



# Targeting Pathogenic Oligomers:

A Disruptive Approach to the  
Treatment of Neurodegenerative Diseases

*May 2025*

# Forward-looking Statements

## FORWARD-LOOKING STATEMENTS

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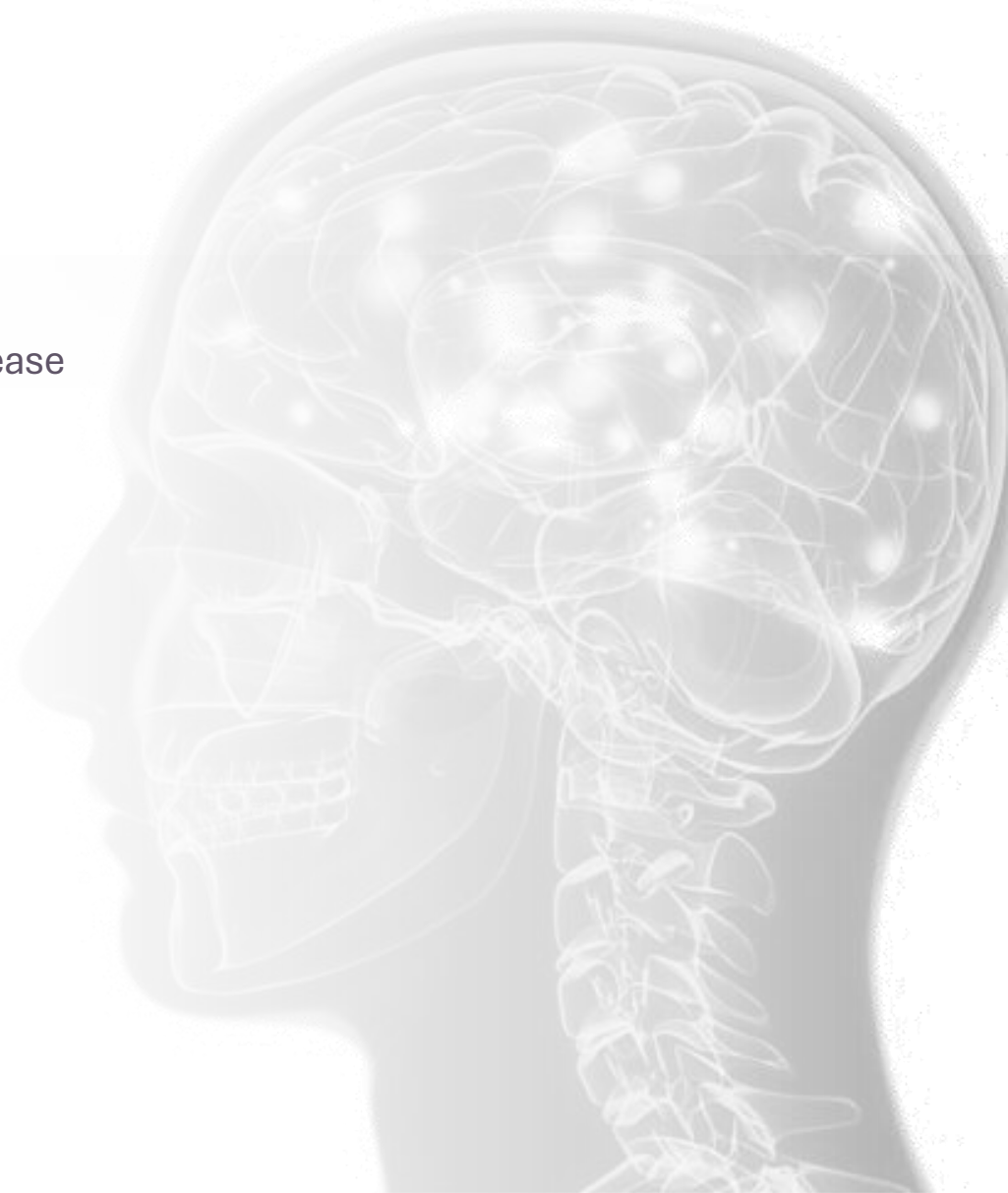
## MARKET & INDUSTRY DATA

*Projections, estimates, industry data and information contained in this presentation, including the size of and growth in key end markets, are based on information from third-party sources and management estimates. Although we believe that these third party-sources are reliable, we cannot guarantee the accuracy or completeness of these sources. Our management’s estimates are derived from third-party sources, publicly available information, our knowledge of our industry and assumptions based on such information and knowledge. Our management’s estimates have not been verified by any independent source. All of the projections, estimates, market data and industry information used in this presentation involve a number of assumptions and limitations, and you are cautioned not to give undue weight to such information. In addition, projections, estimates and assumptions relating to us and our industry’s future performance are necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including, but not limited to, those described above, that could cause future performance to differ materially from our expressed projections, estimates and assumptions or those provided by third parties.*

# Executive Summary

First-in-class oligomer antagonist with compelling efficacy data

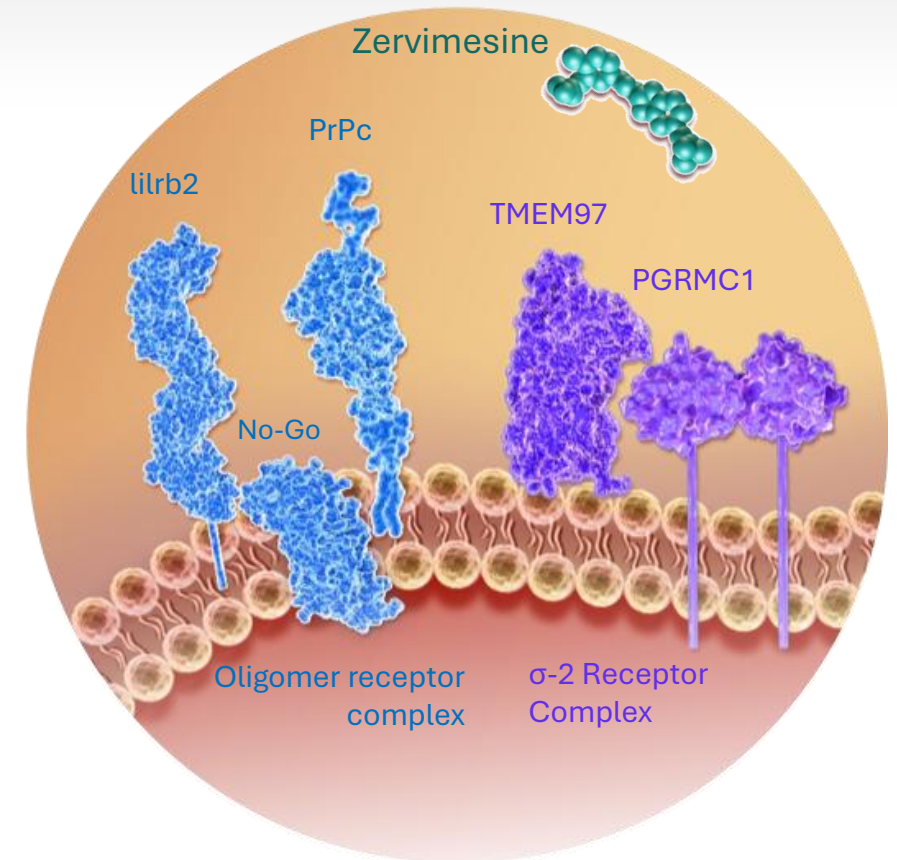
- **Consistent efficacy** in Alzheimer's disease and DLB studies
  - One of few compounds effective in *both* mild & moderate Alzheimer's disease
- **Well tolerated safety** profile
  - **ARIA unexpected** based on MoA
  - Modest side effect profile for use in aging population
- **Oral QD** administration
  - 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



# 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



# Ongoing programs

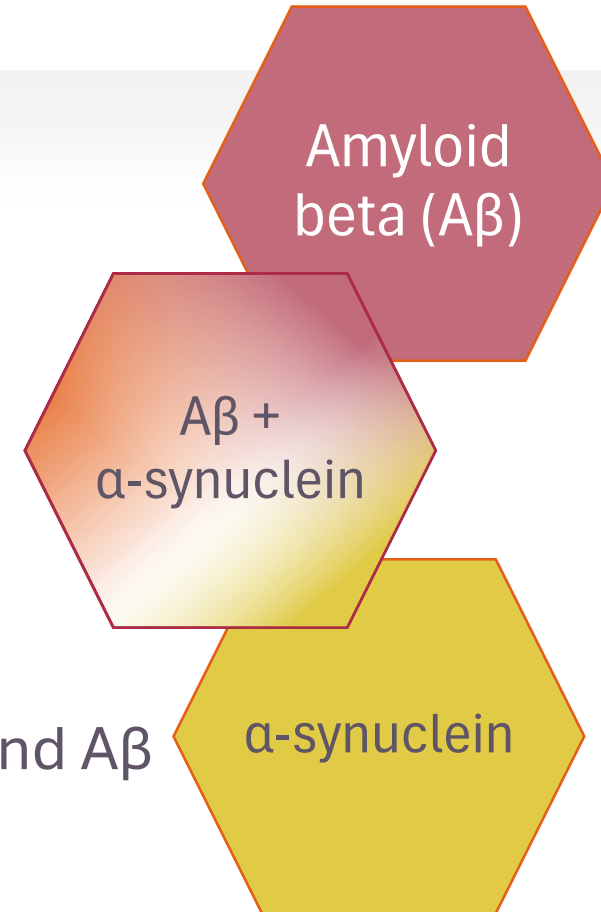
Program	Preclinical	Phase 1	Phase 2	Phase 3
<b>Alzheimer's disease</b> <i>Early-to-mild Alzheimer's disease</i>			Phase 2 COG0203 • START	
<b>Completed Studies</b>				
Mild-to-moderate DLB			Phase 2 COG1201 • SHIMMER	
Mild-to-moderate Alzheimer's disease			Phase 2 COG0201 • SHINE	
<b>Dry age-related macular degeneration</b> <i>GA secondary to dry AMD</i>			Phase 2 COG2201 • MAGNIFY	*

\* We made the strategic decision to voluntarily discontinue the MAGNIFY study to prioritize our resources on our ongoing programs in Alzheimer's and dementia with Lewy bodies. The discontinuation was not the result of any safety concerns.

# AD and DLB: 2 Diseases with Overlapping Pathology

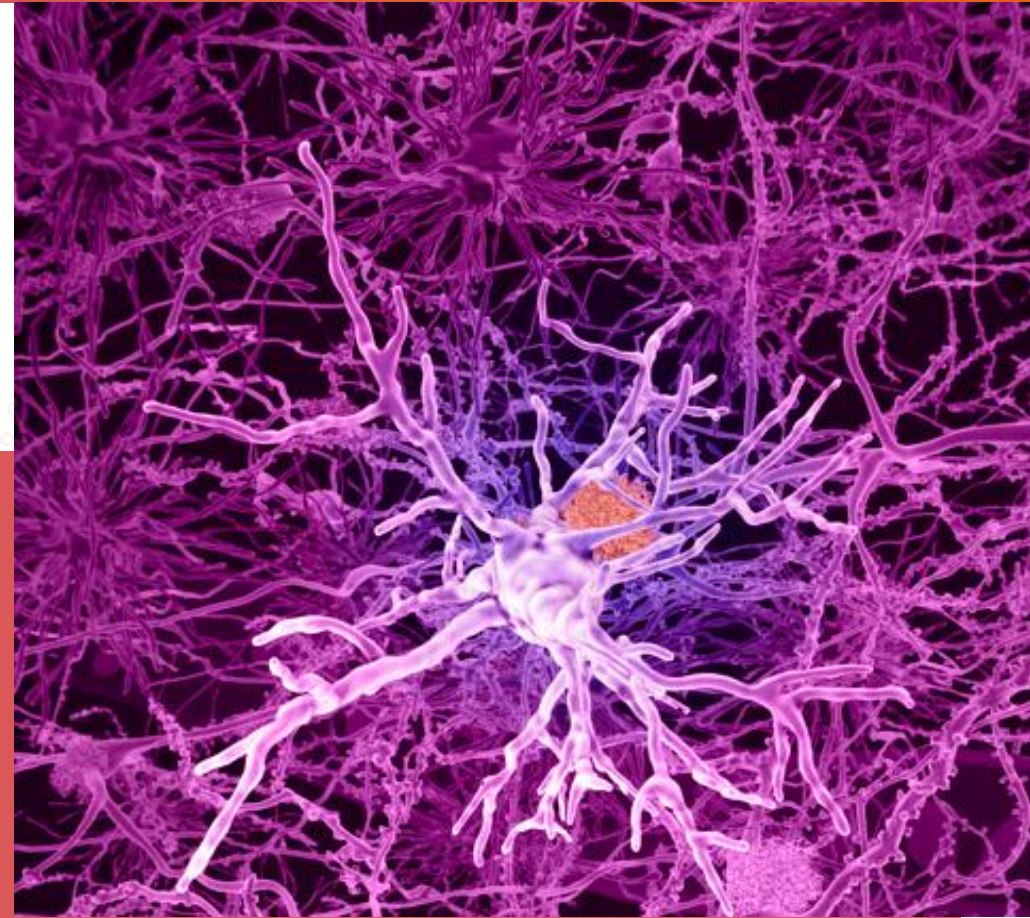
Primary treatment goal – slow the progression of cognitive decline

- A $\beta$ : closely associated with Alzheimer's pathogenesis
- $\alpha$ -synuclein: closely associated with Lewy body dementias
- Co-pathology is common
  - Up to 80% of DLB patients have BOTH  $\alpha$ -synuclein and Amyloid beta (A $\beta$ )<sup>1</sup>
  - Appx 50% of Alzheimer's patients have BOTH A $\beta$  and  $\alpha$ -synuclein<sup>2</sup>
- Zervimesine has shown protective function against  $\alpha$ -synuclein and A $\beta$



# Dementia with Lewy Bodies (DLB)

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



# 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

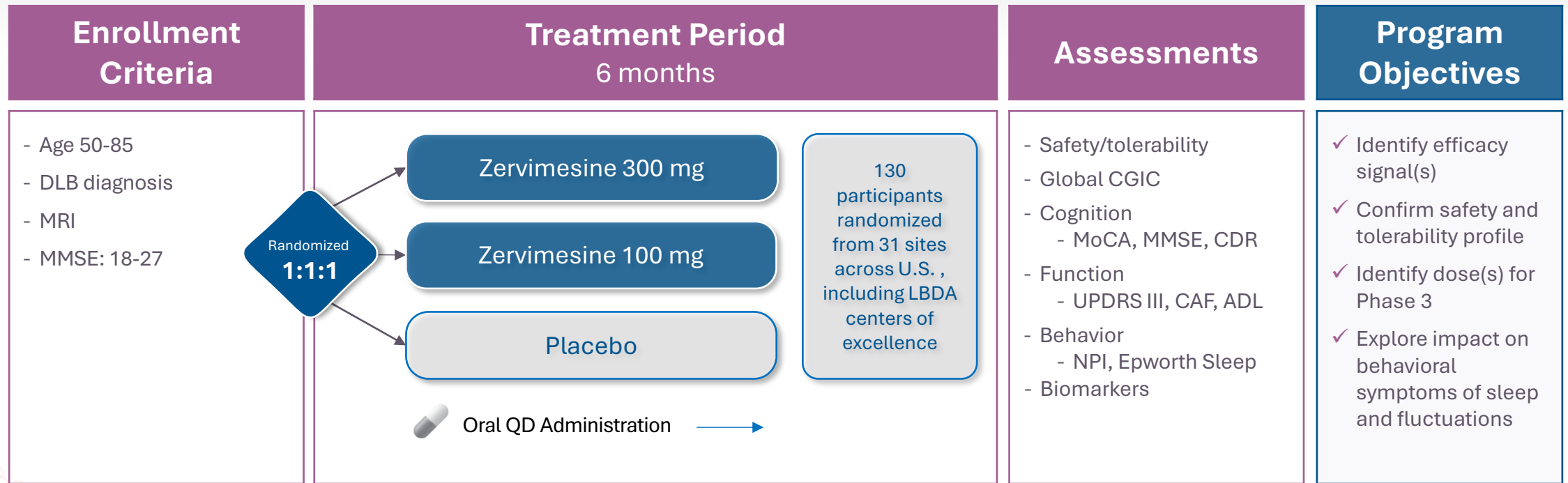
## Core Symptoms of DLB

- 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



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

# Summary of SHIMMER Safety and Tolerability findings





Favorable safety profile vs placebo, AEs well balanced between arms

- ➔ Total AE frequency was similar in CT1812 and placebo
- ➔ Most AEs were mild or moderate
- ➔ Fewer Serious AE occurred in the CT1812 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 CT1812 – 4.5%
  - 300 mg CT1812 – 9.3%
- ➔ Participants with LFT elevations  $\geq 3x$  ULN
  - 100mg CT1812 – 3
  - 300mg CT1812 – 6
  - Placebo – 0
- ➔ Most common AEs\* (other than increased LFTs) in the CT1812 group were diarrhea and abdominal discomfort

	Adverse Events	Serious AEs	Deaths <sup>†</sup>
CT1812	94.3%	10.3%	2 (2.2)%
Placebo	88.1%	19.0%	1 (2.4)%

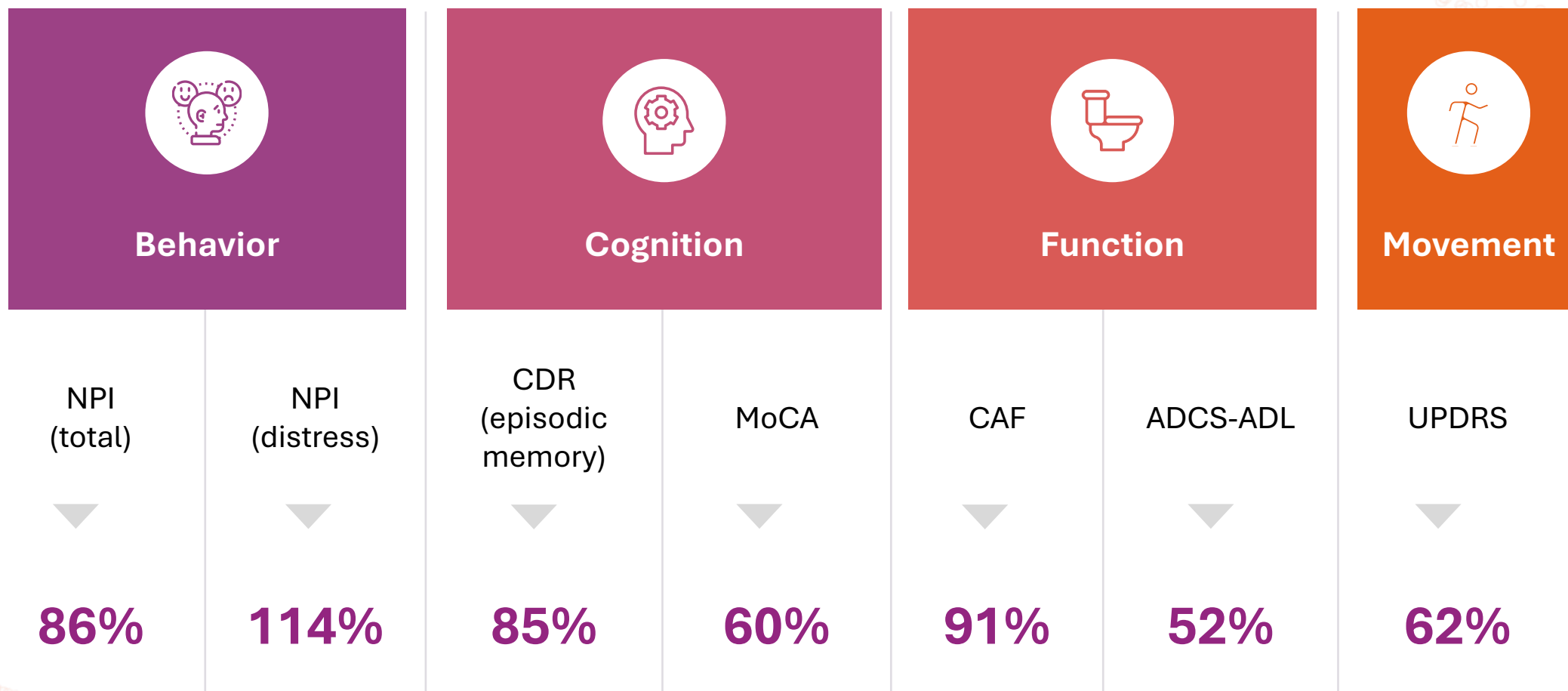
# Four Symptom Domains Drive Lewy Body Disease Burden

“A multifactorial disease with a buffet of symptoms”

	 <b>Behavior</b>	 <b>Cognition</b>	 <b>Function</b>	 <b>Movement</b>
<b>Patient symptom</b>	Hallucinations, anxiety, delusions	Memory and problem solving	Bathing, toileting, shopping, meal preparation	Standing, maintaining balance
<b>Assessment tool</b>	<ul style="list-style-type: none"><li>➔ Neuropsychiatric Inventory (NPI)</li><li>➔ Care Partner’s NPI of “Distress”</li></ul>	<ul style="list-style-type: none"><li>➔ Cognitive Drug Research (CDR) System</li><li>➔ Montreal Cognitive Assessment (MoCA)</li></ul>	<ul style="list-style-type: none"><li>➔ ADCS-Activities of Daily Living (ADL)</li><li>➔ Clinician Assessment of Fluctuation (CAF)</li></ul>	<ul style="list-style-type: none"><li>➔ MDS-Unified Parkinson’s Disease Rating Scale (UPDRS)</li></ul>

# Up to 91% Percent Slowing on Assessments

Strong clinical signals across major DLB symptoms relative to placebo



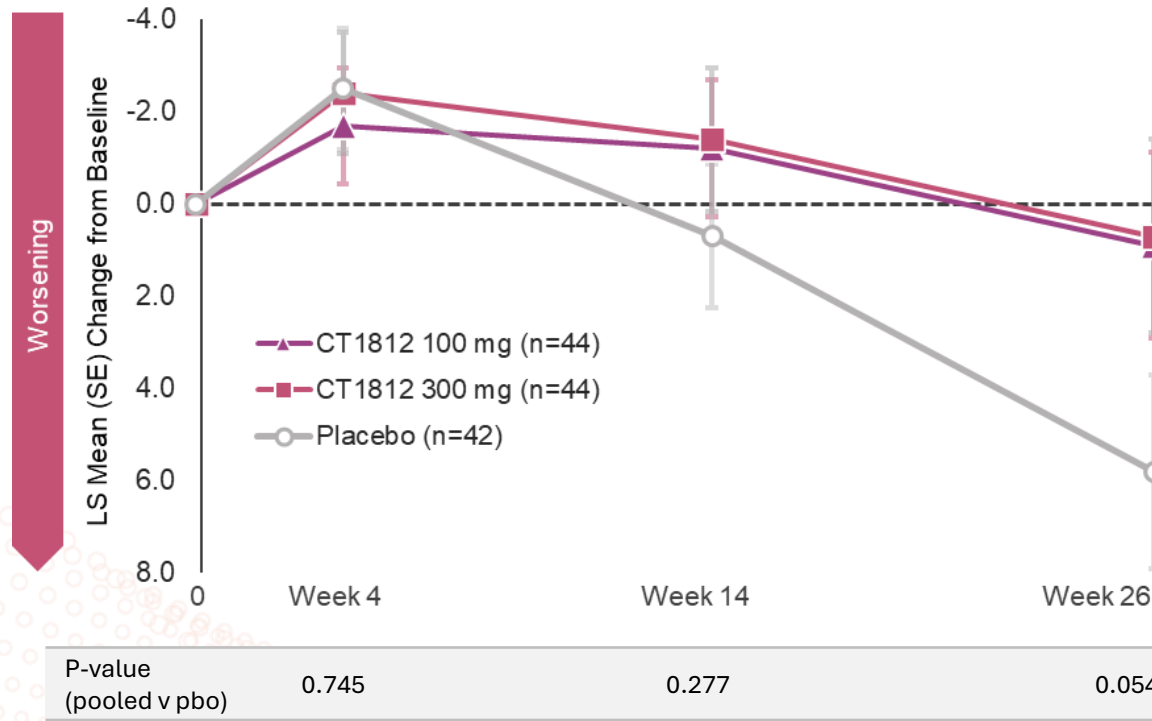
Zervimesine  
Pooled  
(100/300mg)

# Zervimesine Showed Dramatic 86% Impact on Neuropsychiatric Measures

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

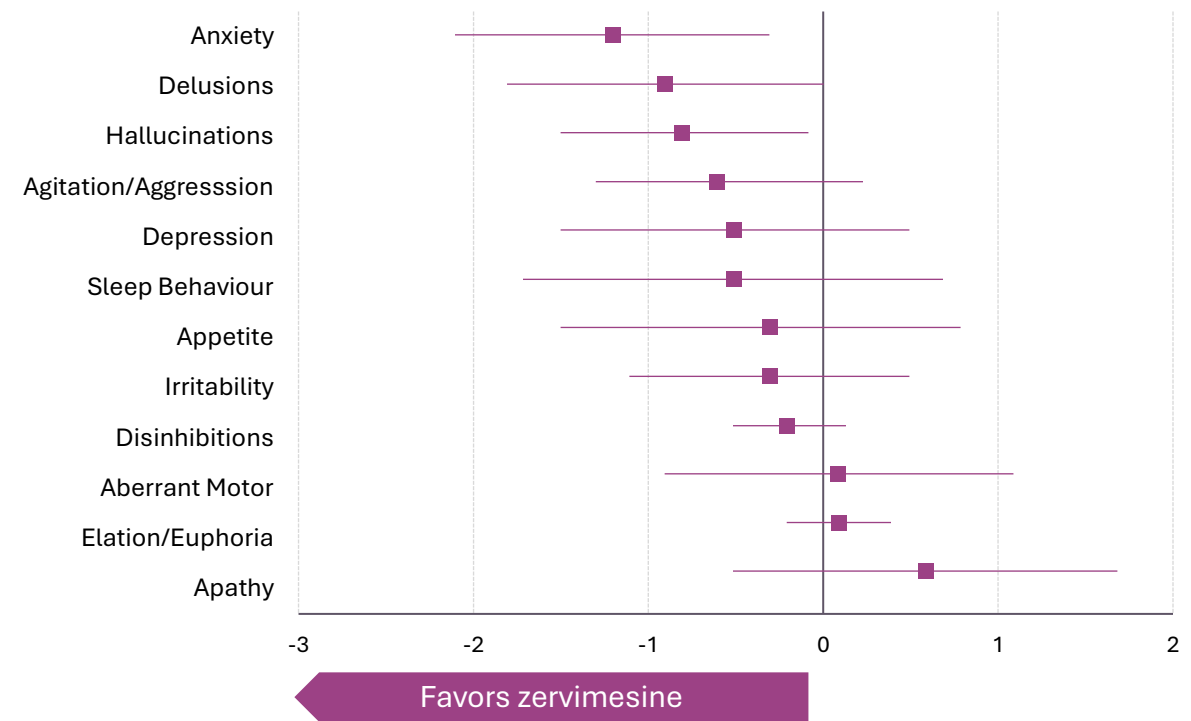
## NPI

NPI Total Score (A-L)



## NPI favor Treatment with Zervimesine

LS Mean Difference from Placebo 95% CI



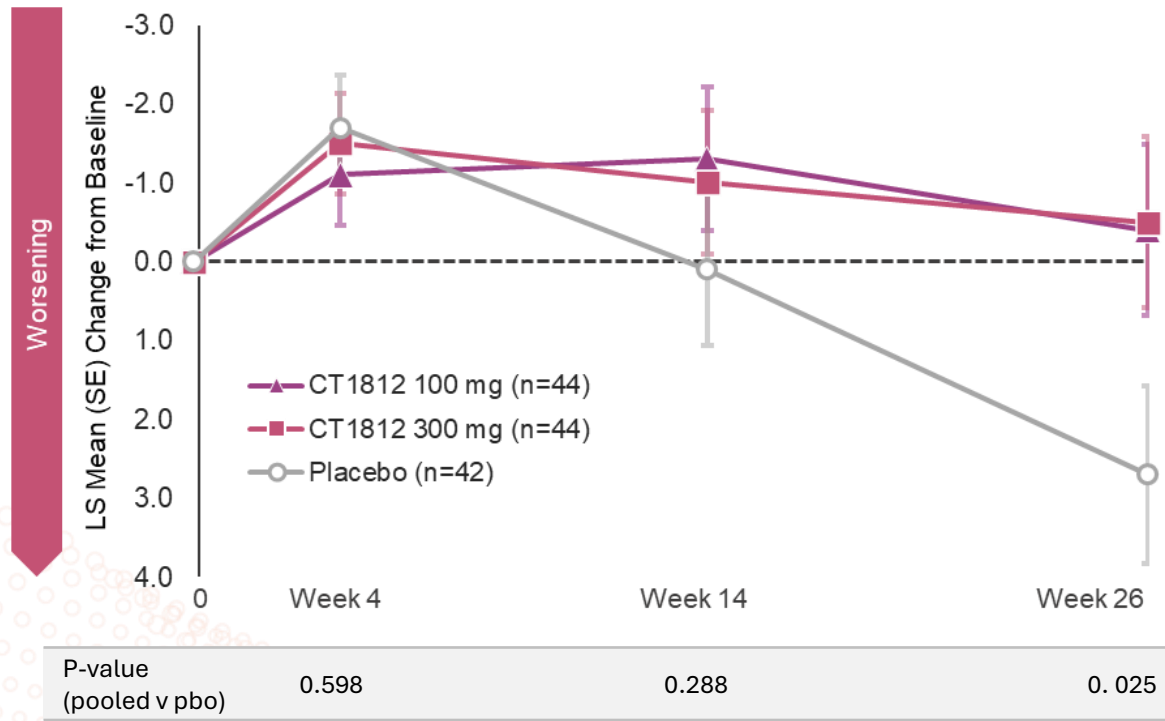
# Because Participants Improved in Hallucinations, Delusions & Anxiety, Caregivers were Notably Better

New tool created to measure caregiver burden in DLB

## NPI Distress

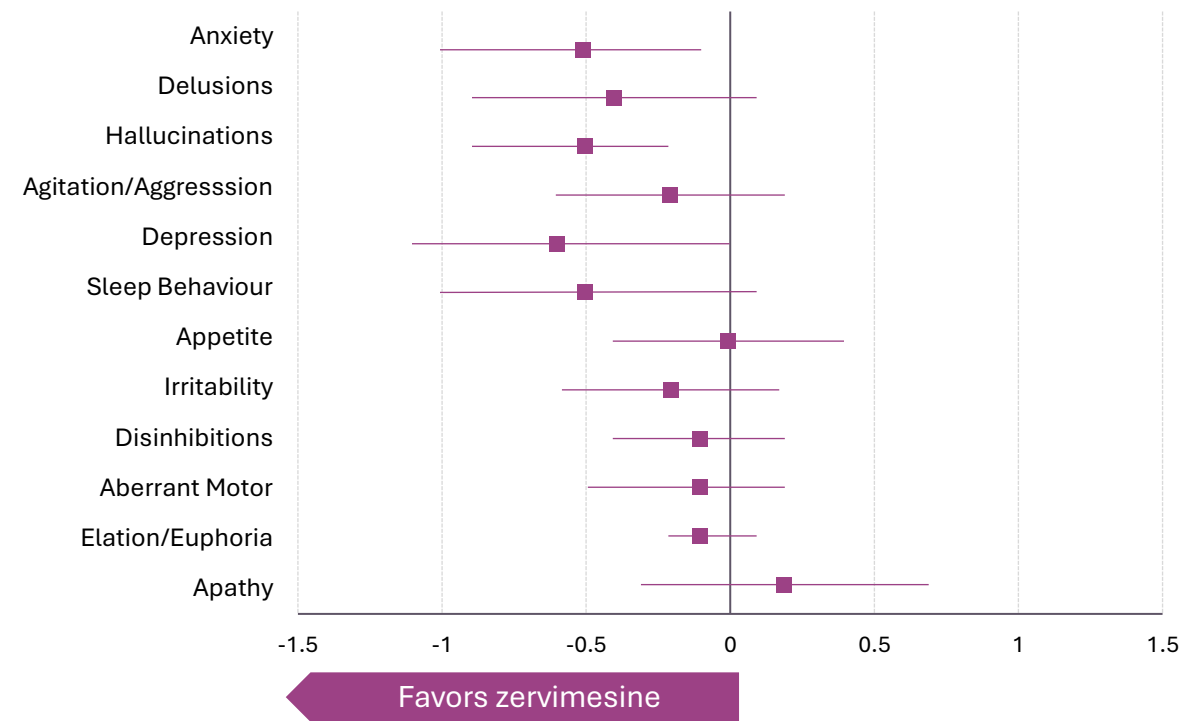
NPI Total Score (A-L) Caregiver Distress

114% Slowing



## NPI Distress favors Treatment with Zervimesine

LS Mean Difference from Placebo 95% CI

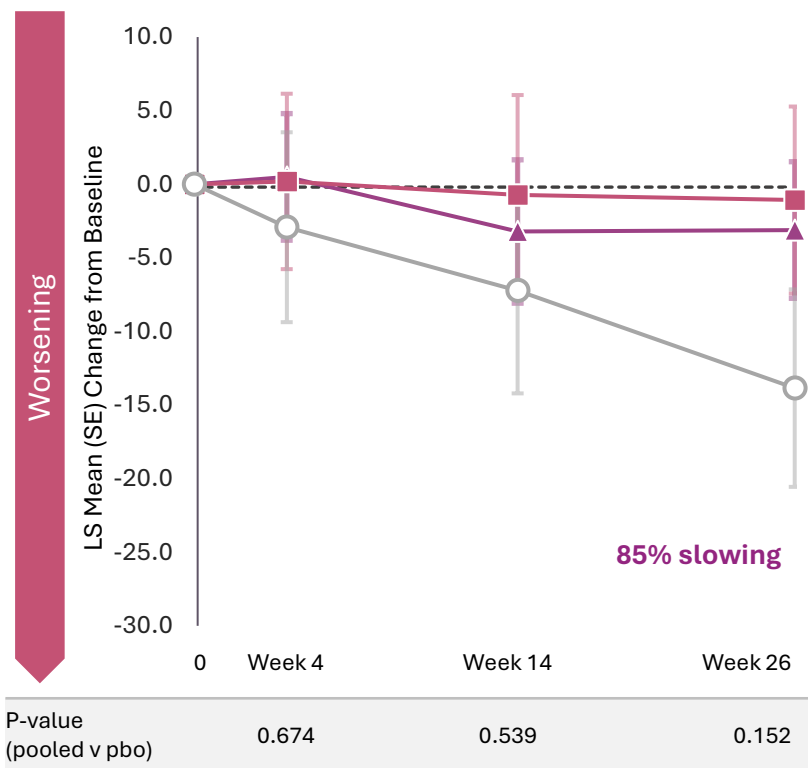


# Up to 91% Slowing of Cognitive Decline Across Assessments

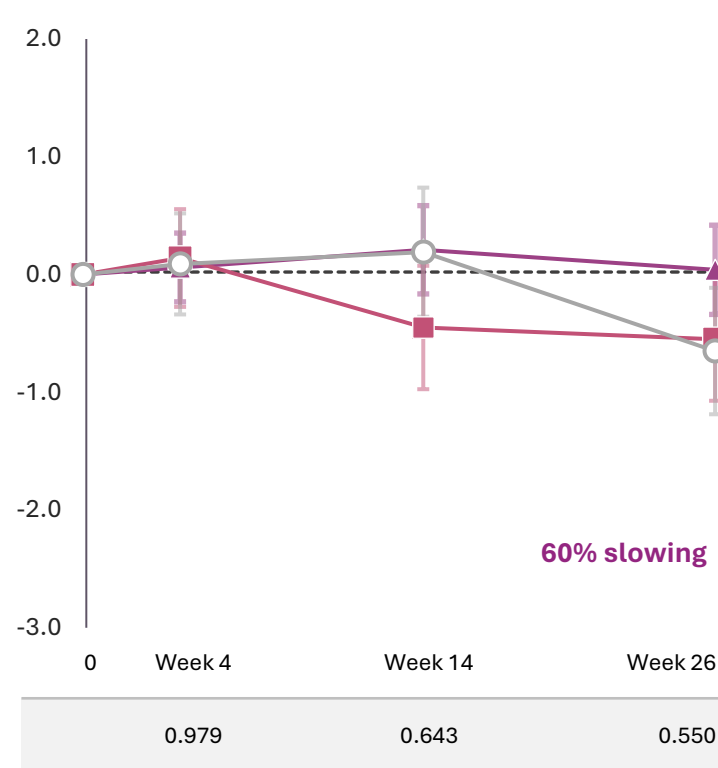
Zervimesine improved patients' attentiveness and problem solving

- CT1812 100mg (n=44)
- CT1812 300mg (n=44)
- Placebo (n=42)

### CDR - Episodic Memory (ITT)



### MoCA (ITT)



### CAF (Fluctuations) (ITT)

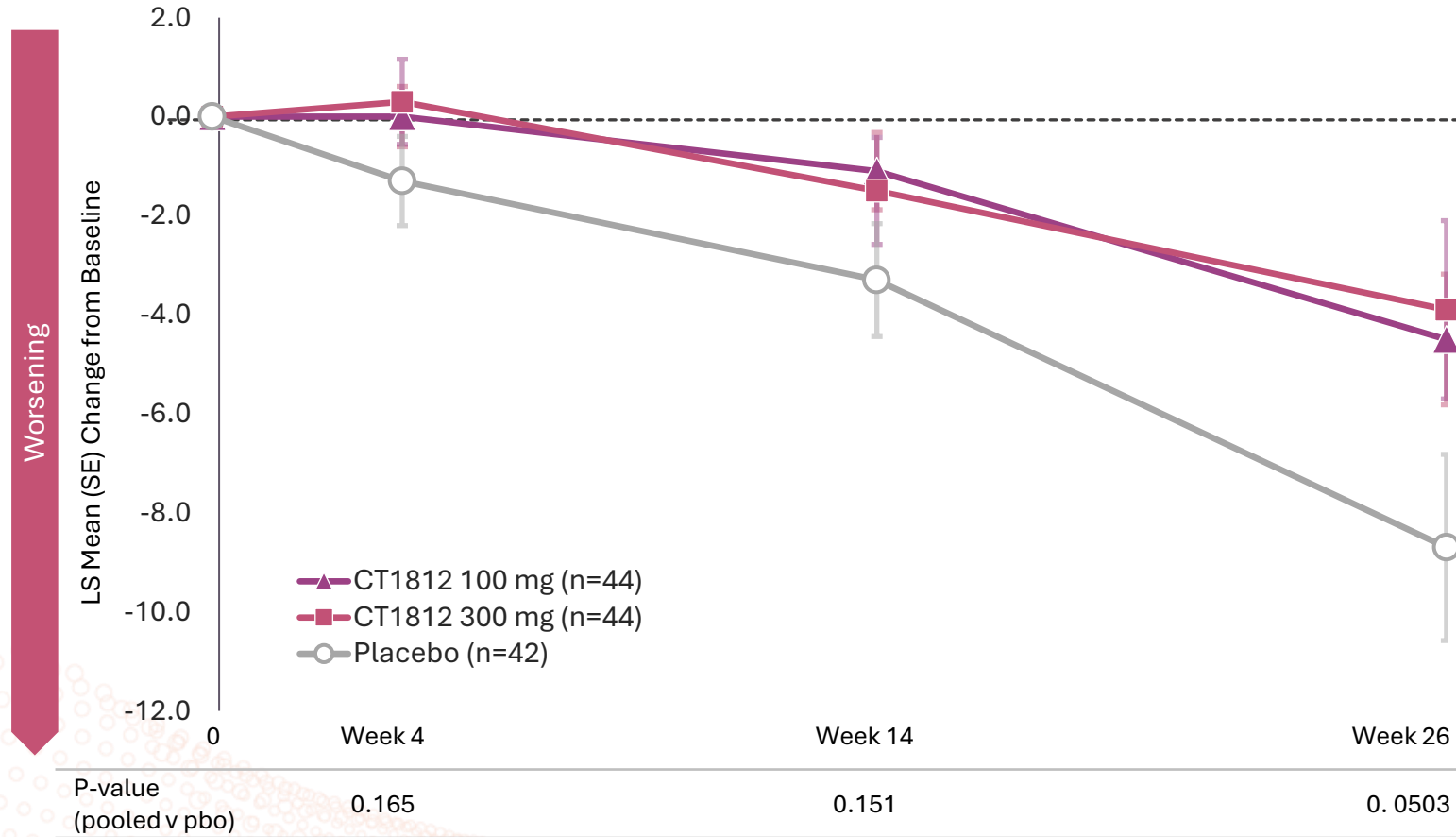


# People on Zervimesine Maintained Self-care

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

## ADCS-ADL

52% slowing



## Components of ADL Score



Bathing



Dressing



Grooming



Feeding



Toileting



Conversing



Shopping



Writing

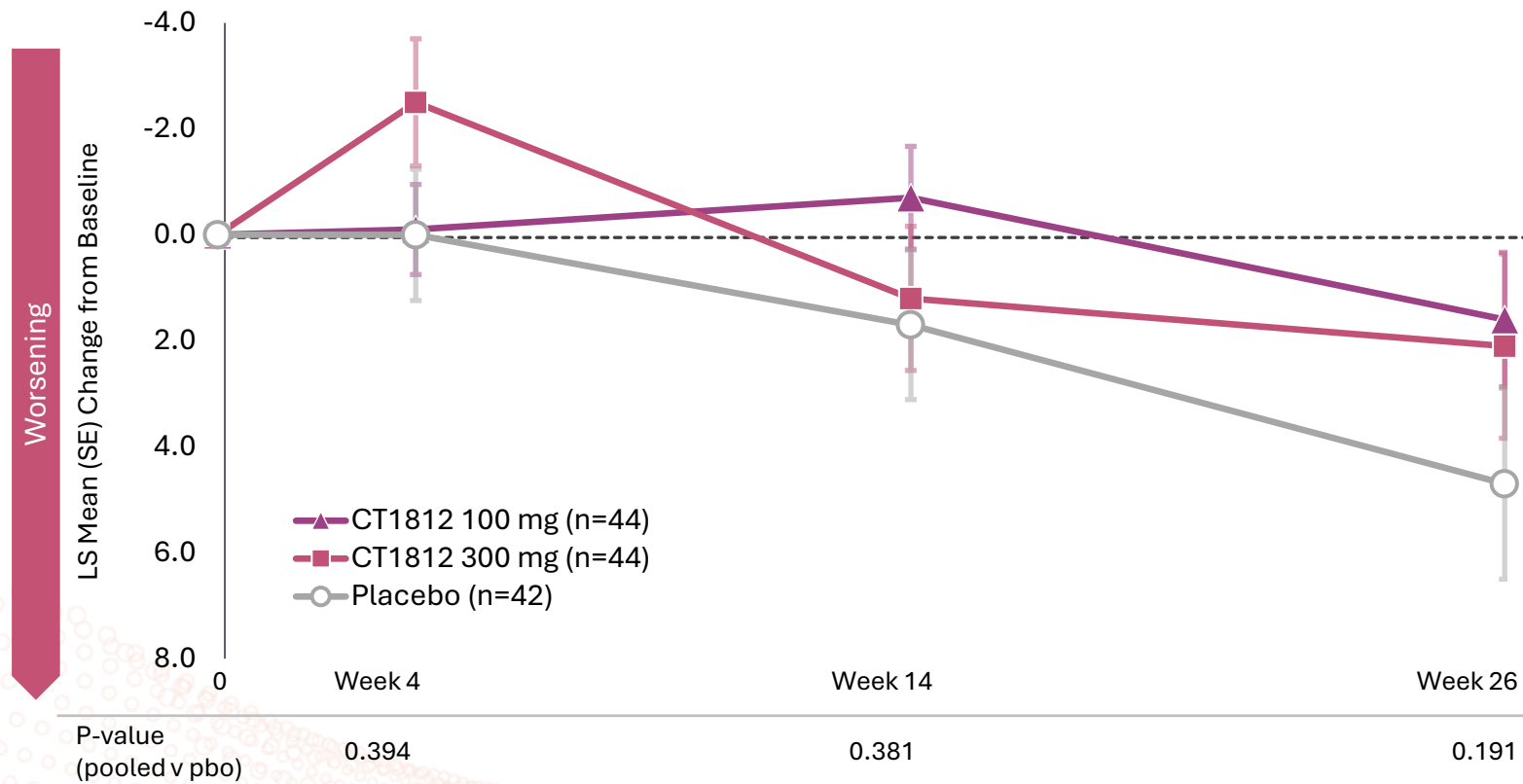


# People Treated with Zervimesine Maintained Motor Function

62% preservation in measures of movement

## MDS-UPDRS3

62% slowing



## Components of UPDRS:



Balance



Gait



Speech



Facial expression



Rigidity



Tremor

# 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

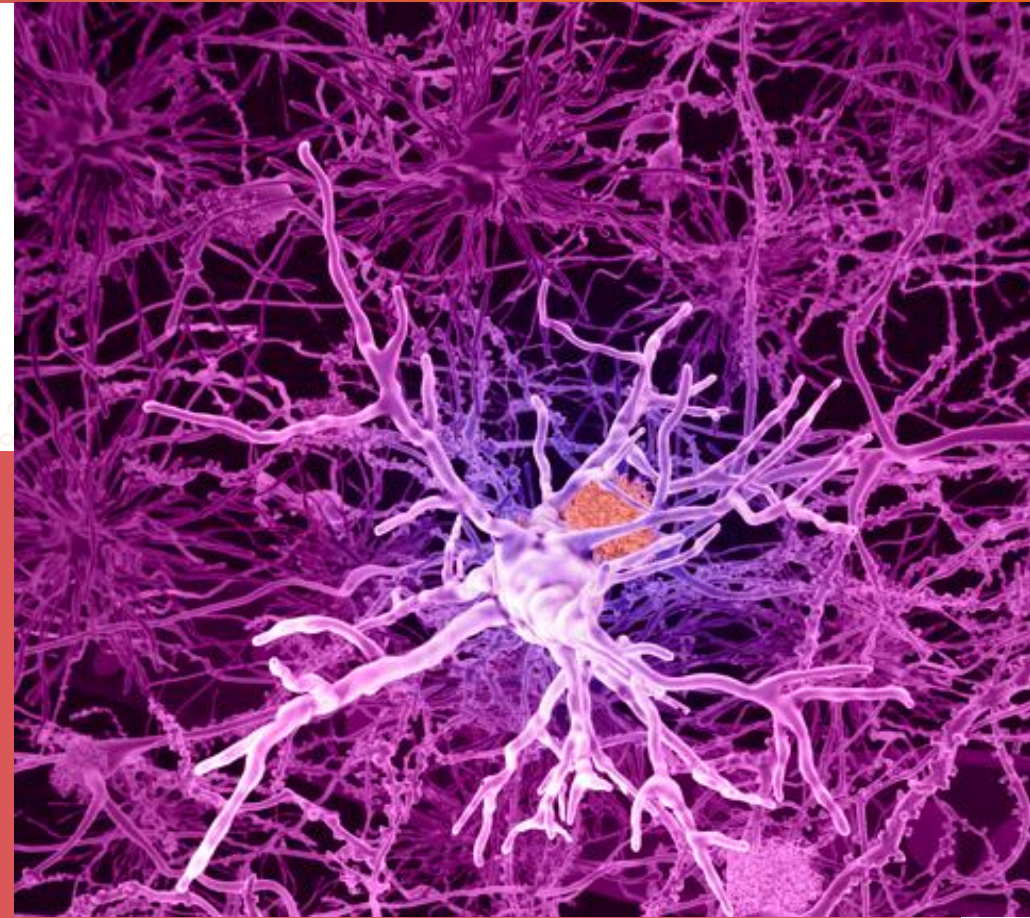
- Across Behavioral, Cognitive, Functional and Motor domains
- Treatment differences increased over 6 months



**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

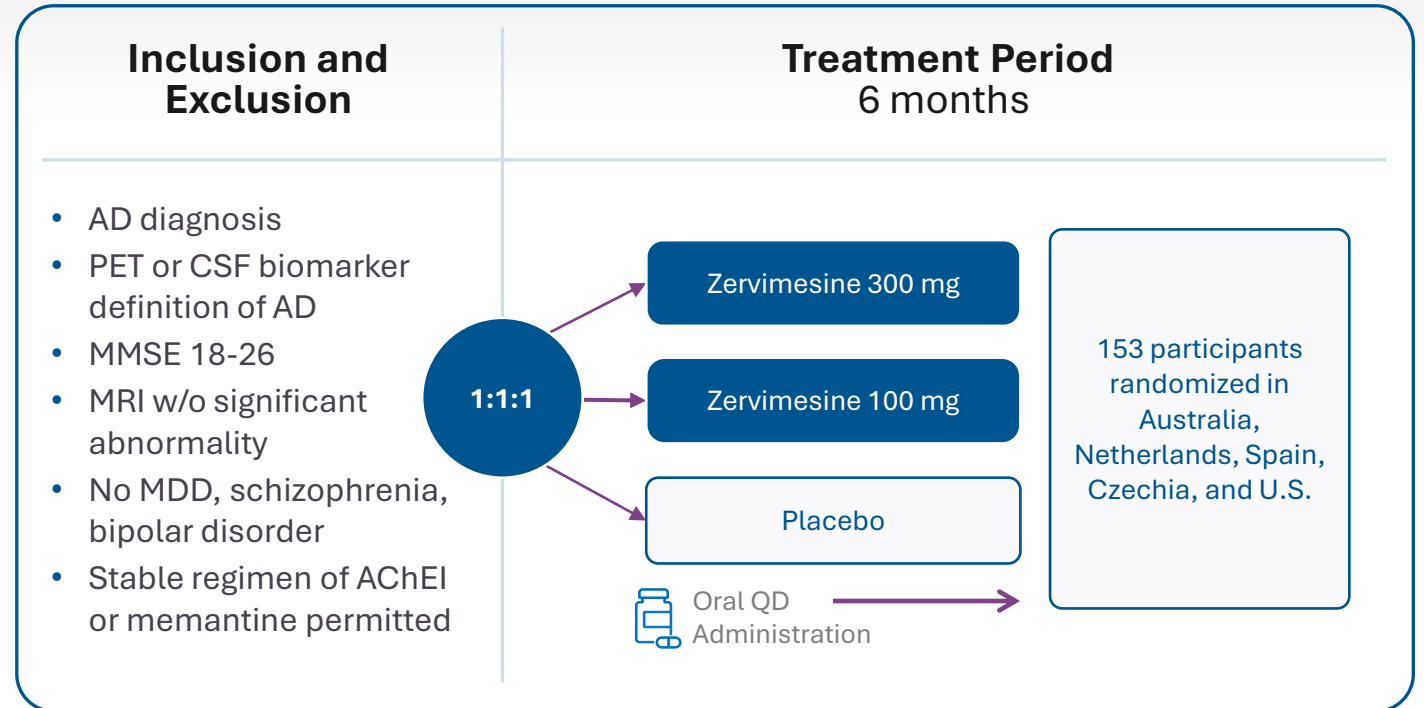


# SHINE: Phase 2 PoC in Mild-to-Moderate Alzheimer's Disease

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



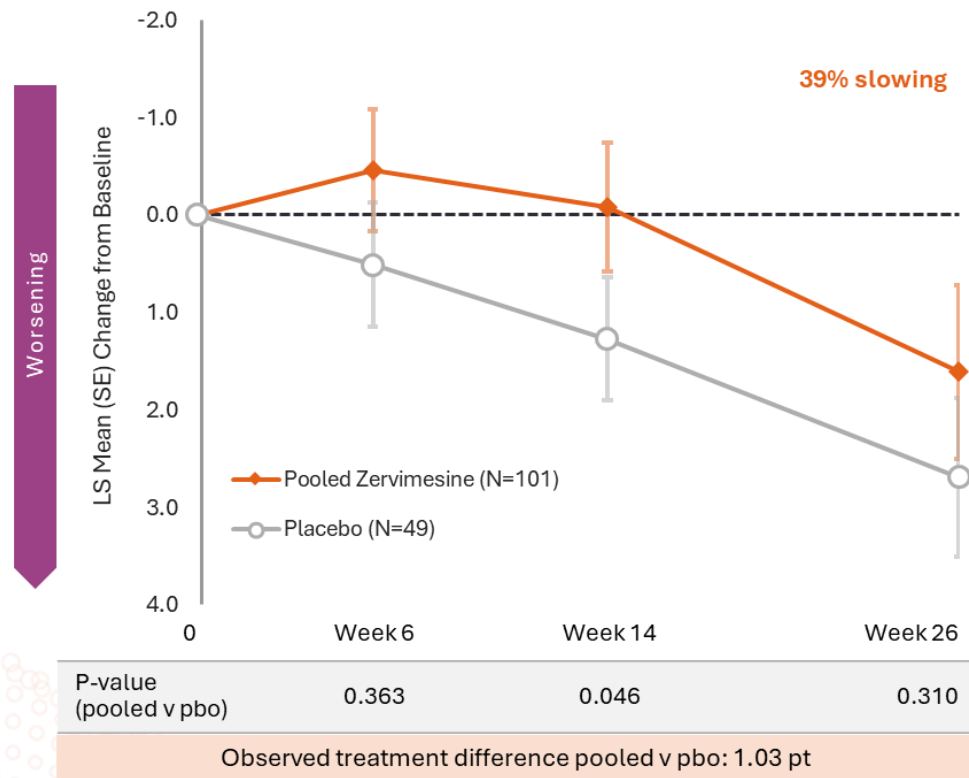
SHINE COG0201 study (NCT03507790) partially funded by \$31M NIA grant R01AG058660

**SHINE**  
COG0201

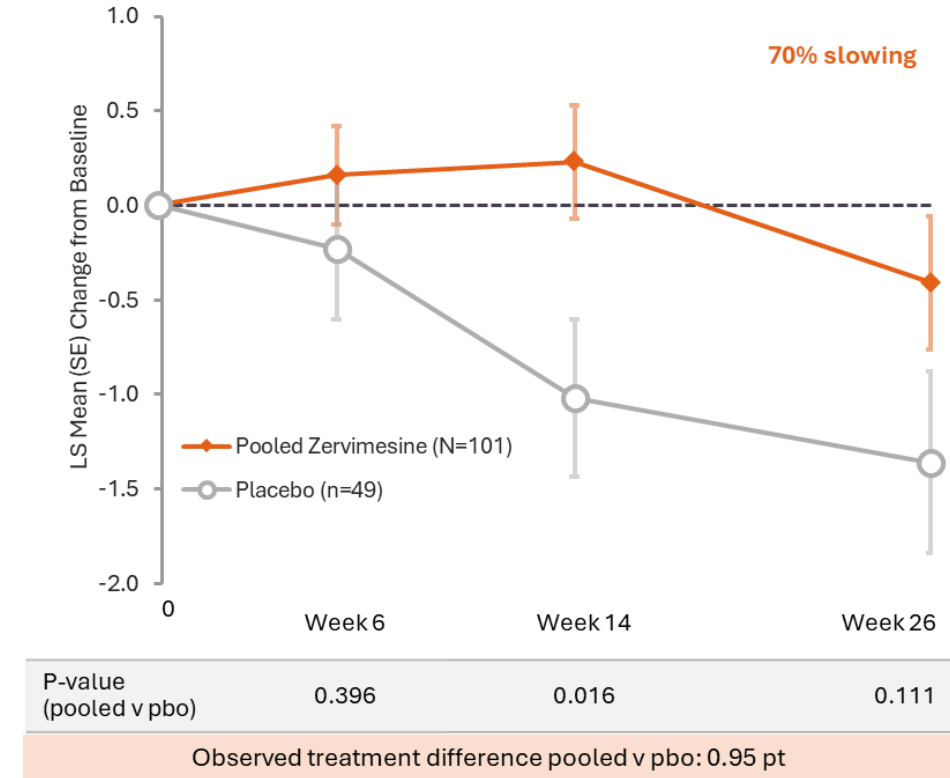
# SHINE Cognitive Endpoints: ADAS-Cog 11 and MMSE

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

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



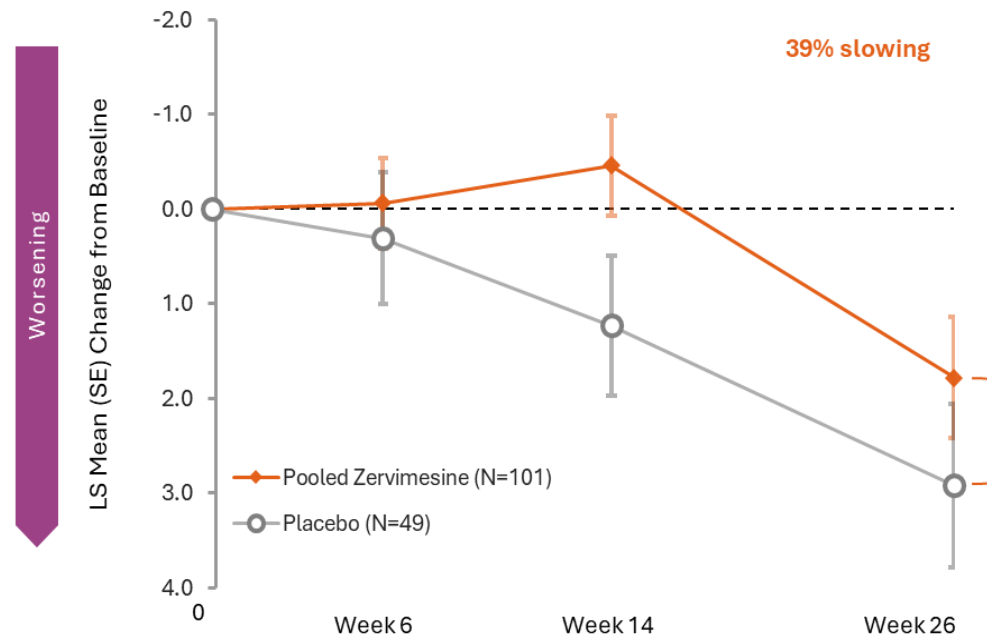
MMSE mITT population (n=150)



# SHINE Cognitive Endpoints: ADAS-Cog 13, Cognitive Composite

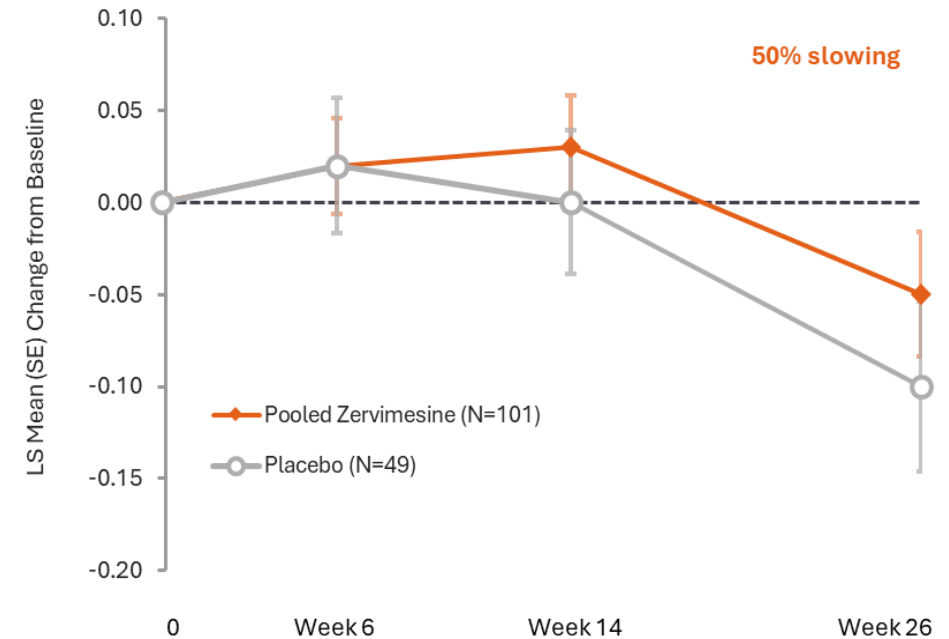
Consistent results across multiple cognitive endpoints

### ADAS-Cog 13



P-value (pooled v pbo)	0.656	0.063	0.290
Observed treatment difference pooled v pbo: 1.14 pt			

### Cognitive Composite

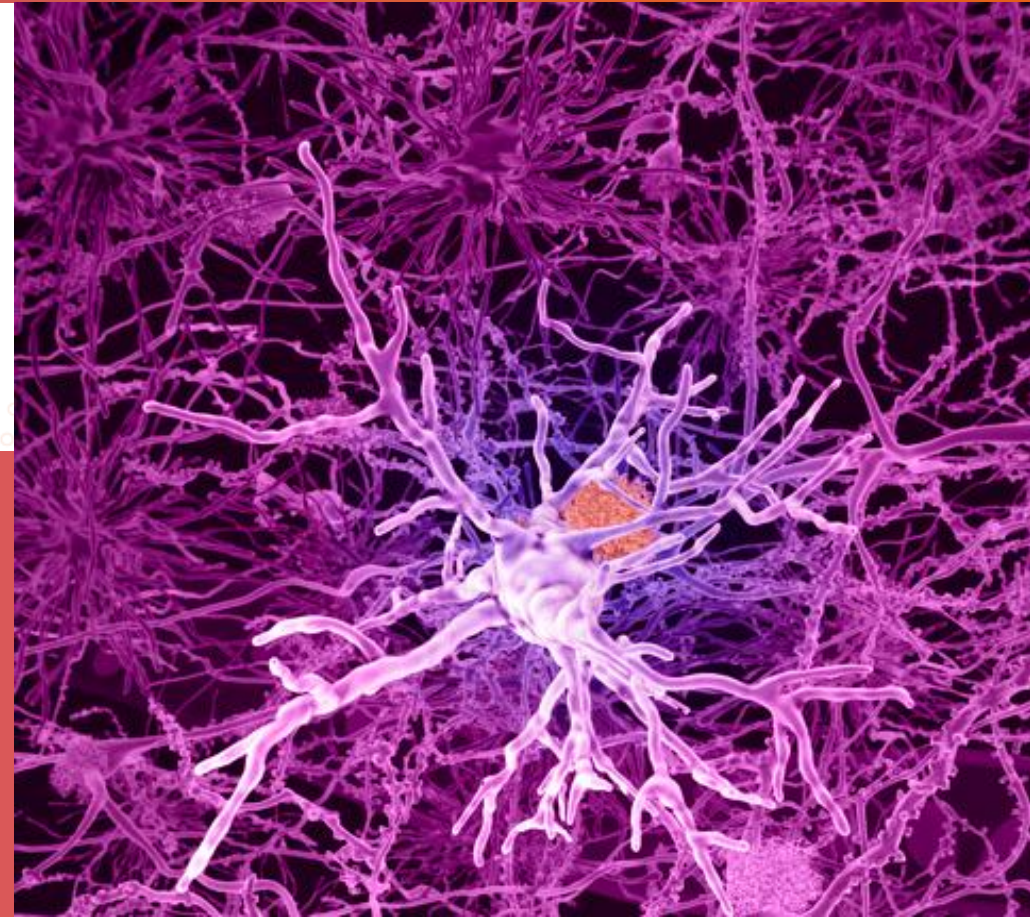


P-value (pooled v pbo)	0.913	0.502	0.364
Observed treatment difference pooled v pbo: 0.05 pt			

# 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*



# Tau Burden in Amyloid-related AD Clinical Trials

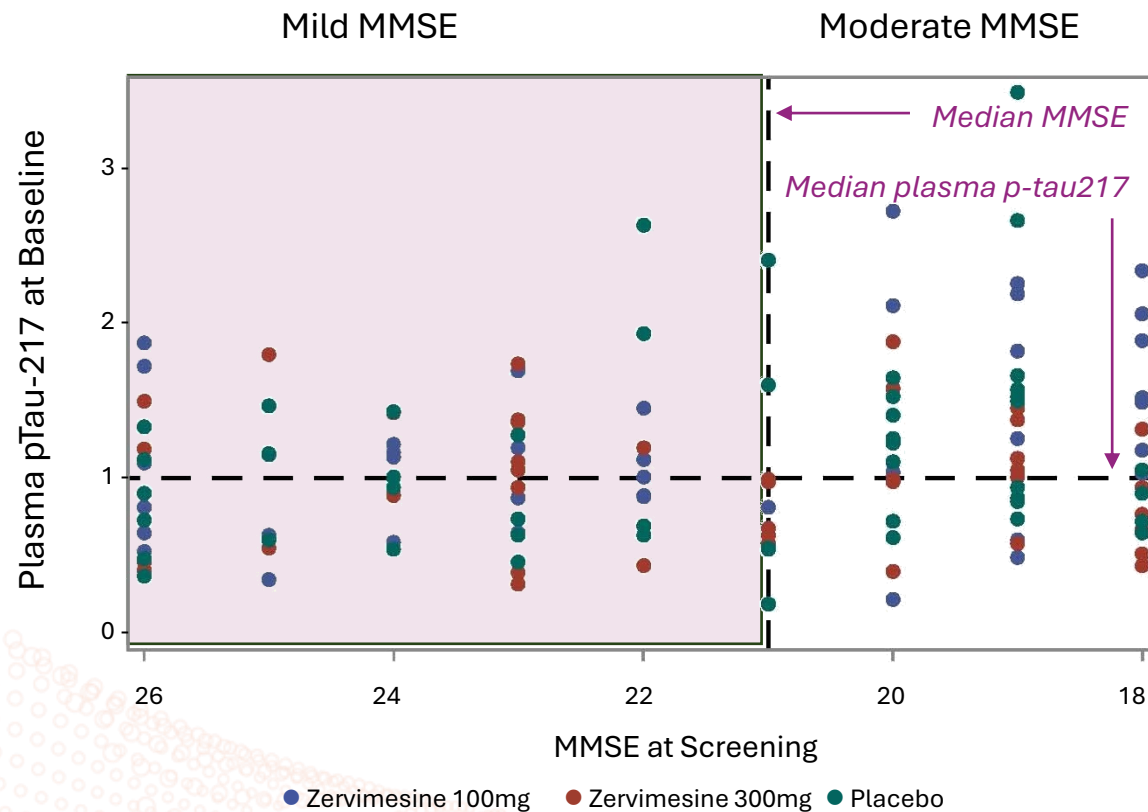
Baseline plasma p-tau217: a **predictive biomarker of response** to therapy

- 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 A $\beta$  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



# Participants Evenly Distributed by Median p-tau217 and MMSE Severity

MMSE at Screening vs p-tau217 at Baseline in SHINE



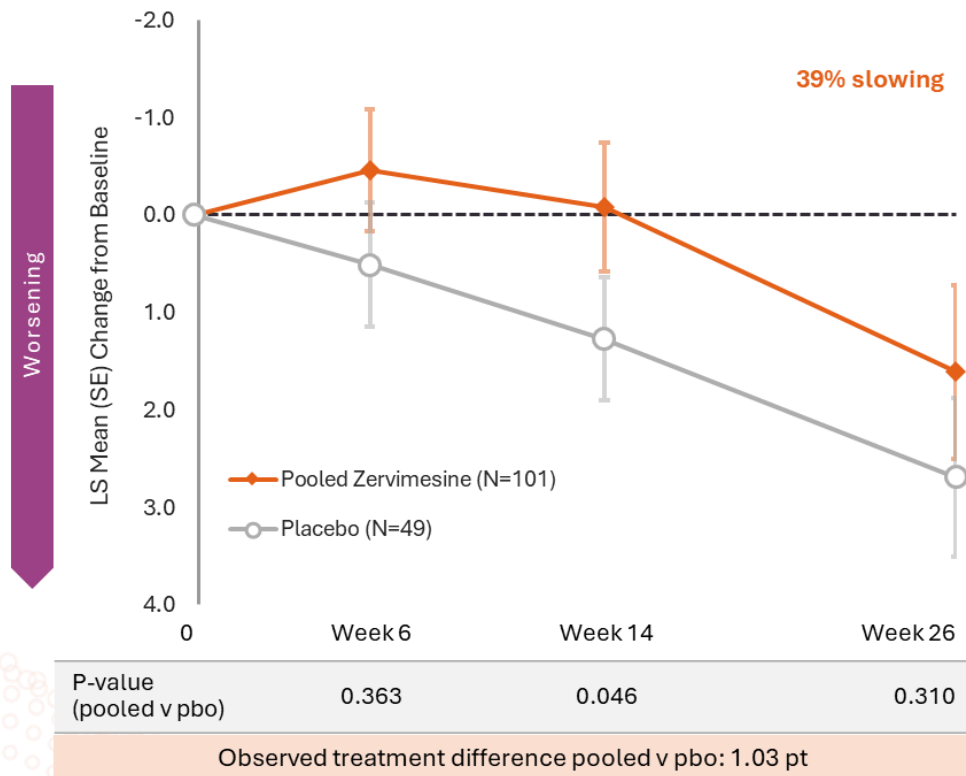
**Baseline Plasma p-tau217**

MMSE at Screening	Below Median	Above Median	Total
Mild (22-26)	35	32	67
Moderate (18-21)	34	37	71
<b>Total</b>	<b>69</b>	<b>69</b>	<b>138</b>

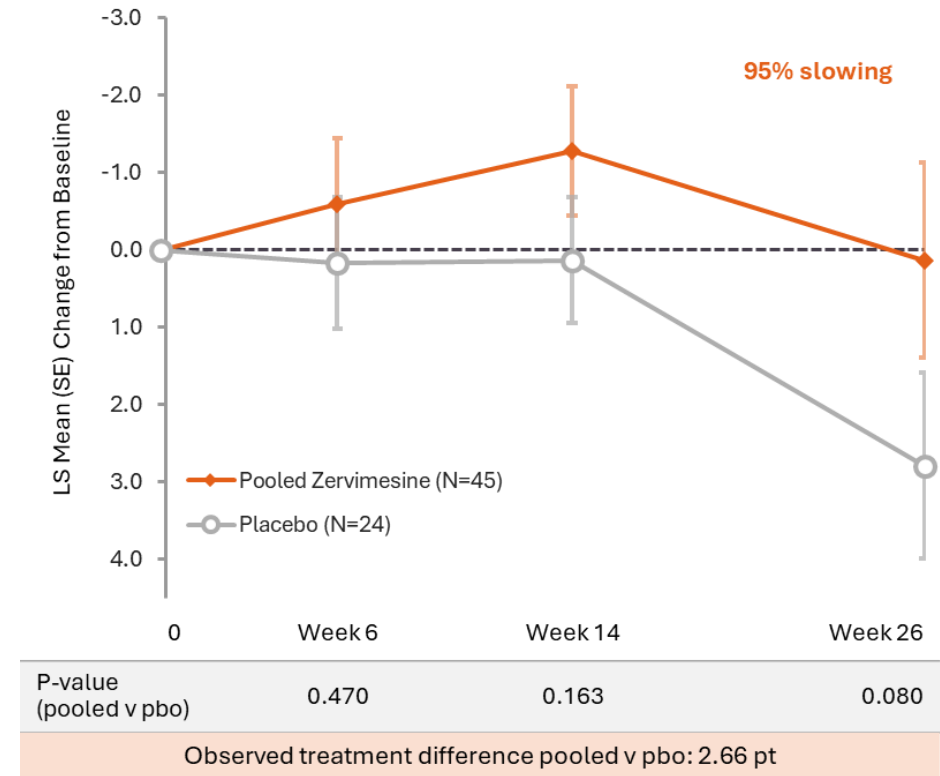
# Below Median p-tau217, Treated Participants Experienced Profound Cognitive Effect

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

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



Below median p-tau217 (n=69)



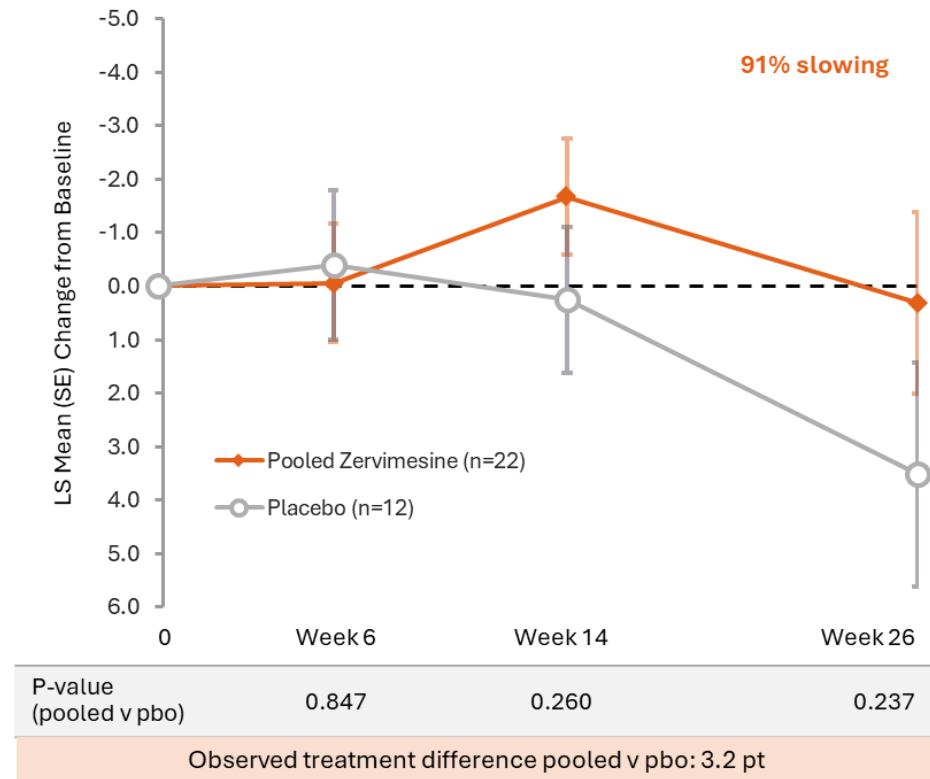
# Treatment Impact in Below Median p-tau217 Consistent Across Baseline MMSE scores

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

Zervimesine-Treated **Mild** (MMSE 22-26)



Zervimesine-Treated **Moderate** (MMSE 18-21) Participants



# 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<sup>†</sup>

Zervimesine	0
Placebo	1 (cancer)

# Zervimesine SHINE Study: Summary and Conclusions

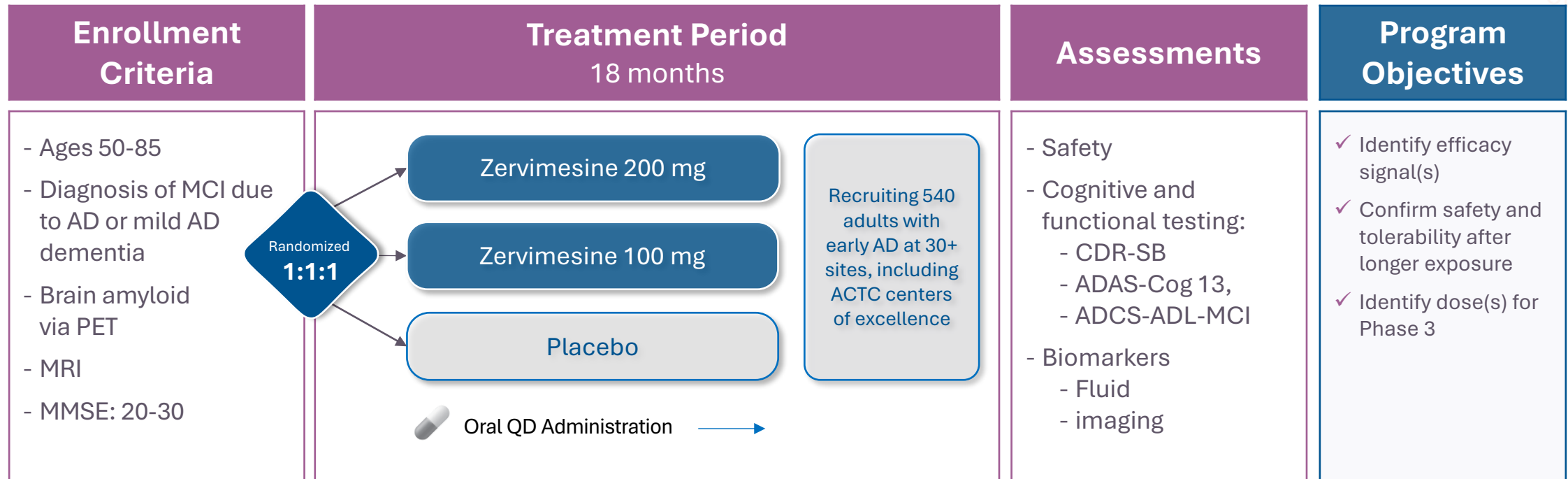
Plasma p-tau217 biomarker identifies strong zervimesine-treatment responder group

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

Next steps: Requested End-of-Phase 2 meeting with FDA to establish protocol for Phase 3 in population defined by plasma p-tau217

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

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

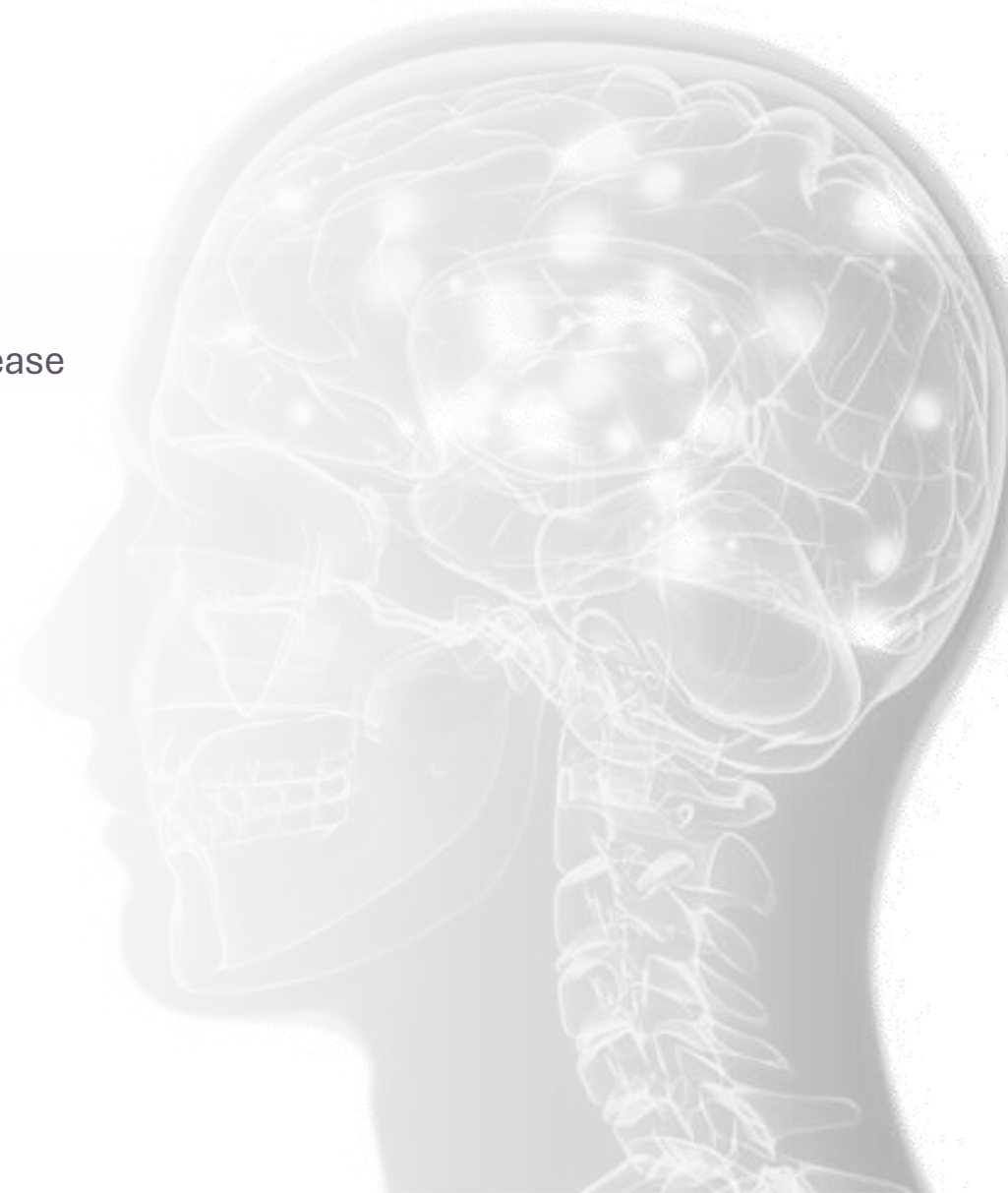


START COG0203 study (NCT05531656) partially funded by \$81M NIA grant R01AG065248

# 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



# Current Financial Position

As of quarter ended March 31, 2025

**Cash and cash equivalents** \$16.4 M

## Grant funding for zervimesine studies

Preclinical through Phase 2 ~\$171 M

Approximate funding used (\$124 M)

Remaining grant funding \$47M







# Thank You

Lisa Ricciardi  
President & CEO  
[info@cogrx.com](mailto:info@cogrx.com)

