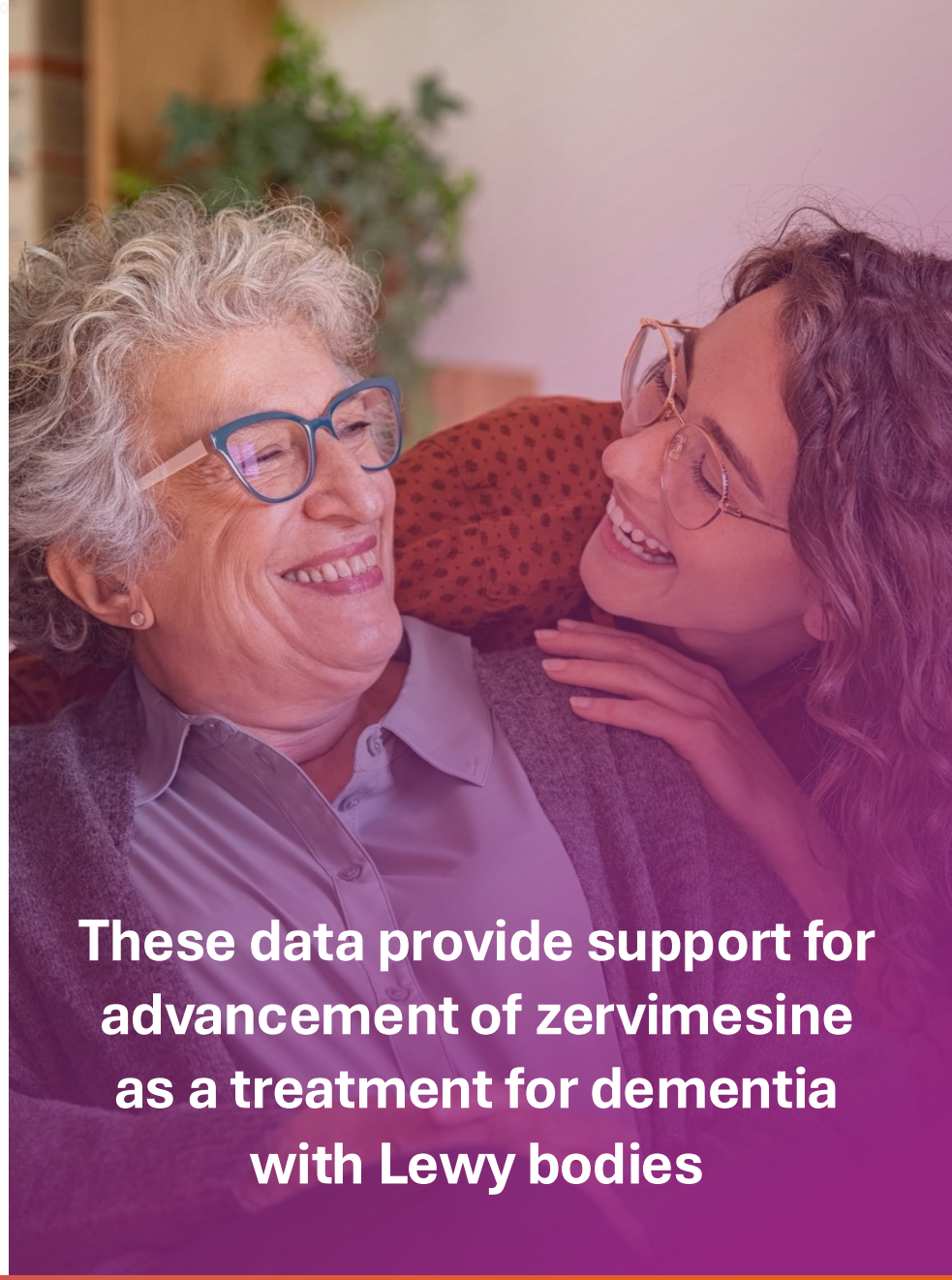
Identified consistent signals of efficacy with a favorable tolerability profile

COG1201 SHIMMER was a phase 2a safety and tolerability study seeking signals of efficacy in people with dementia with Lewy bodies

The safety and tolerability profile was similar to past experience with CT182

Clear signals of efficacy were observed

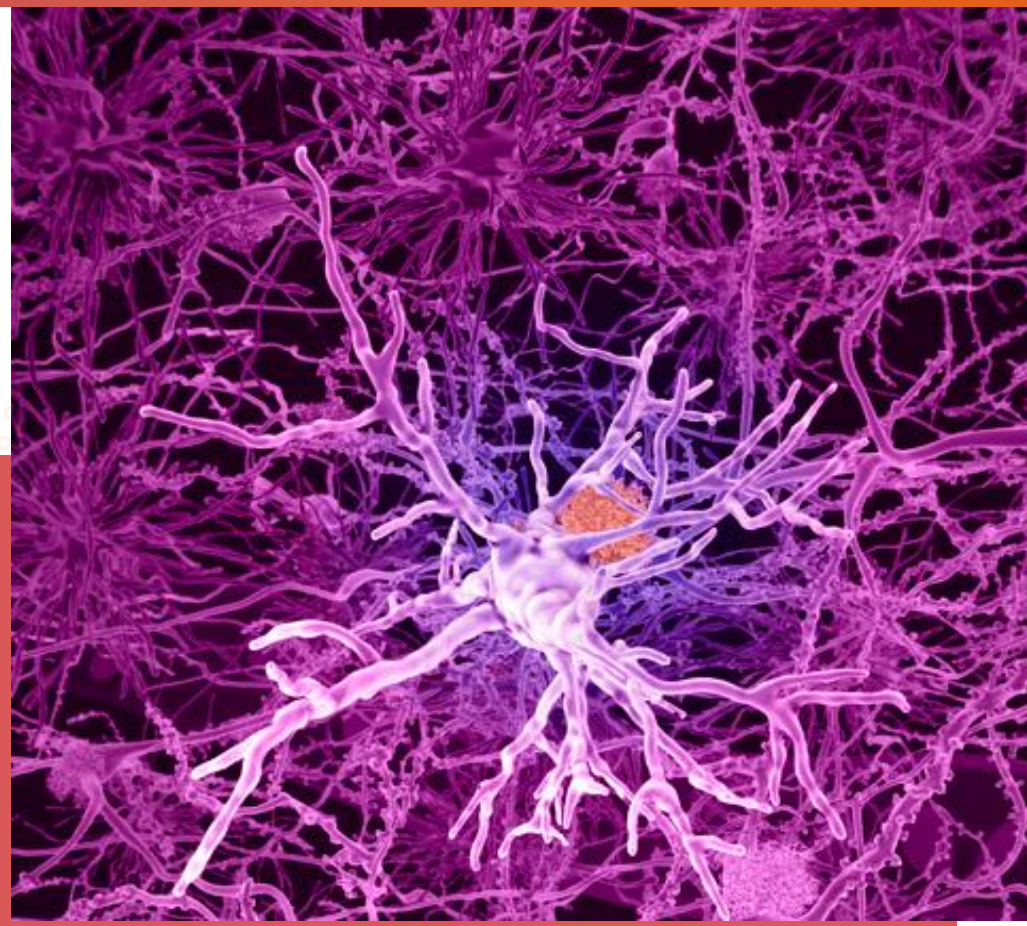
- Across Behavioral, Cognitive, Functional and Motor domains
- Treatment differences increased over 6 months



These data provide support for advancement of zervimesine as a treatment for dementia with Lewy bodies

Alzheimer's Disease

Extensive preclinical and clinical testing culminating in positive results in Phase 2 PoC 'SHINE' trial



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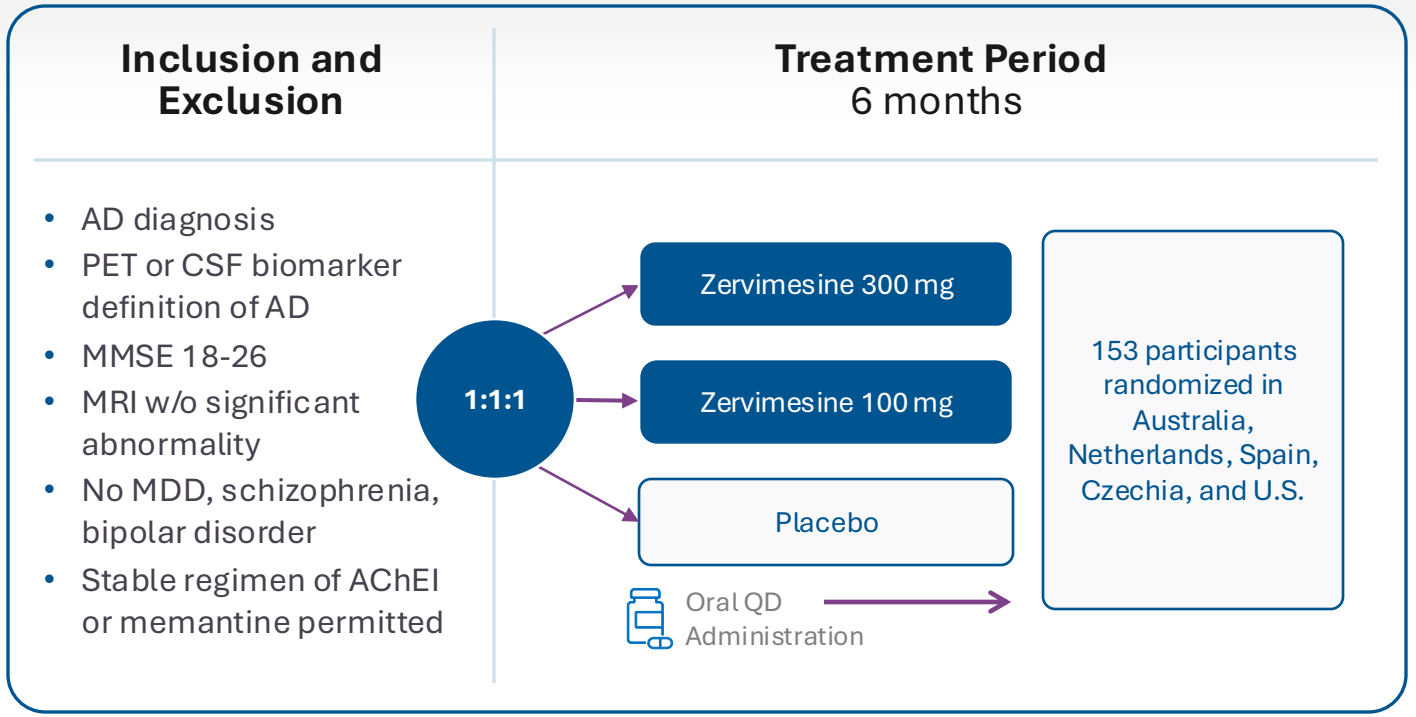
SHINE: Phase 2 PoC in Mild-to-Moderate Alzheimer's Disease

Well-executed, over-enrolled study, supports advancing clinical development

Enrolled Population:

- PET- or biomarker-confirmed AD
- Majority of participants were female (60%), Caucasian (96%), ~ 72 yo
- Mean MMSE score upon entry: 21.37
- ~60% of patients carry the ApoE4 gene
- Characteristics well-balanced between all 3 arms



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

SHINE COG0201

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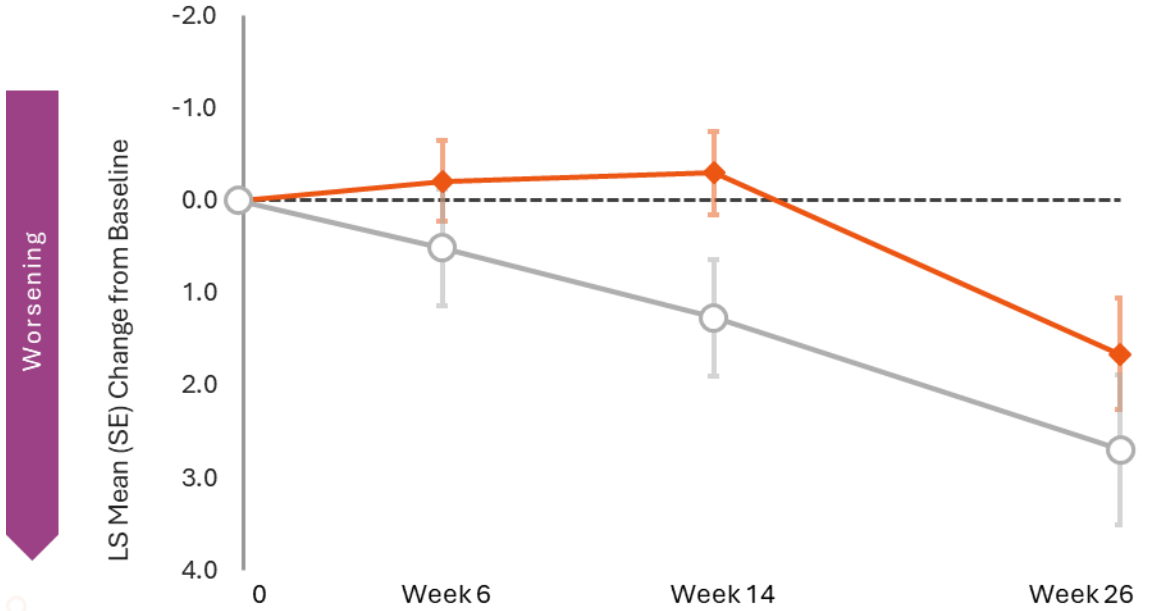
SHINE Cognitive Endpoints: ADAS-Cog 11 and MMSE

Magnitude of ADAS-Cog 11 decline at 6 months similar to approved MAbs

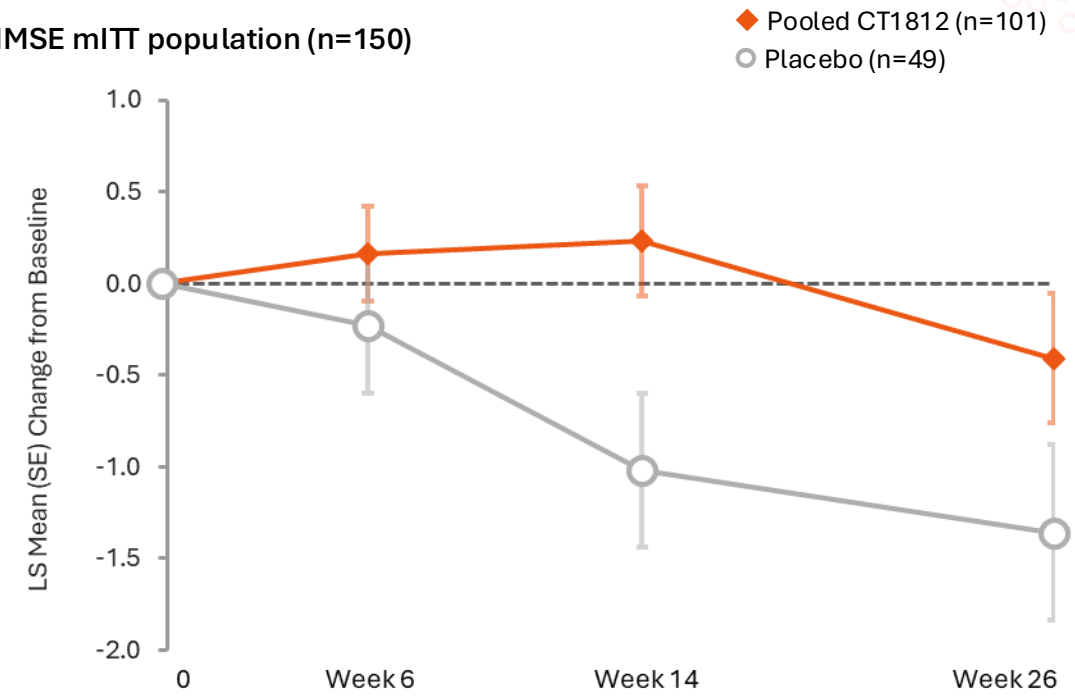
ADAS-Cog 11* mITT population (n=150)



	Week 6	Week 14	Week 26
P-value (pooled v pbo)	0.35	0.04	0.30

Observed treatment difference v pbo: 1.04 pt

MMSE mITT population (n=150)



	Week 6	Week 14	Week 26
P-value (pooled v pbo)	0.40	0.02	0.11

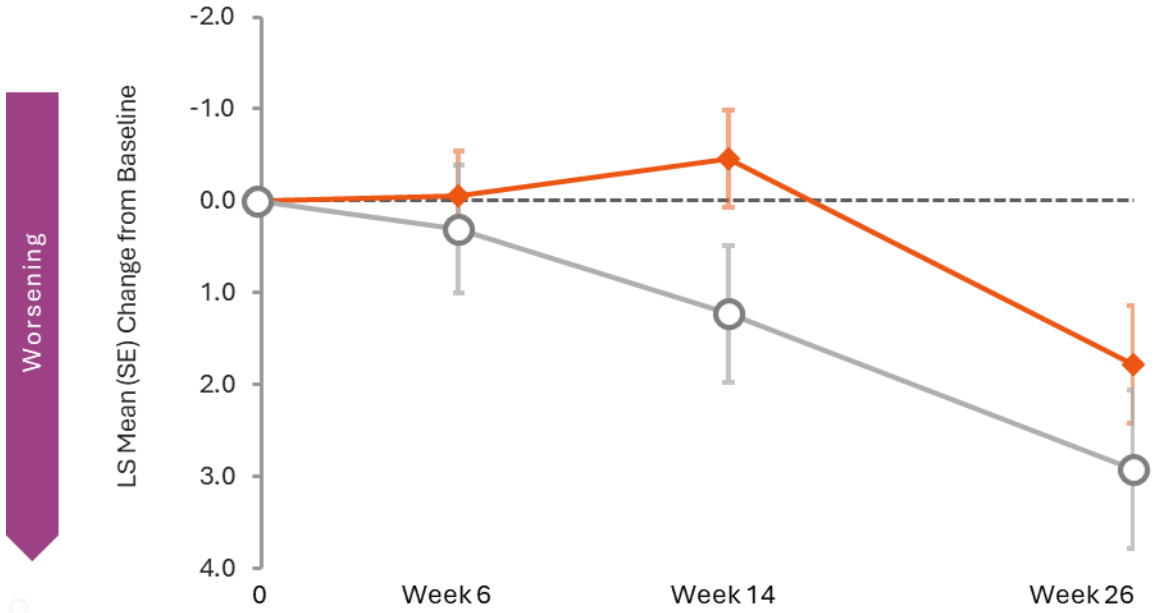
Observed treatment difference v pbo: 0.95 pt

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

SHINE Cognitive Endpoints: ADAS-Cog 13, Cognitive Composite

Consistent results across multiple cognitive endpoints

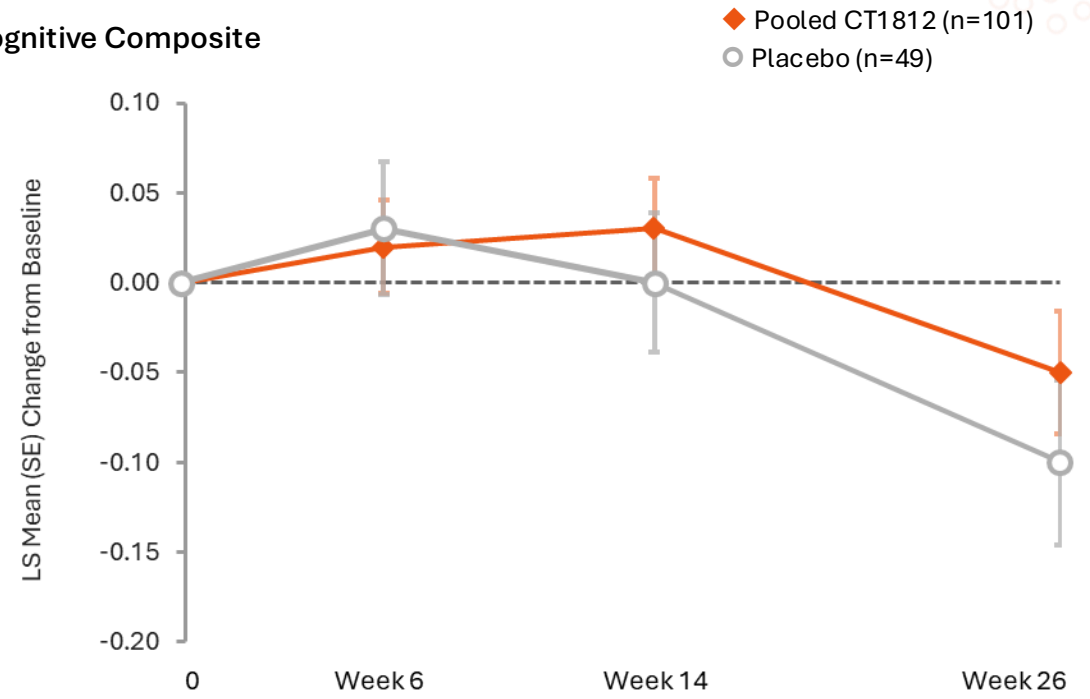
ADAS-Cog 13



P-value (pooled v pbo)	0.66	0.06	0.29

Observed treatment difference v pbo: 1.14 pt

Cognitive Composite



P-value (pooled v pbo)	0.85	0.56	0.40

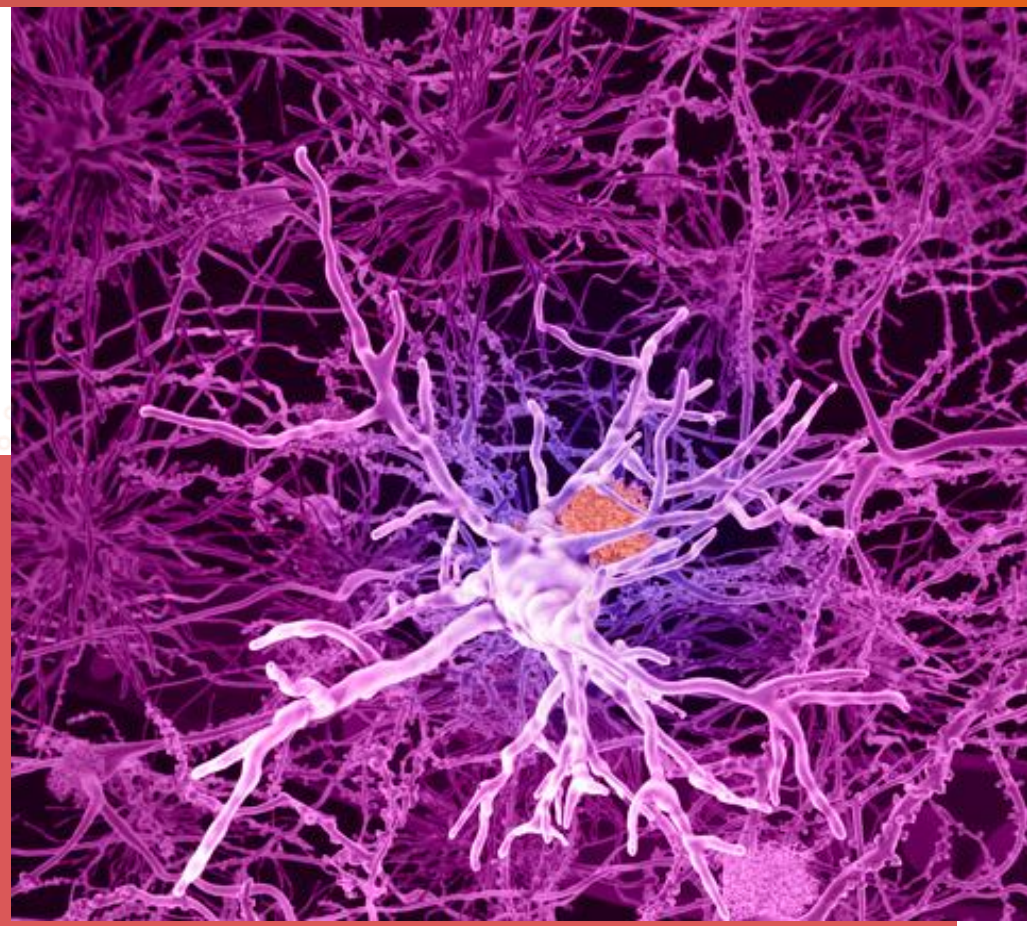
Observed treatment difference v pbo: 0.05 pt

Note: n's are at Day 182

Prespecified Subgroup Analysis from Phase 2

95% slowing of cognitive decline in lower-p-tau217 'SHINE' participants

Amyloid positivity confirmed for all participants by CSF or PET



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Tau Burden in Amyloid-related AD Clinical Trials

Baseline plasma p-tau217: a 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 zervimesine'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

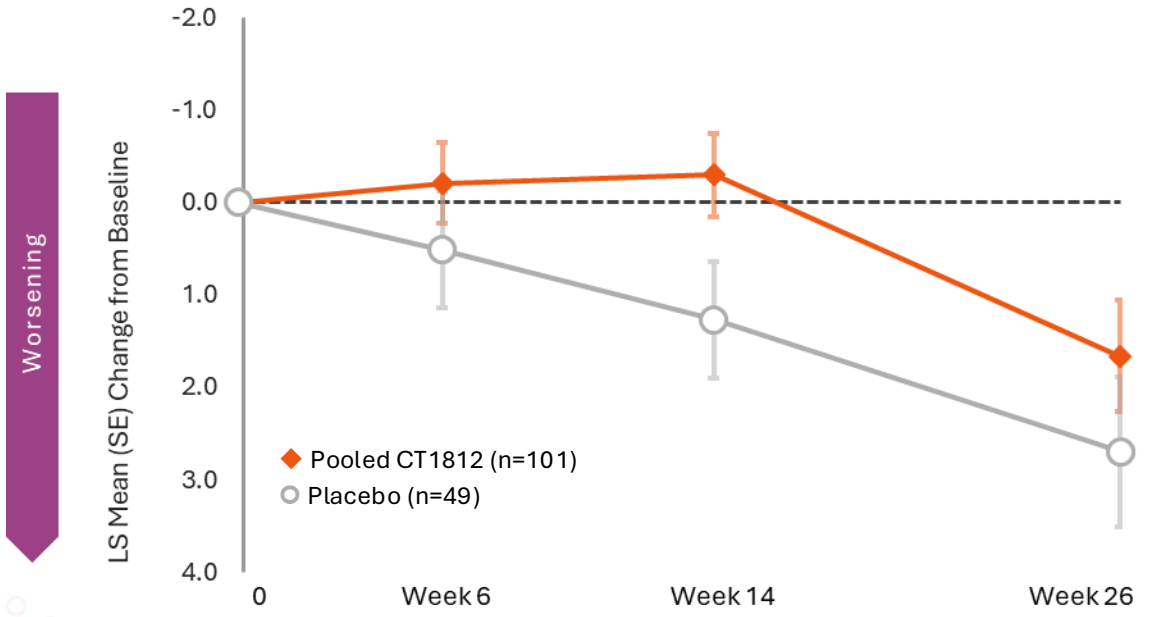
* Mintun MA et al. slides presented at CTAD 2023

iARDS, Integrated Alzheimer's Disease Rating Scale

Below Median p-tau217, Treated Participants Experienced Profound Cognitive Effect

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

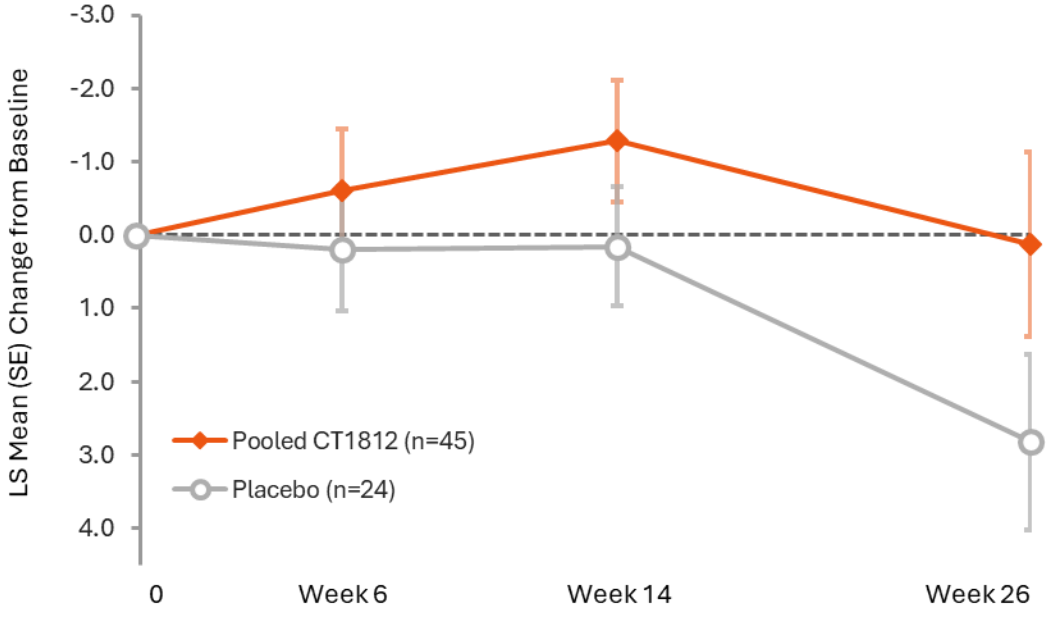
ADAS-Cog 11* mITT population (n=150)



P-value (pooled v pbo)	0.35	0.04	0.30

Observed treatment difference v pbo: 1.04 pt

Below median p-tau217 (n=69)



P-value (pooled v pbo)	0.45	0.15	0.08

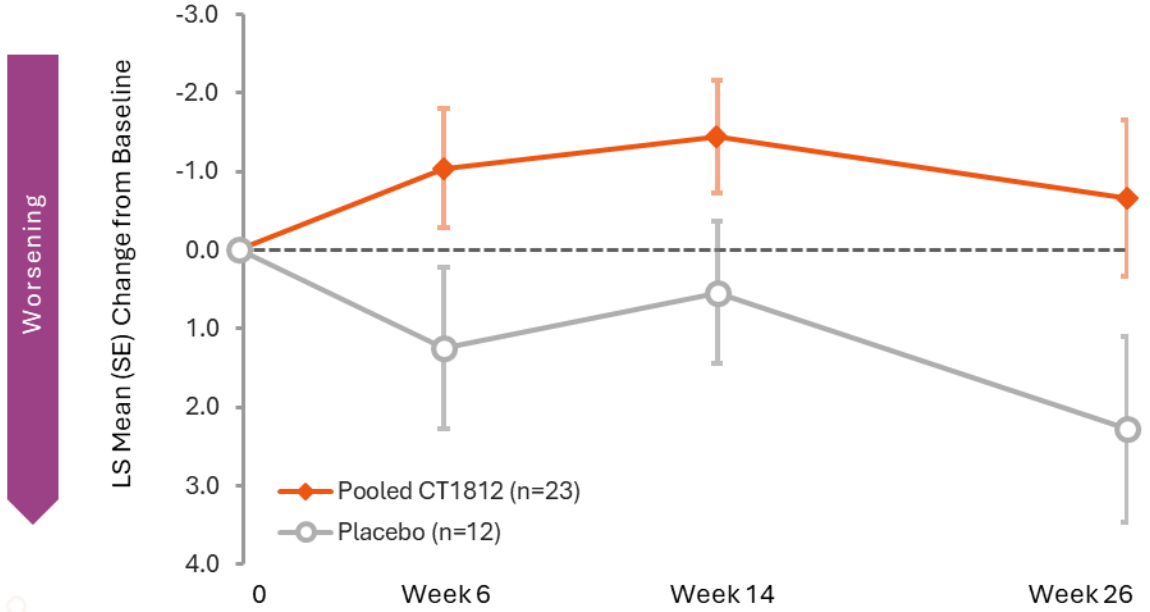
Observed treatment difference v pbo: 2.7 pt

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

Treatment Impact in Below Median p-tau217 Consistent Across Baseline MMSE scores

Cognitive preservation (ADAS-Cog 11) observed across MMSE range

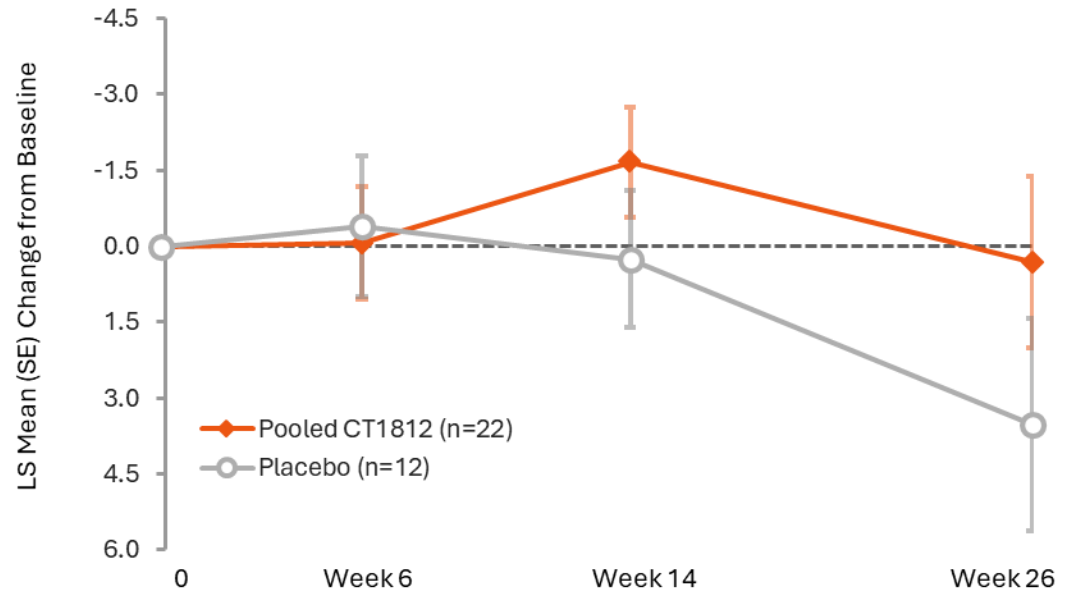
Zervimesine-Treated Mild (MMSE 22-26)



P-value (pooled v pbo)	0.09	0.10	0.07

Observed treatment difference v pbo: 2.9 pt

Zervimesine-Treated Moderate (MMSE 18-21) Participants



P-value (pooled v pbo)	0.85	0.26	0.24

Observed treatment difference v pbo: 3.2 pt

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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

Zervimesine SHINE Study: Summary and Conclusions

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

- Zervimesine generally safe and well tolerated
  - Similar percentages of AEs in pooled treated and placebo groups
- All cognitive and functional measures trended in favor of zervimesine

Full CTAD Presentation

- Large cognitive impact observed in below-median plasma p-tau217 subgroup
- Will assess optimal plasma p-tau217 cut-point for future studies

Next steps: End-of-Phase 2 meeting with FDA to establish protocol for Phase 3 in mild-to-moderate Alzheimer's disease in population defined by plasma p-tau217

Ongoing Studies Expand into Related Patient Populations

COG0203 - START	Enrolling ~540 with MCI / early Alzheimer's disease	Supported by appx $81M NIA award	Enrollment commenced 2023 with ACTC
About Early AD:	Current treatments require burdensome monitoring	ARIA risk may limit adoption	Combining MAbs with small molecules holds potential
COG2201 - MAGNIFY	Enrolling ~243 with GA secondary to dry AMD		
About geographic atrophy (GA):			Combining MAbs with small molecules holds potential

START - A 540-Person Study in Amyloid-positive Early AD

First study to allow lecanemab as background therapy in combination with zervimesine

Enrollment Criteria	Treatment Period 18 months	Assessments	Program Objectives

- Ages 50-85
- Diagnosis of MCI due to AD or mild AD dementia
- Brain amyloid via PET
- MRI
- MMSE: 20-30
	Randomized 1:1:1
	Zervimesine 200 mg
	Zervimesine 100 mg
	Placebo
	Oral QD Administration
	Recruiting 540 adults with early AD at 30+ sites, including ACTC centers of excellence
		- Safety
		- Cognitive and functional testing:
		  - CDR-SB
		  - ADAS-Cog 13,
		  - ADCS-ADL-MCI
		- Biomarkers
		  - Fluid
		  - imaging
			✓ Identify efficacy signal(s)
			✓ Confirm safety and tolerability after longer exposure
			✓ Identify dose(s) for Phase 3

START COG0203 study (NCT05531656) partially funded by $81M NIA grant R01AG065248

MCI, mild cognitive impairment; CDR-SB, Clinical Dementia Rating Scale Sum of Boxes; ADAS-Cog, Alzheimer's Disease Assessment Scale–Cognitive; ADL, activities of daily living; QD, daily; NIA, National Institute on Aging; ACTC, Alzheimer's Clinical Trials Consortium

START COG0203 COGNITION Therapeutics

MAGNIFY Trial in dAMD/GA

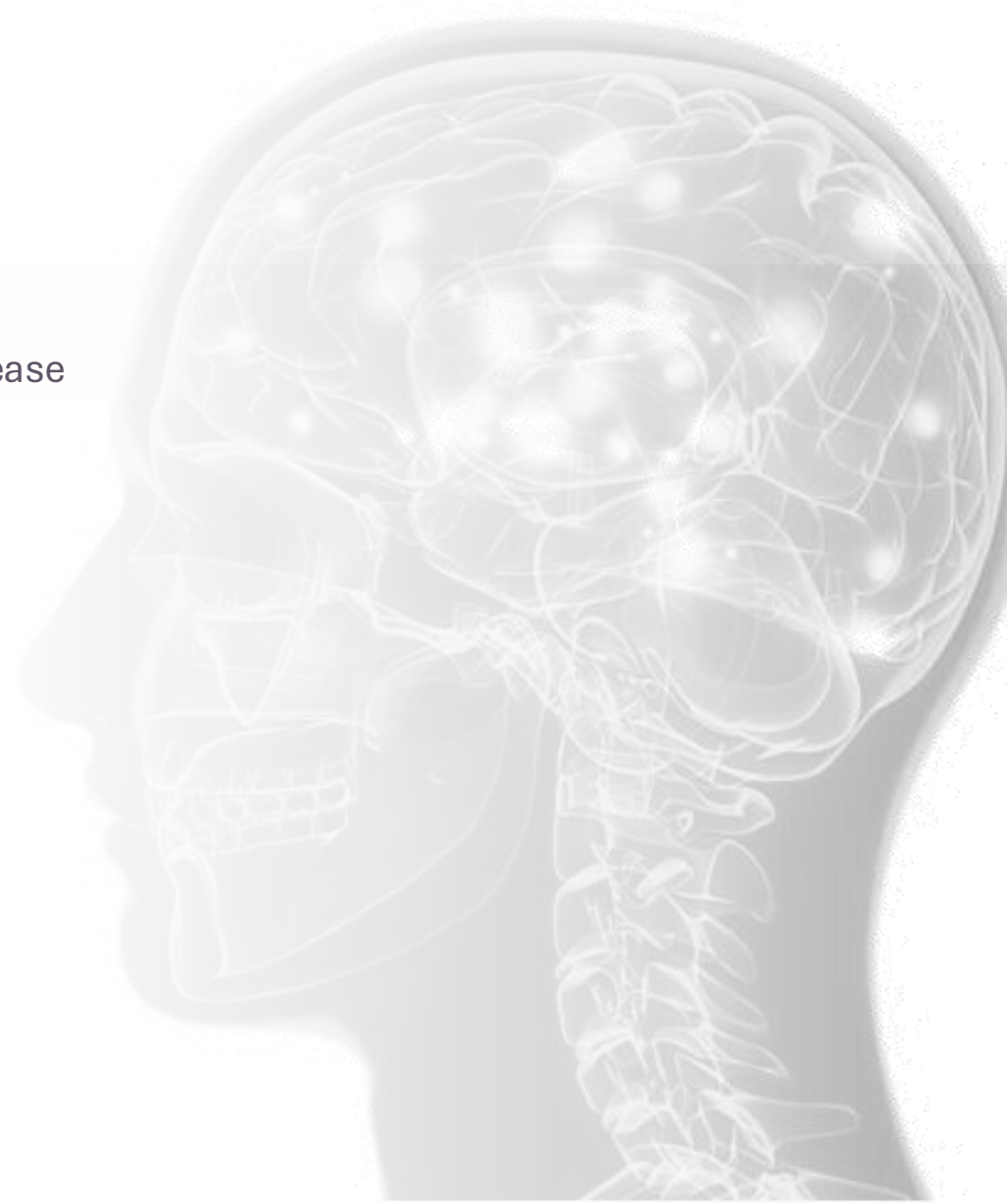
Potential first oral drug for geographic atrophy

Enrollment Criteria	Treatment Period 24 months	Assessments	Program Objectives
- Age: ≥ 50 - Diagnosis of dry AMD - BCVA ≥ 24 letters (ETDRS) - GA lesion ≥ 2.5 and ≤17.5mm2	Randomized 1:1 Zervimesine 200 mg Placebo Recruiting 246 adults with GA secondary to dry AMD Oral QD Administration	- Change in GA lesion area (FAF) - Ellipsoid zone area (SD-OCT) - Drusen volume (SD-OCT) - Safety	✓ Identify efficacy signal(s) ✓ Assess potential to treat two eyes simultaneously ✓ Confirm safety and tolerability profile at 200mg dose

BVCA, best corrected visual acuity; FAF, fundus autofluorescence; SD-OCT, spectral domain optical coherence tomography

Executive Summary

First-in-class oligomer antagonist with compelling efficacy data



- **Consistent efficacy** in Alzheimer's disease and DLB studies
  - One of few compounds effective in *both* mild & moderate Alzheimer's disease
- **Well tolerated safety** profile
  - ARIA unexpected based on MoA
  - Modest side effect profile for use in aging population
- **Oral QD** administration
  - No need for IV therapy or imaging surveillance
- **Potential first-to-market for dementia with Lewy bodies (DLB)**
  - Strong responses across behavioral, functional, cognitive, and movement measures in Phase 2 SHIMMER study
- **Robust intellectual property** covering platform & compounds, including zervimesine (CT1812) through 2040 with PTE

ARIA: amyloid-related imaging abnormalities; MoA: mechanism of action; PTE: patent term extension

Current Financial Position

As of quarter ended September 30, 2024

Cash and cash equivalents $22.0 M

Grant funding for zervimesine studies

Preclinical through Phase 2	~$171 M
Approximate funding used	($117.4 M)
Remaining grant funding	$53.6M

COGNITION™ Therapeutics

Thank You

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