Phase 2 Study of CT1812 in Mild-to-Moderate Dementia with Lewy Bodies: Topline Results

International Lewy Body Dementia Conference 2025
Amsterdam, The Netherlands
31 January 2025

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MILLER SCHOOL of MEDICINE

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Disclosures

Presenter Disclosures:

- Grants from the National Institutes of Health
- Consultant for Alpha Cognition, Biogen, Bristol Meyers Squibb, DiagnaMed, Eisai, Eli Lilly, GE Healthcare, Genentech, Lundbeck, Roche, and Thema Medical
- Chief Scientific Officer for Cognivue, Inc
- Clinical trial investigator with Cognition Therapeutics, CervoMed, and CND Life Sciences
- Board of Directors for the Lewy Body Dementia Association, Lewy Body Dementia Resource Center, and South Florida Chapter of the Alzheimer Association

Product Disclosure:

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

*CT1812 assigned USAN name: zervimesine

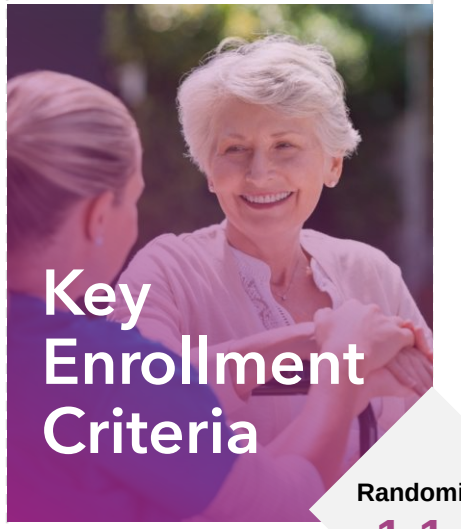
Four Symptom Domains Drive Lewy Body Disease Burden

"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)	➲ ADCS-Activities of Daily Living (ADL) ➲ Clinician Assessment of Fluctuation (CAF)	➲ MDS-Unified Parkinson's Disease Rating Scale (UPDRS)

SHIMMER Study Designed to Assess Multifactorial Burden

Conducted in Collaboration with LBDA Centers of Excellence, Academic Centers and Industry
Partially funded by NIA (R01AG071643)



- ☑ Age 50-85
- ☑ MRI
- ☑ DLB diagnosis
- ☑ MMSE: 18-27

Randomized 1:1:1

Treatment Period
6 months

130 participants randomized from 31 sites across U.S. including LBDA centers of excellence

- **CT1812 300 mg**
- **CT1812 100 mg**
- **Placebo**

Oral QD Administration

Assessments

- Safety/tolerability
- Behavior: NPI
- Cognition: MoCA, CDR
- Function: ADCS-ADL, CAF
- Motor: UPDRS III
- Epworth Sleep
- Global CGIC
- Biomarkers

Study Objectives

- Confirm safety and tolerability profile
- Explore impact on behavior, movement, cognition and function
- Identify dose(s) for Phase 3

For full details on clinicaltrials.gov: NCT05225415

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; ADCS-CGIC, Clinicians Global Impression of Change

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Patient Characteristics Consistent with Typical DLB Population

Well balanced between treatment and placebo arms

	100mg CT1812 (n=44)	300mg CT1812 (n=44)	Placebo (n=42)	Total (n=130)
Age – years*	72.6 (7.82)	72.1 (5.90)	73.7 (6.25)	72.8 (6.69)
Gender: % Male	79.5	86.4	78.6	81.5
Race: % White	95.5	88.6	90.5	91.5
Non-Hispanic or Latino %	97.7	100	92.9	96.9
MMSE*	24.6 (2.64)	23.6 (2.61)	23.8 (2.69)	24.0 (2.66)
MoCA*	19.5 (4.34)	17.8 (5.42)	17.9 (4.62)	18.4 (4.85)
CAF*	4.8 (3.75)	5.9 (3.43)	4.2 (3.41)	5.0 (3.58)
MDS-UPDRS III*	29.2 (13.93)	25.4 (12.95)	28.1 (13.41)	27.6 (13.43)
ADCS-ADL*	62.7 (10.33)	60.7 (12.85)	63.3 (9.77)	62.2 (11.04)
Alpha Syn Skin Biopsy Positive %	86.4	79.5	73.8	80.0
Amyloid positivity (APS2) %	27.3	25.0	35.7	29.2
AChE inh or memantine %	81.8	81.8	83.3	82.3
Dopaminergic agents %	34.1	31.8	45.2	36.9

*Means (SD)

Participant Disposition

293 Screened

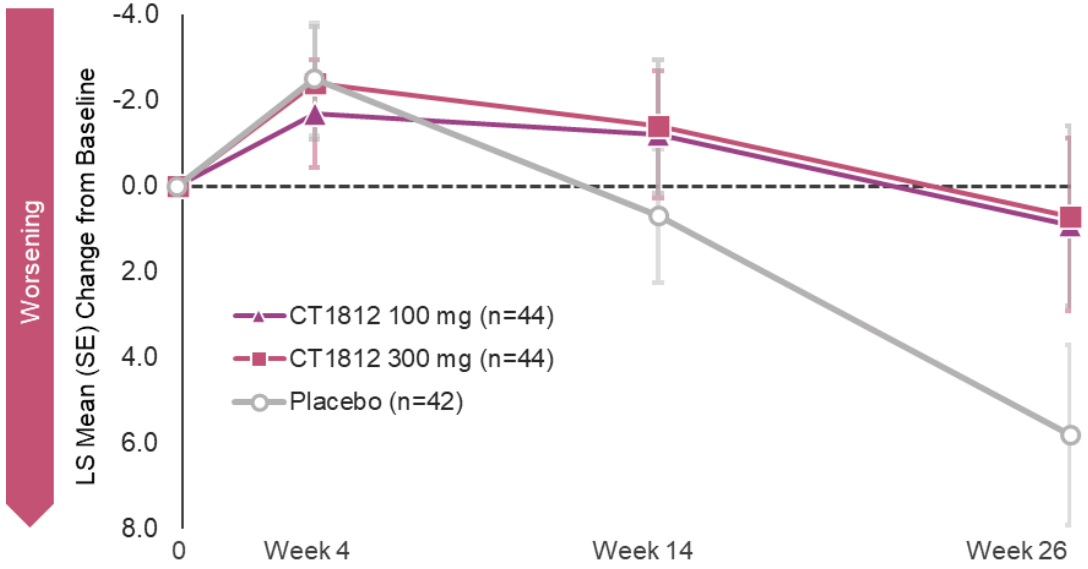
130 Randomized

44 Randomized to 100mg CT1812	**44 Randomized** to 300mg CT1812	**42 Randomized** to placebo
40 Completed study	**33 Completed study**	**36 Completed study**
4 Discontinued Tx ➲ 4 (9.1%) DC due to AE	**11 Discontinued Tx** ➲ 9 (20.5%) DC due to AE ➲ 2 (4.6%) Withdrawal	**8 Discontinued Tx** ➲ 5 (11.9%) DC due to AE ➲ 3 (7.1%) Withdrawal
Analysis populations	**Analysis populations**	**Analysis populations**
➲ ITT: 44 ➲ Safety: 44	➲ ITT: 44 ➲ Safety: 43	➲ ITT: 42 ➲ Safety: 42

CT1812 Showed 86% Impact on Neuropsychiatric Measures

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

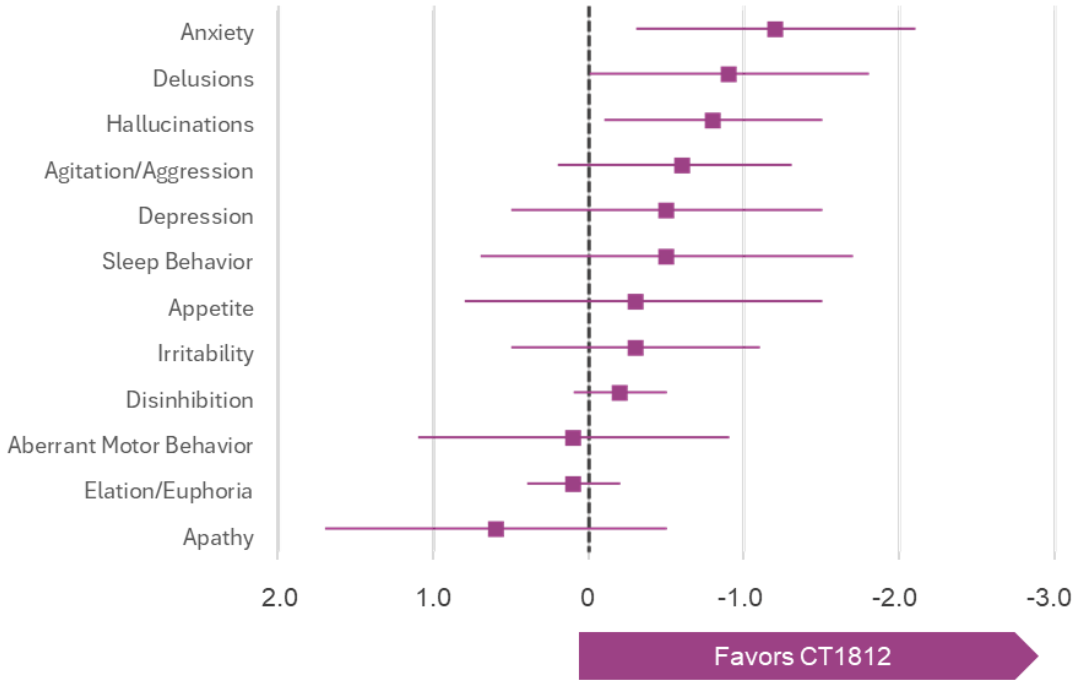
NPI Total Score (A-L)



P-values			
100mg v pbo	0.642	0.361	0.097
300mg v pbo	0.918	0.326	0.093

NPI Favors Treatment with CT1812

LS Mean (SE) Difference from Placebo (95% CI)



NPI: Neuropsychiatric inventory

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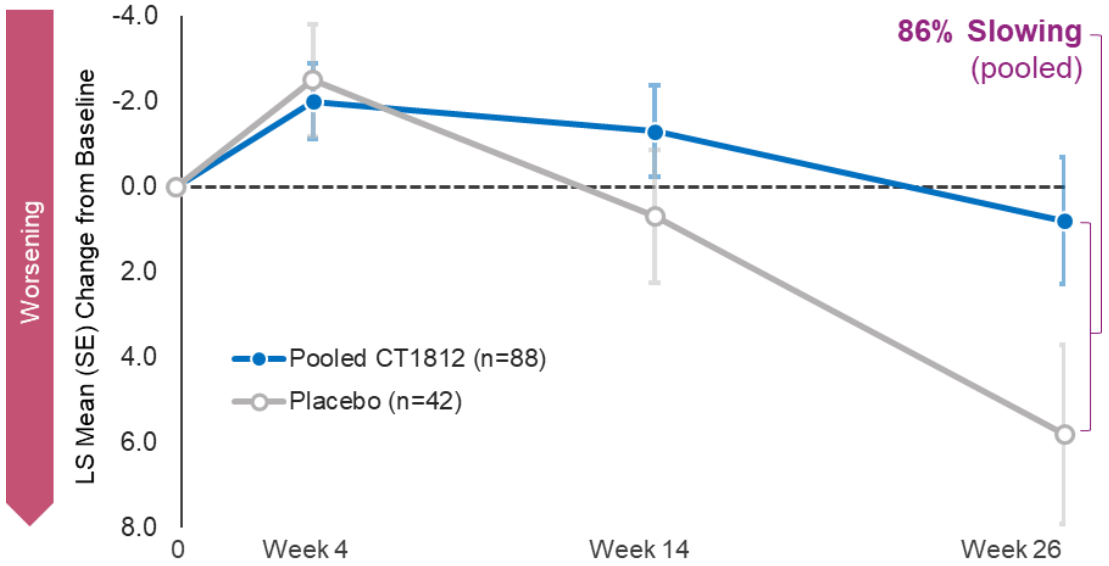
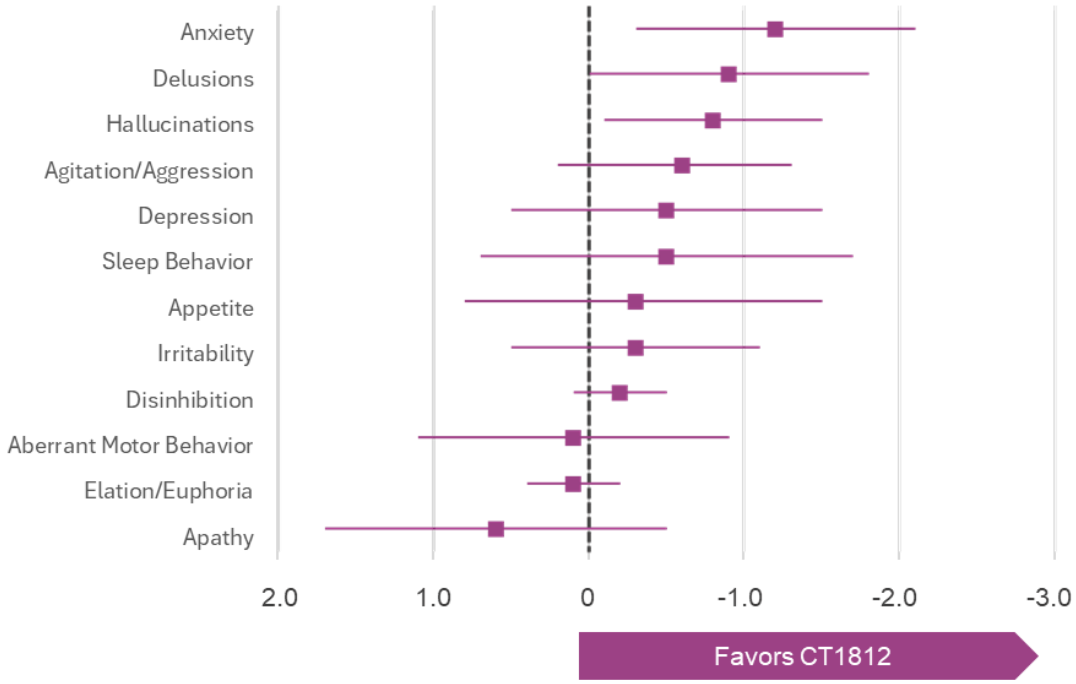


P-values

100mg v pbo	0.642	0.361	0.097
300mg v pbo	0.918	0.326	0.093
pooled v pbo	0.745	0.277	0.055

NPI Favors Treatment with CT1812

LS Mean (SE) Difference from Placebo (95% CI)



NPI: Neuropsychiatric inventory

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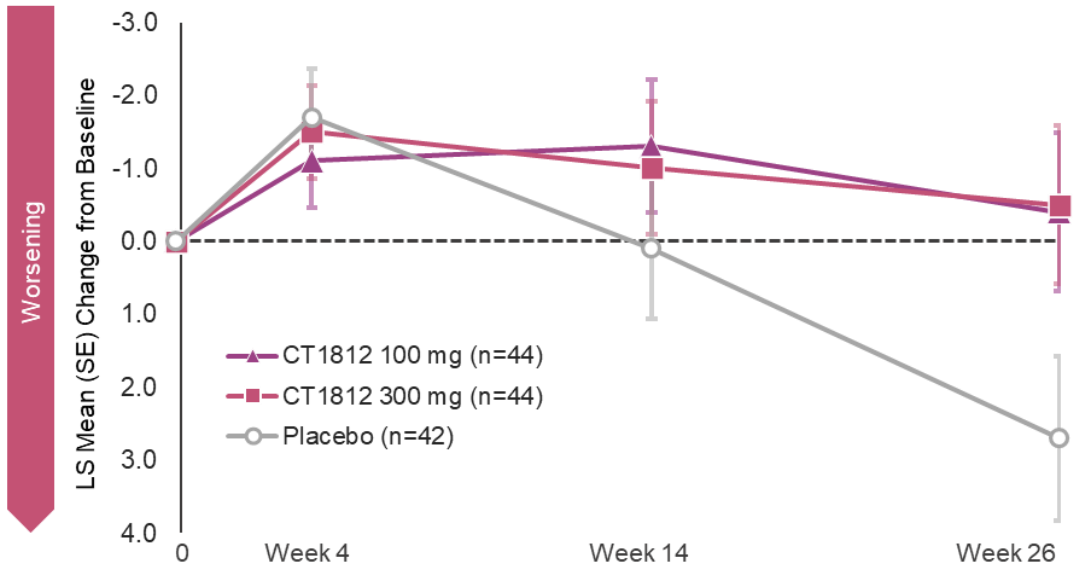
CT1812 Reduced Caregiver Distress

‘NPI Distress’ measures levels of care partner distress in DLB (p=0.025)

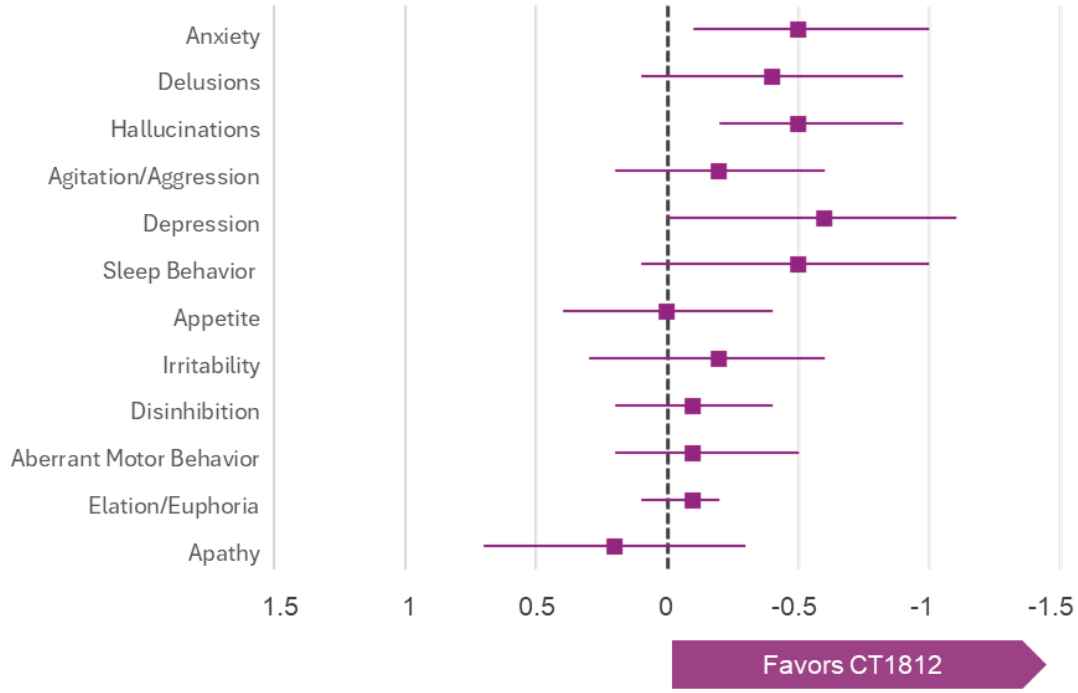
NPI A-L Distress: Caregiver Distress



P-values			
100mg v pbo	0.505	0.302	0.051
300mg v pbo	0.800	0.410	0.053

NPI *Distress* Favors Treatment with CT1812

LS Mean (SE) Difference from Placebo (95% CI)

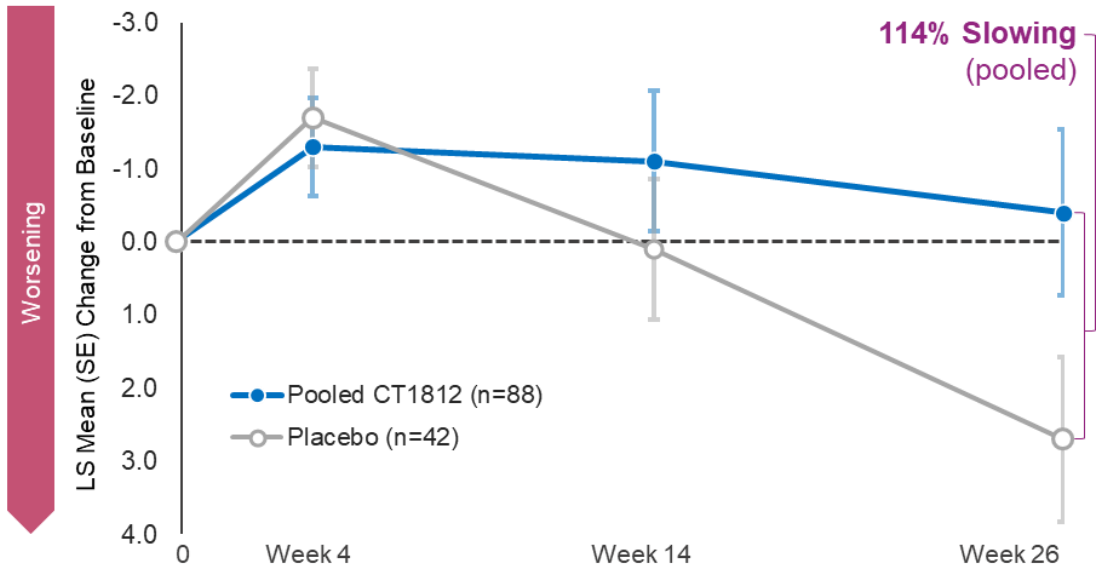


COGNITION Therapeutics

CT1812 Reduced Caregiver Distress

‘NPI Distress’ measures levels of care partner distress in DLB (p=0.025)

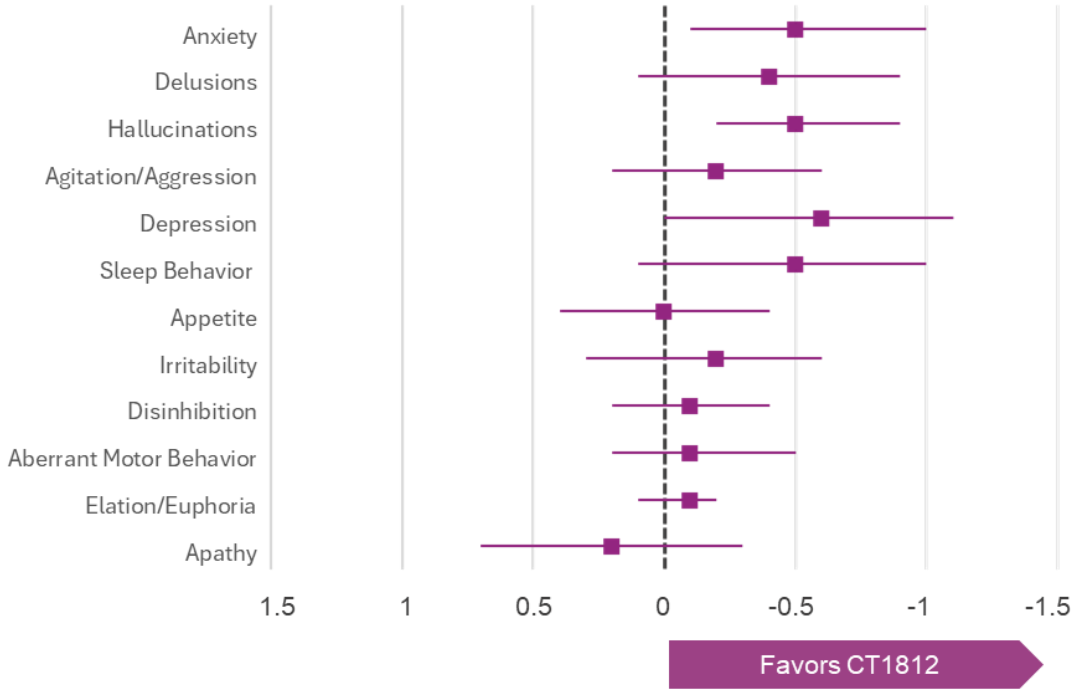
NPI A-L Distress: Caregiver Distress



P-values			
100mg v pbo	0.505	0.302	0.051
300mg v pbo	0.800	0.410	0.053
pooled v pbo	0.598	0.288	0. 025

NPI *Distress* Favors Treatment with CT1812

LS Mean (SE) Difference from Placebo (95% CI)



NPI Distress: Neuropsychiatric inventory (Care Partner Distress)

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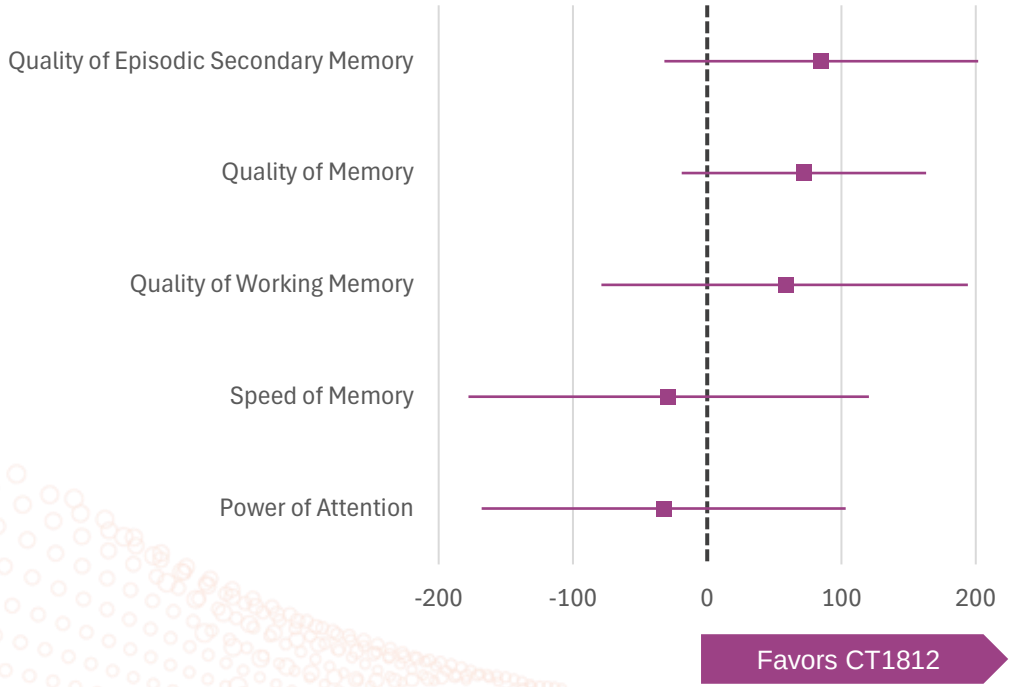
CDR Memory-related Item Scores Reflect Improvements in Factors Identified as Important in Patients with DLB*

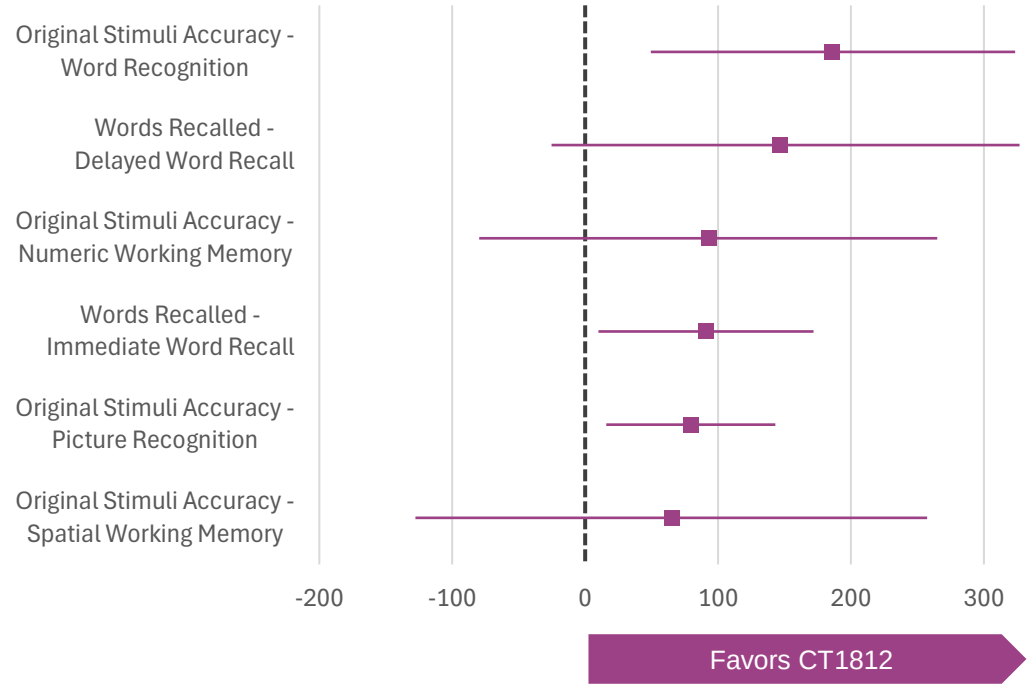
Improved memory accuracy for word recall, picture recognition and working memory

Pooled CT1812 (100mg + 300mg) vs. Placebo (ITT)

Percent Slowing for 5 Composites Relative to Placebo (95% CI)



Percent Slowing for CDR Memory-related Items Relative to Placebo (95% CI)



* Wesnes KA et al. *Dement Geriatr Cogn Disord* 2002;13:183–192 doi.org/10.1159/000048651

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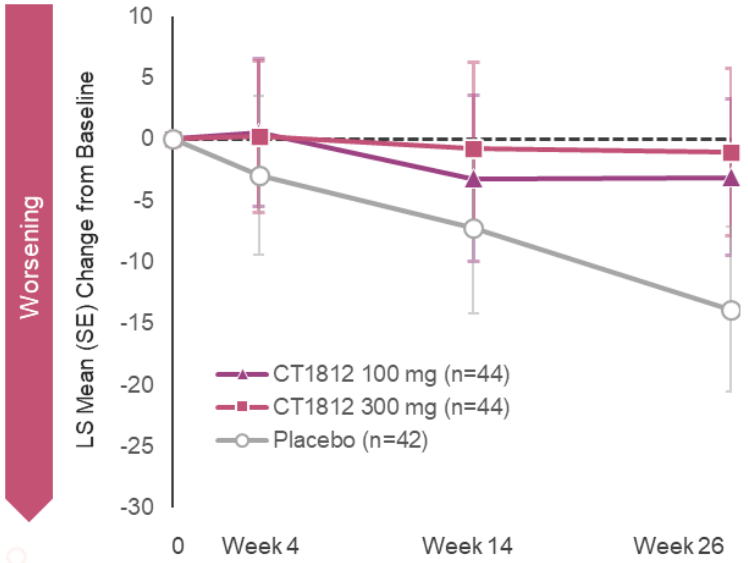
Up to 85% Slowing of Decline Across CDR Domains

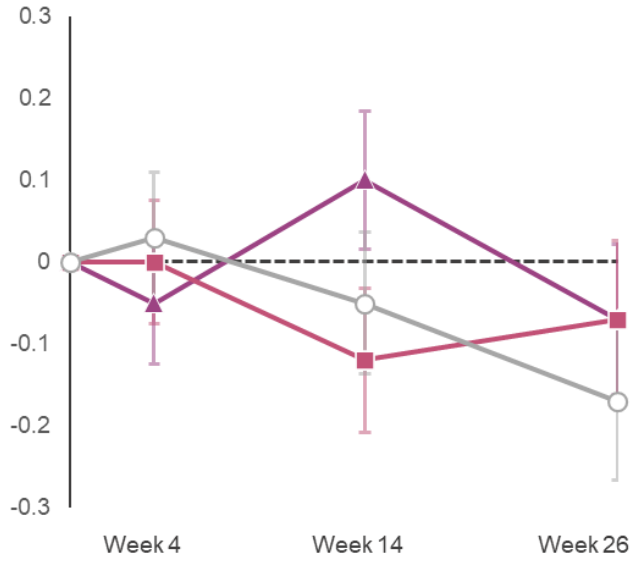
CT1812 improved patients' attentiveness and problem solving

CDR – Quality of Episodic 2° Memory (ITT)



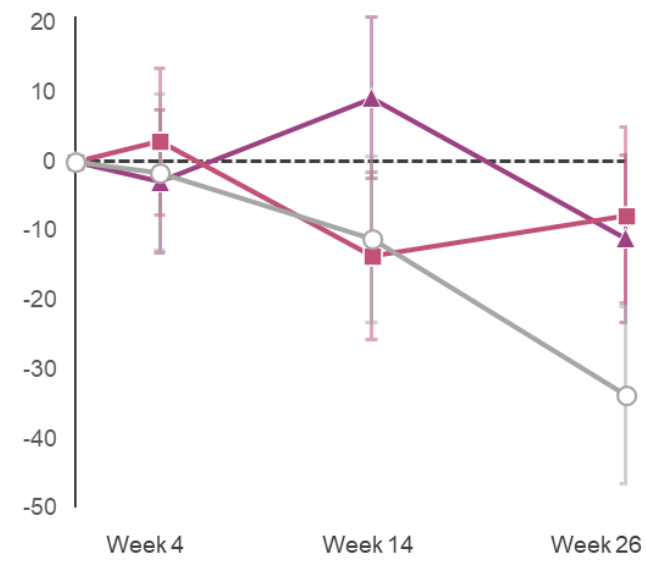
P-values			
100mg v pbo	0.698	0.682	0.248
300mg v pbo	0.728	0.513	0.183

CDR – Quality of Working Memory (ITT)



0.436	0.205	0.471
0.786	0.563	0.464

CDR – Quality of Memory (ITT)



0.931	0.224	0.201
0.773	0.887	0.153

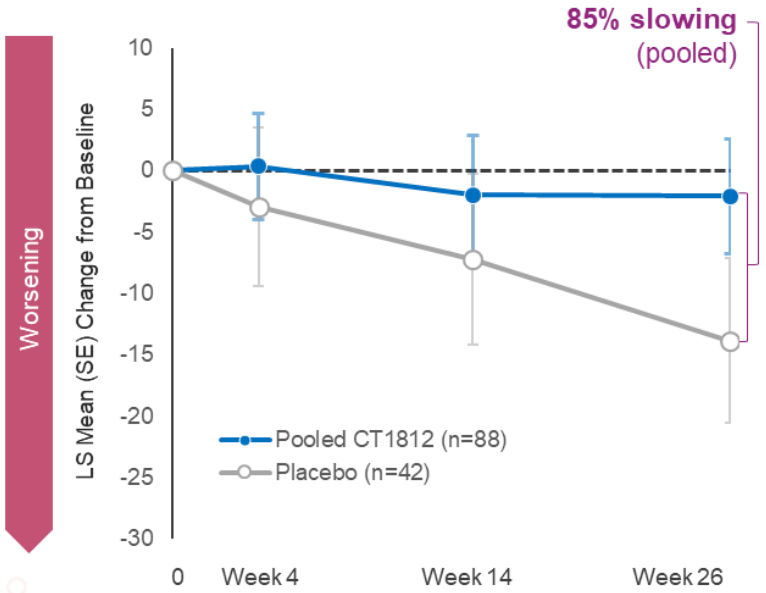
CDR: Cognitive Drug Research System

COGNITION™ Therapeutics

Up to 85% Slowing of Decline Across CDR Domains

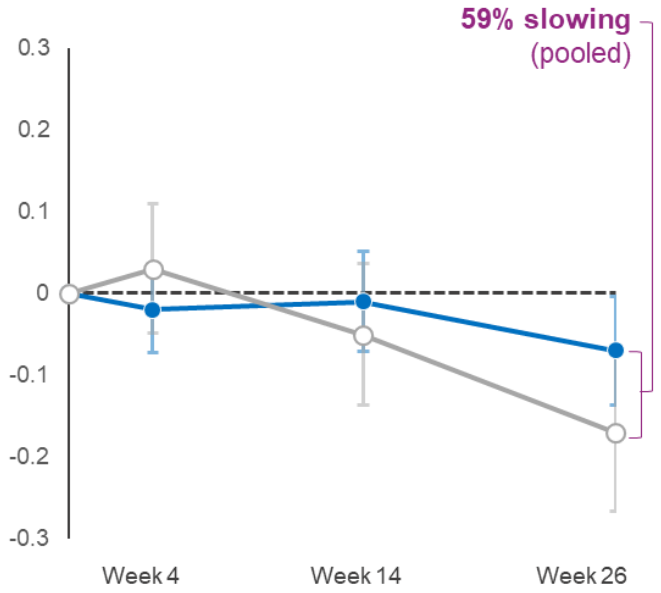
CT1812 improved patients' attentiveness and problem solving

CDR – Quality of Episodic 2° Memory (ITT)



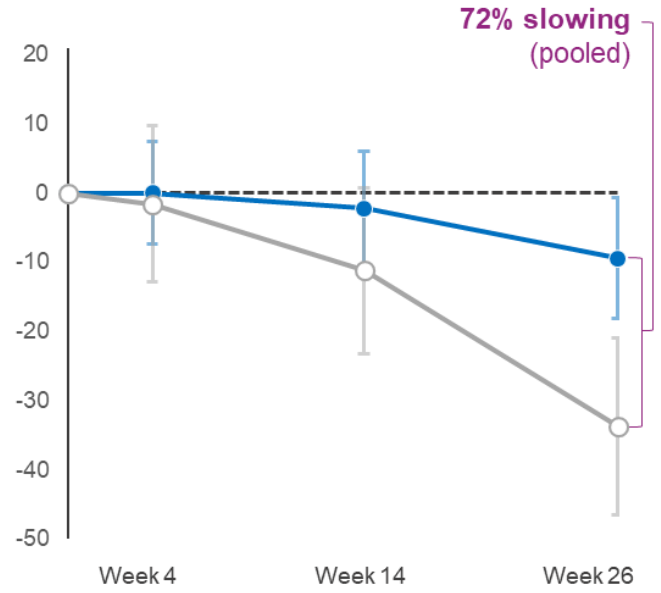
P-values			
100mg v pbo	0.698	0.682	0.248
300mg v pbo	0.728	0.513	0.183
pooled v pbo	0.674	0.539	0.153

CDR – Quality of Working Memory (ITT)



0.436	0.205	0.471
0.786	0.563	0.464
0.549	0.698	0.403

CDR – Quality of Memory (ITT)



0.931	0.224	0.201
0.773	0.887	0.153
0.907	0.539	0.120

CDR: Cognitive Drug Research System

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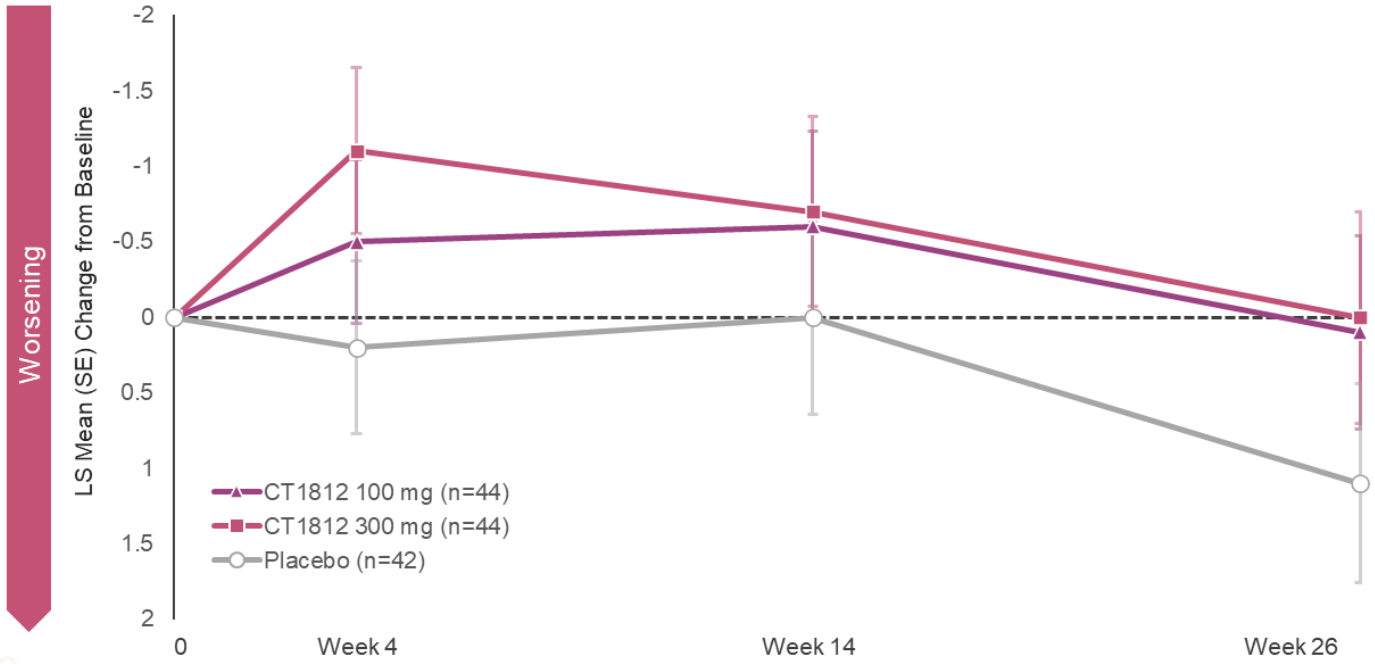
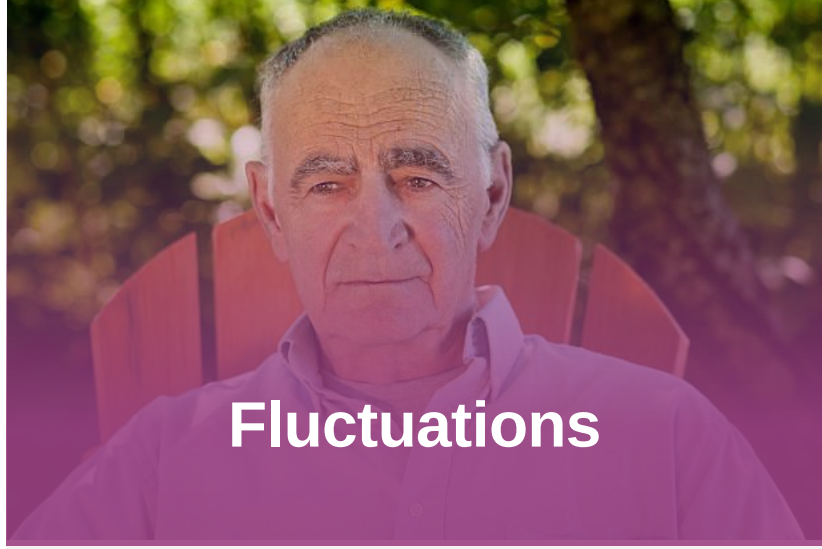
Fewer Fluctuations with CT1812

91% reduction of cognitive fluctuations (CAF)

Clinicians Assessment of Fluctuations (CAF)



P-values			
100mg v pbo	0.356	0.551	0.311
300mg v pbo	0.096	0.437	0.248



- Inconsistent
- Reduced responsiveness
- Variable attention
- Altered consciousness

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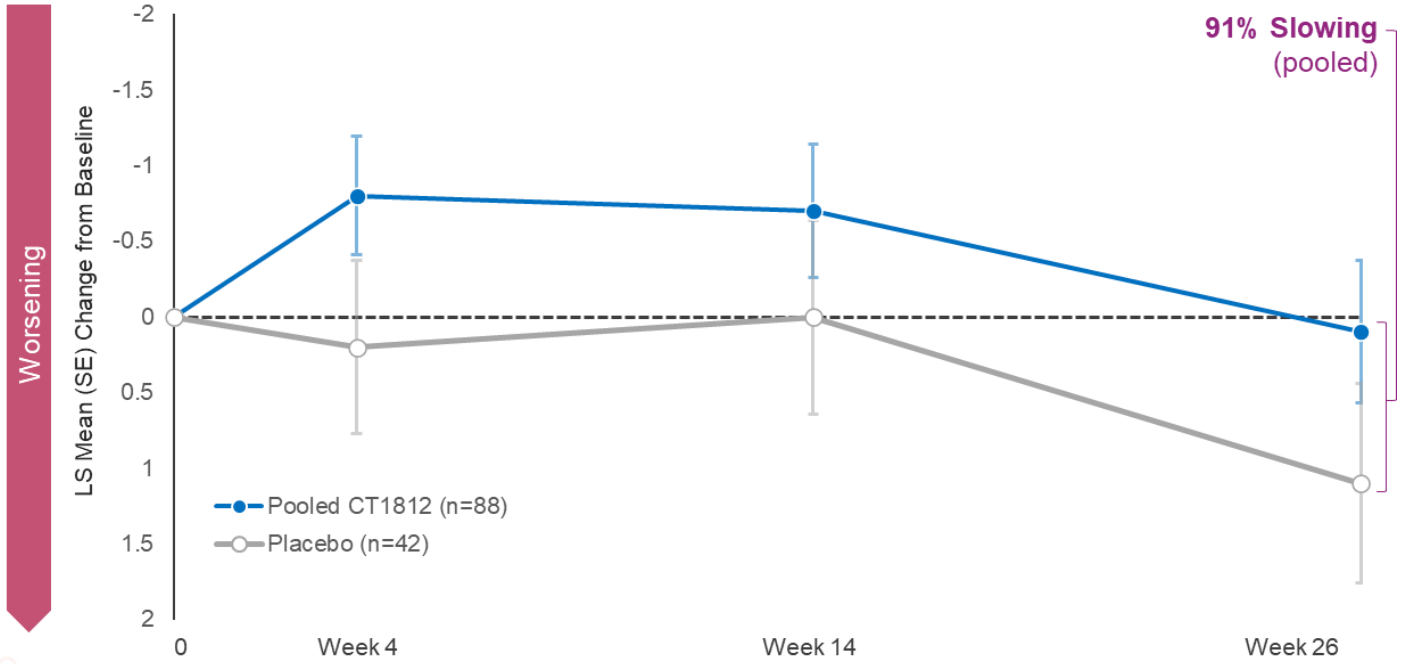
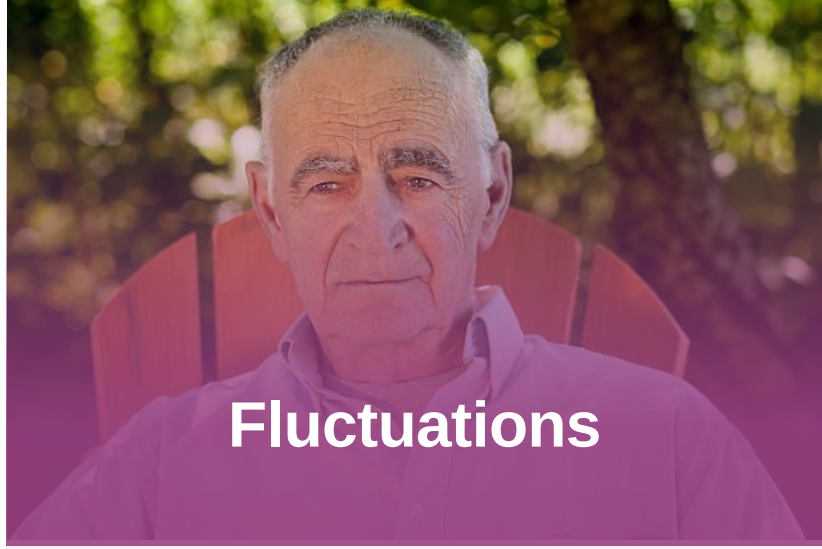
Fewer Fluctuations with CT1812

91% reduction of cognitive fluctuations (CAF)

Clinicians Assessment of Fluctuations (CAF)



P-values			
100mg v pbo	0.356	0.551	0.311
300mg v pbo	0.096	0.437	0.248
pooled v pbo	0.137	0.429	0.210



- Inconsistent
- Reduced responsiveness
- Variable attention
- Altered consciousness

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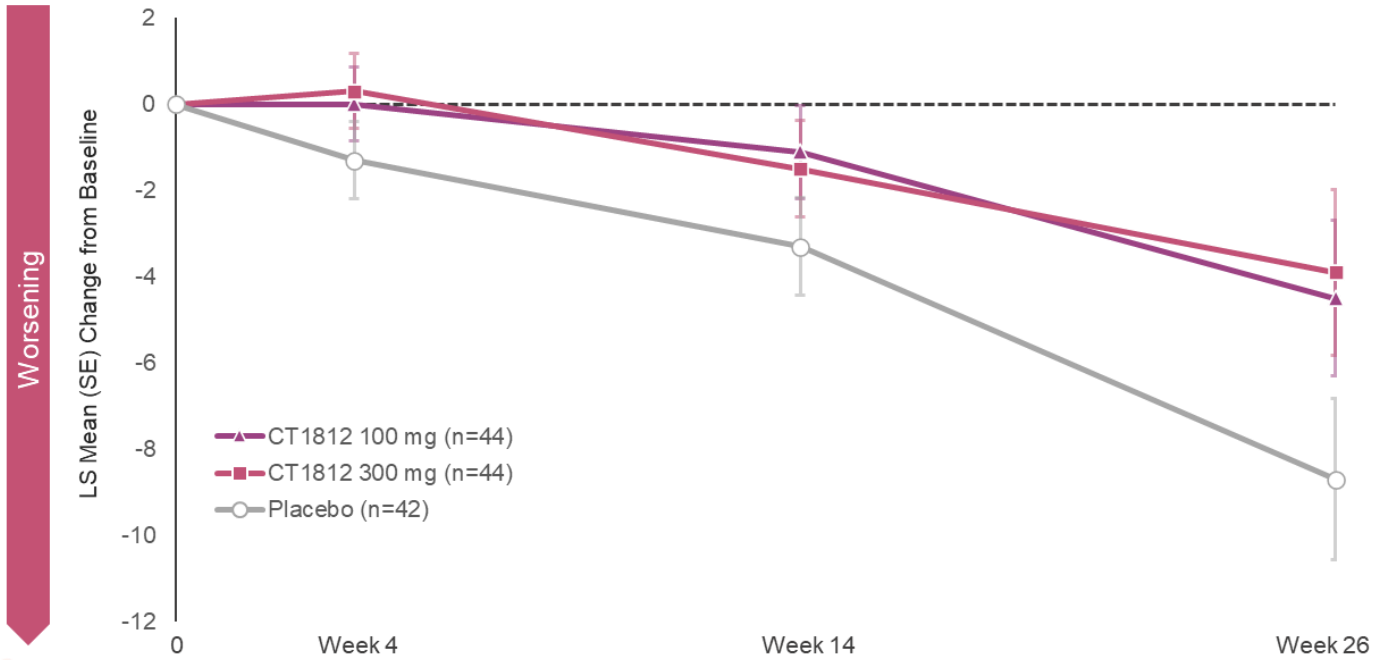
People on CT1812 Maintained ADLs

52% preservation in activities of daily living (ADL) with p=0.05

ADCS - Activities of Daily Living (ADL)



P-values			
100mg v pbo	0.275	0.165	0.105
300mg v pbo	0.185	0.266	0.075

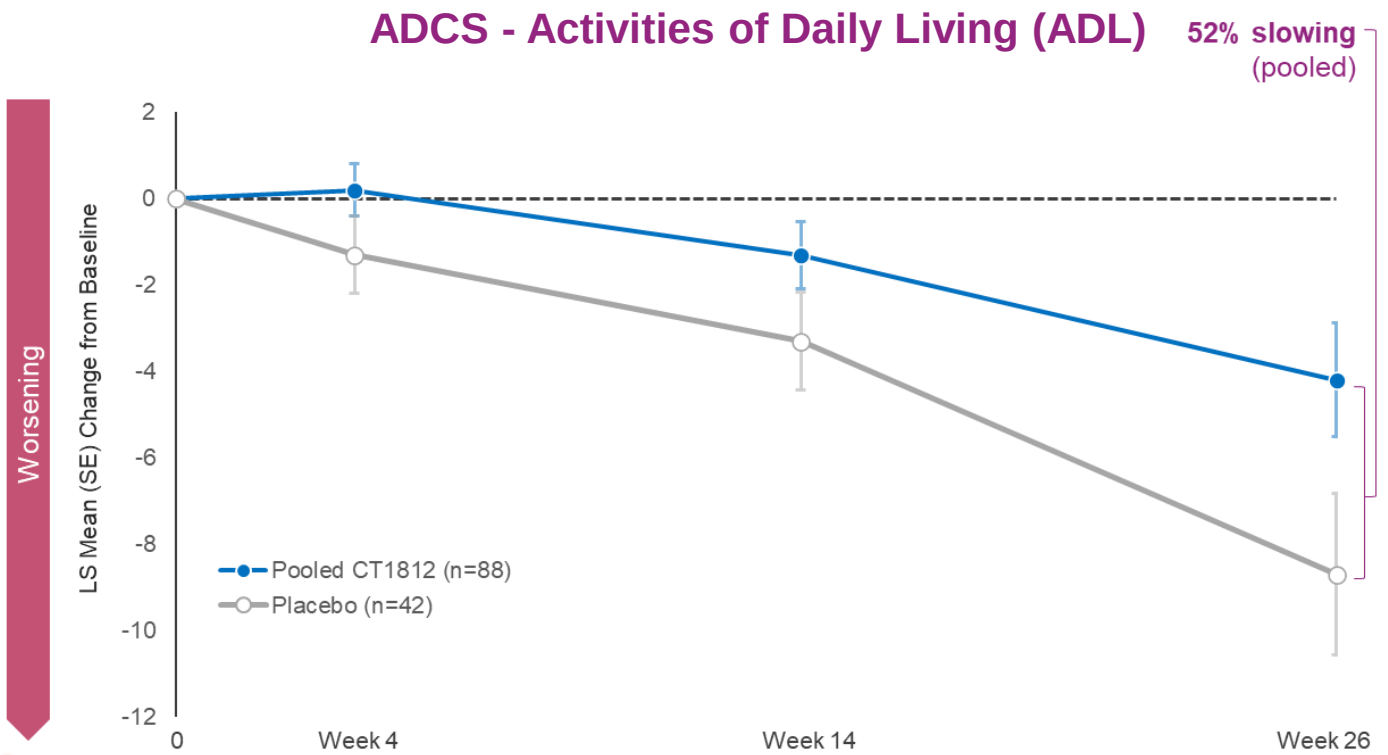
Components of ADL Score

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

COGNITION™ Therapeutics

People on CT1812 Maintained ADLs

52% preservation in activities of daily living (ADL) with p=0.05



P-values			
100mg v pbo	0.275	0.165	0.105
300mg v pbo	0.185	0.266	0.075
pooled v pbo	0.165	0.151	0.050

Components of ADL Score

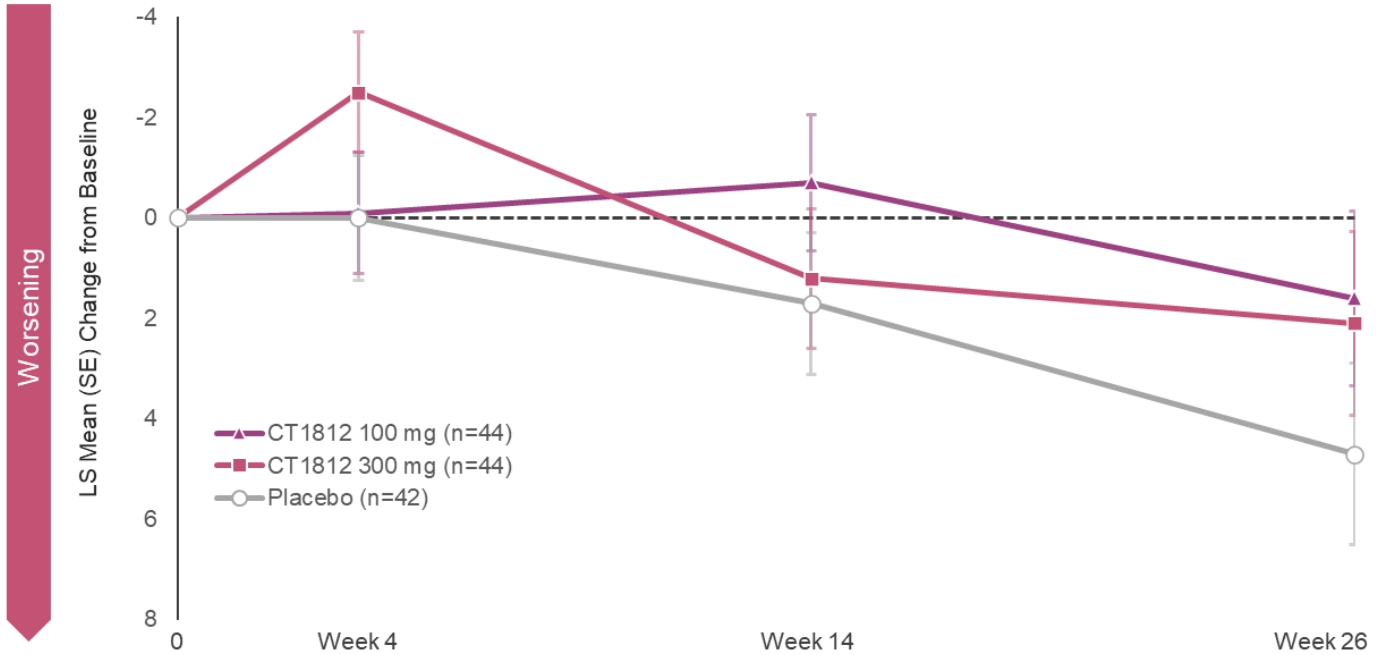
- Bathing
- Toileting
- Dressing
- Conversing
- Grooming
- Shopping
- Feeding
- Writing

COGNITION™ Therapeutics

People on CT1812 Maintained Motor Function

62% preservation in measures of movement

MDS-UPDRS (Part 3)



P-values

100mg v pbo	0.957	0.207	0.211
300mg v pbo	0.155	0.790	0.307

Components of UPDRS:

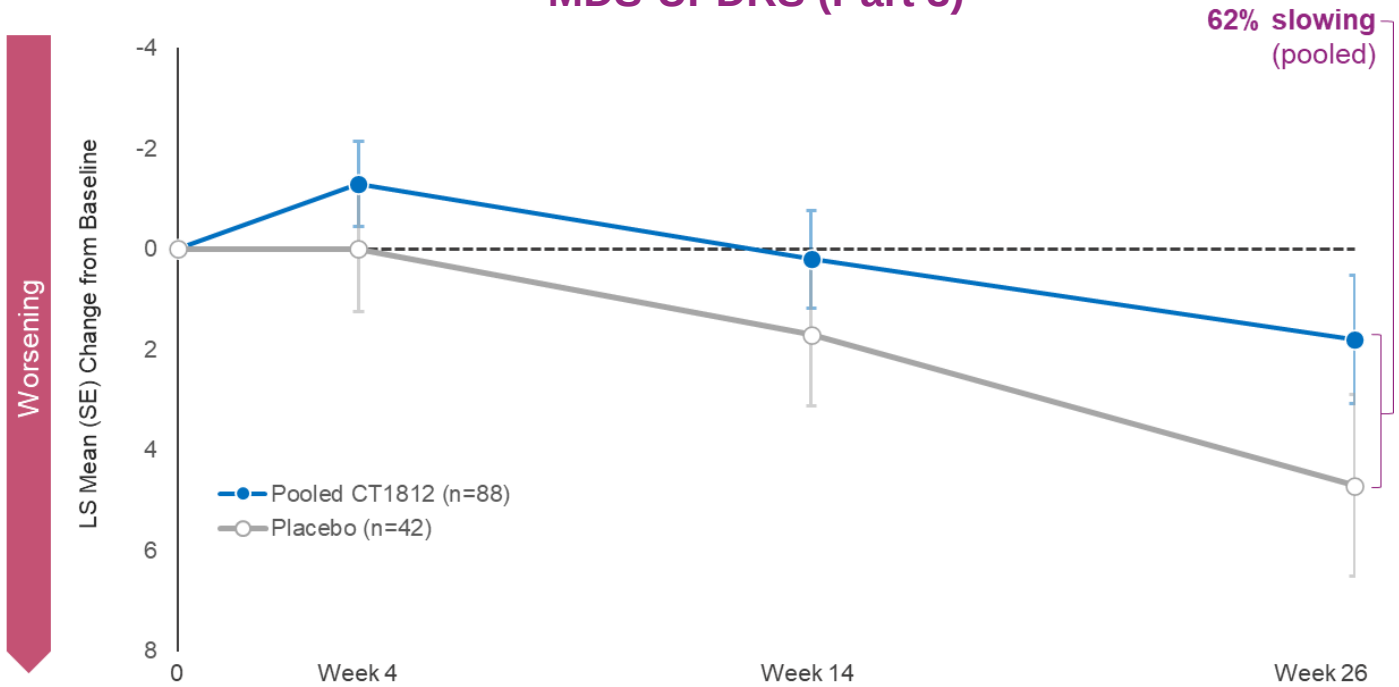
- Balance
- Gait
- Speech
- Facial expression
- Rigidity
- Tremor

MDS-UPDRS: MDS-Unified Parkinson's Disease Rating Scale (Part III)

People on CT1812 Maintained Motor Function

62% preservation in measures of movement

MDS-UPDRS (Part 3)



P-values			
100mg v pbo	0.957	0.207	0.211
300mg v pbo	0.155	0.790	0.307
pooled v pbo	0.394	0.381	0.191

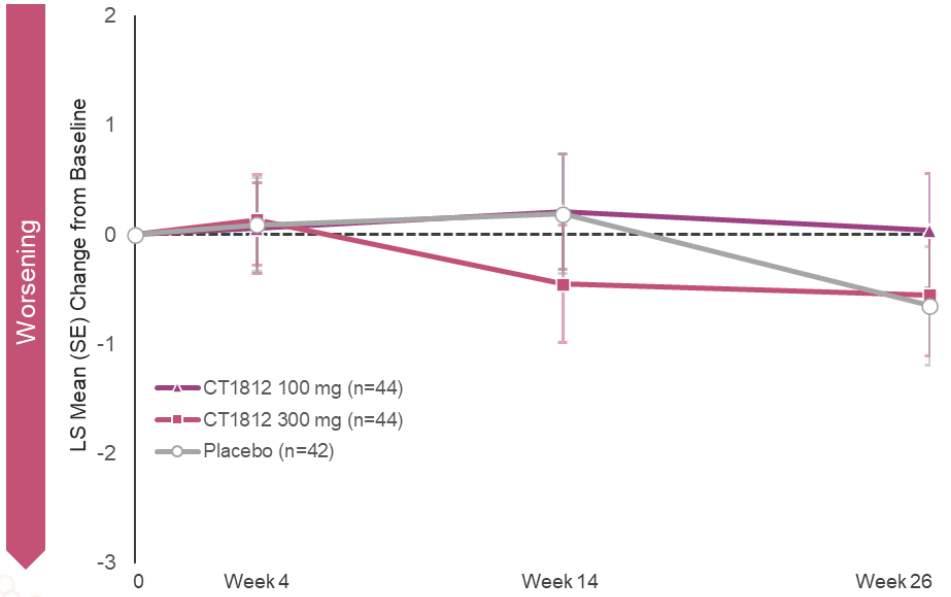
Components of UPDRS:

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

MDS-UPDRS: MDS-Unified Parkinson's Disease Rating Scale (Part III)

Minimal Changes Observed in MoCA or ESS

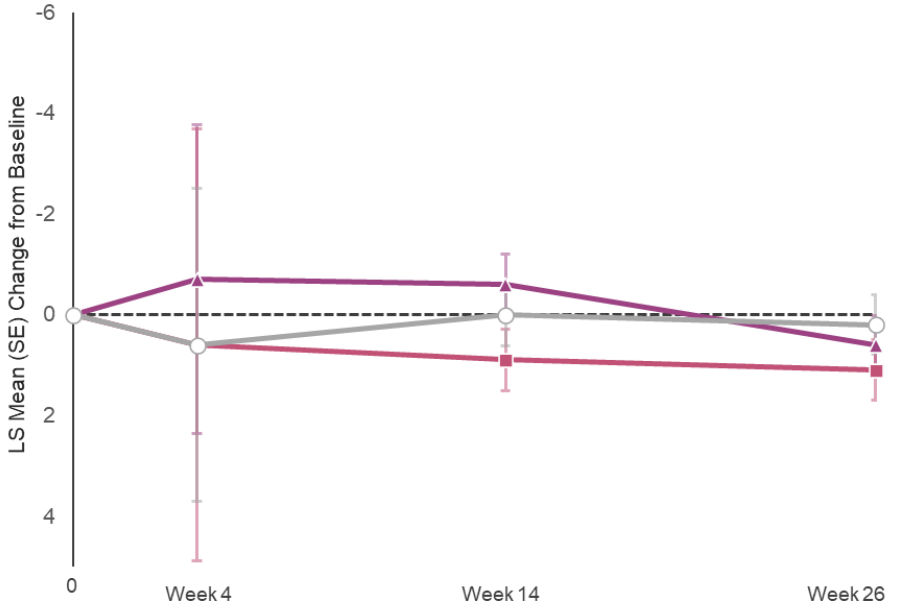
Montreal Cognitive Assessment (MoCA)



P-values			
100mg v pbo	0.964	0.977	0.361
300mg v pbo	0.928	0.406	0.897

Epworth Sleep Scale (ESS)

Only one participant reported lethargy (105-0001)



P-values			
100mg v pbo	0.085	0.532	0.604
300mg v pbo	0.951	0.305	0.277

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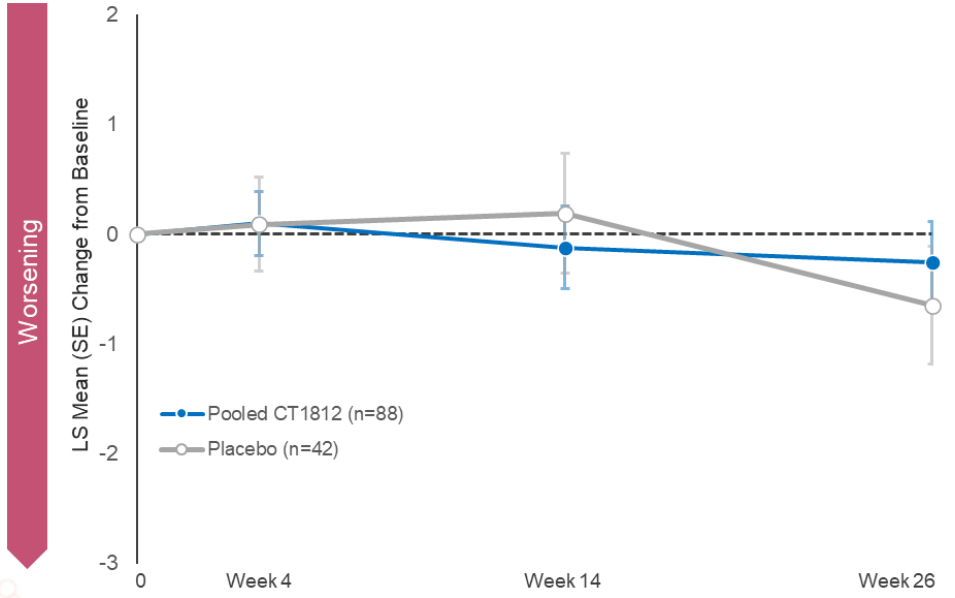
Minimal Changes Observed in MoCA or ESS

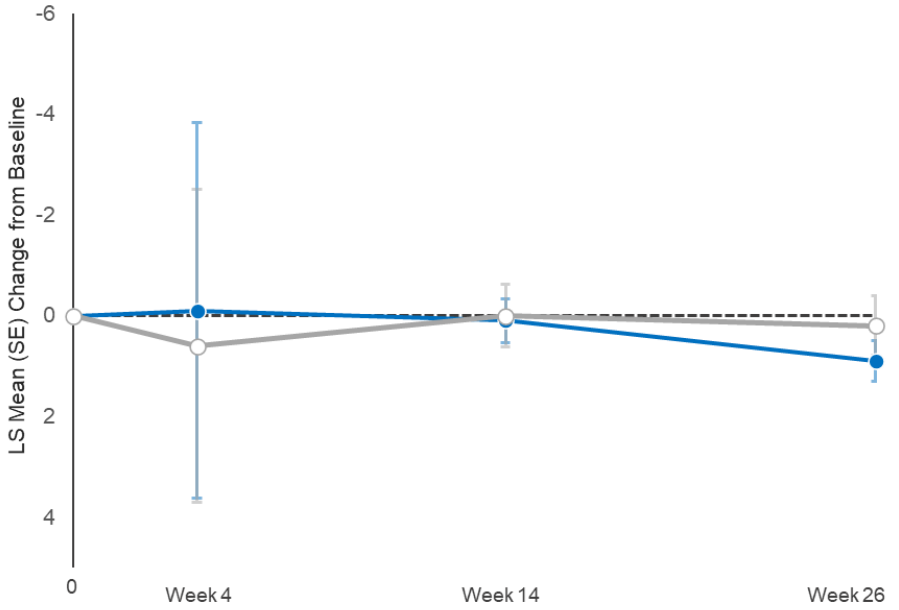
Montreal Cognitive Assessment (MoCA)



P-values			
100mg v pbo	0.964	0.977	0.361
300mg v pbo	0.928	0.406	0.897
pooled v pbo	0.979	0.643	0.550

Epworth Sleep Scale (ESS)

One participant reported mild, transient lethargy



P-values			
100mg v pbo	0.085	0.532	0.604
300mg v pbo	0.951	0.305	0.277
pooled v pbo	0.339	0.810	0.351

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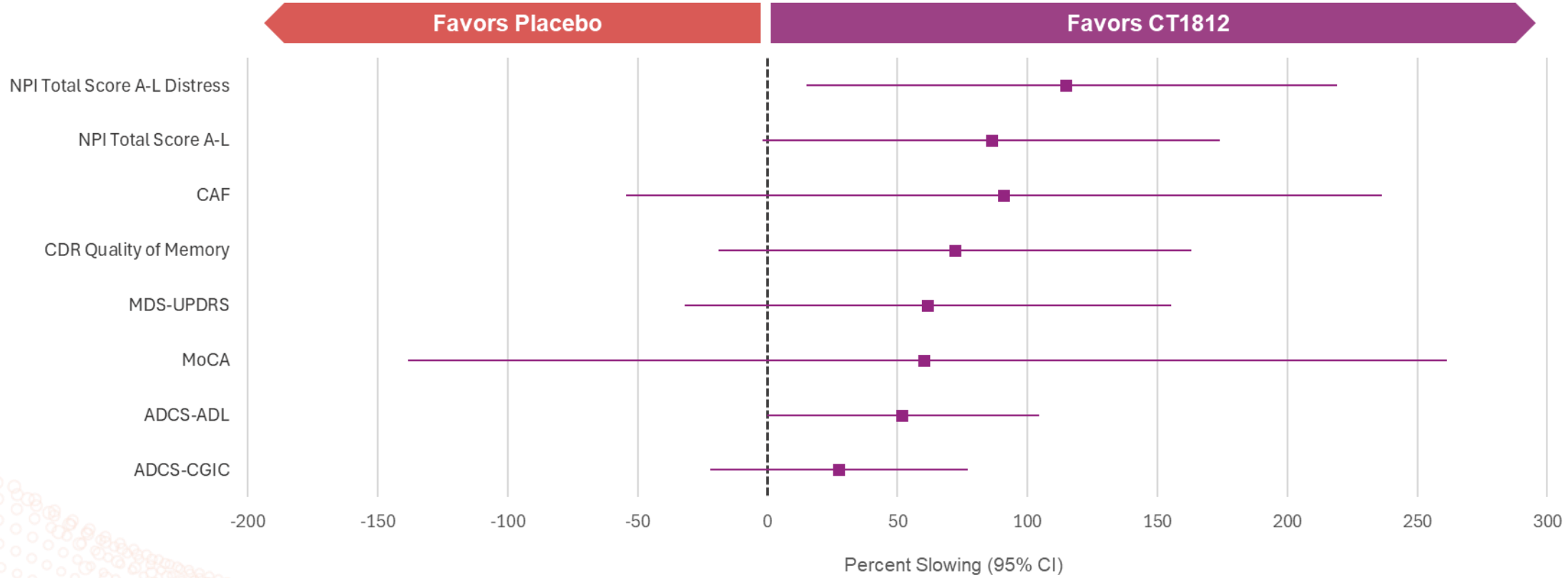
Percent Slowing at Day 182 for Exploratory Efficacy Endpoints of Interest

Pooled CT1812 100mg +300 mg vs. Placebo
ITT Population



Note: The 95% CI for ESS is (-1050, 400) which is too wide to present in this plot alongside the other efficacy endpoints.

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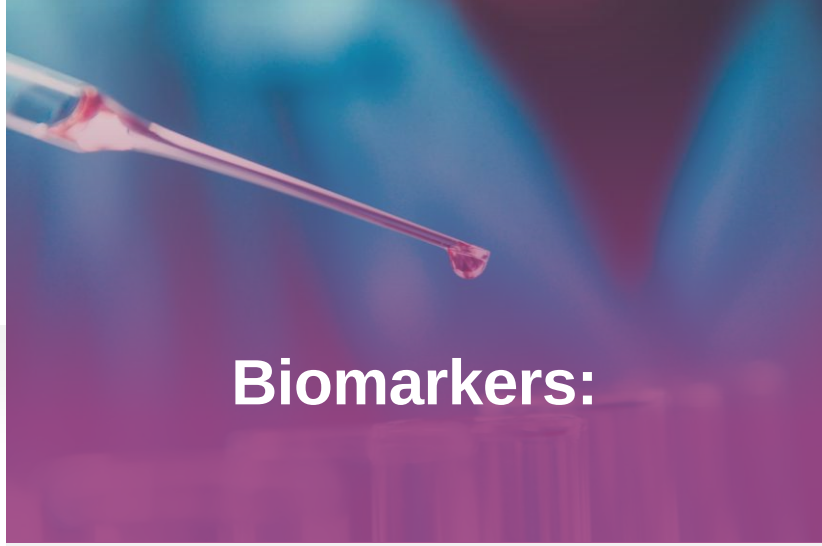
Biomarkers

No significant treatment differences were observed

- Change from baseline levels in plasma were assessed for known markers of neuroinflammation and disease biology
- Change from baseline in phosphorylated alpha-synuclein 129 via skin biopsy was assessed
- Reduction in NfL (p>0.10) observed with CT1812 treatment similar to COG0201 in mild-to-moderate AD
- Additional exploratory proteomics may be performed



- Aβ monomers (1-40, 1-42) & ratio
- Neurofilament light chain (NfL)
- Glial fibrillary acid protein (GFAP)
- Phosphorylated Tau 181
- Phosphorylated Tau 217
- DOPA decarboxylase
- α-synuclein
- Phosphorylated α-synuclein

COG1201 (SHIMMER): Safety Summary

Favorable safety and tolerability profile

Subjects with:	CT1812		Placebo (N=42)	Total (N=129)
	100 mg (N=44)	300 mg (N=43)		
At least one TEAE	42 (95.5%)	40 (93.0%)	37 (88.1%)	119 (92.2%)
At least one TEAE related to treatment	14 (31.8%)	21 (48.8%)	16 (38.1%)	51 (39.5%)
At least one TEAE leading to discontinuation of treatment	4 (9.1%)	9 (20.9%)	5 (11.9%)	18 (14.0%)
At least one TEAE leading to discontinuation of study	4 (9.1%)	9 (20.9%)	2 (4.8%)	15 (11.6%)
AEs leading to death	0	2 (4.7%)	1 (2.4%)	3 (2.3%)
At least one SAE	4 (9.1%)	5 (11.6%)	8 (19.0%)	17 (13.2%)
At least one SAE related to treatment	0	1 (2.3%)	0	1 (0.8%)
AE of Special Interest: LFTs ≥ 3x ULN (AST or ALT)	3 (6.8%)	6 (14.0%)	0	9 (7.0%)
AE Severity - subjects with:				
Mild	25 (56.8%)	14 (32.6%)	15 (35.7%)	54 (41.9%)
Moderate	16 (36.4%)	22 (51.2%)	17 (40.5%)	55 (42.6%)
Severe	1 (2.3%)	4 (9.3%)	5 (11.9%)	10 (7.8%)

The SAE that was related to IP was for subject 125-0003 (CT1812 300mg). The Preferred Term was 'Metabolic encephalopathy'. Severity was moderate, drug was interrupted, it was rated as "probably related", and the outcome was recovered/resolved. It emerged on Day 120 and ended on Day 190.

ULN: upper limit of normal; AST: aspartate aminotransferase; ALT: alanine transaminase

Most Common Treatment-Emergent Adverse Events (TEAEs)

Nature and severity of adverse event (AE) profile is similar to prior CT1812 trials

Preferred Term n (%)	CT1812		Placebo (N=42)	Total (N=129)
	100 mg (N=44)	300 mg (N=43)		
Fall	7 (15.9%)	14 (32.6%)	10 (23.8%)	31 (24.0%)
Headache	4 (9.1%)	7 (16.3%)	8 (19.0%)	19 (14.7%)
Lipase increase	5 (11.4%)	7 (16.3%)	6 (14.3%)	18 (14.0%)
Urinary tract infection	3 (6.8%)	3 (7.0%)	8 (19.0%)	14 (10.9%)
Dizziness	3 (6.8%)	4 (9.3%)	5 (11.9%)	12 (9.3%)
COVID-19	3 (6.8%)	5 (11.6%)	3 (7.1%)	11 (8.5%)
Diarrhea	4 (9.1%)	5 (11.6%)	2 (4.8%)	11 (8.5%)
Fatigue	4 (9.1%)	4 (9.3%)	3 (7.1%)	11 (8.5%)
ALT Increase	3 (6.8%)	7 (16.3%)	0	10 (7.8%)
Constipation	2 (4.5%)	4 (9.3%)	4 (9.5%)	10 (7.8%)
Anxiety	3 (6.8%)	3 (7.0%)	3 (7.1%)	9 (7.0%)
AST Increase	4 (9.1%)	5 (11.6%)	0	9 (7.0%)
Confusional state	1 (2.3%)	5 (11.6%)	3 (7.1%)	9 (7.0%)
Abdominal discomfort	1 (2.3%)	5 (11.6%)	0	6 (4.7%)

TEAEs by Preferred Term occurring in 5% of the total safety population, or those in at least 10% of CT1812 treated participants and at least twice the rate of placebo

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 ≥ 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

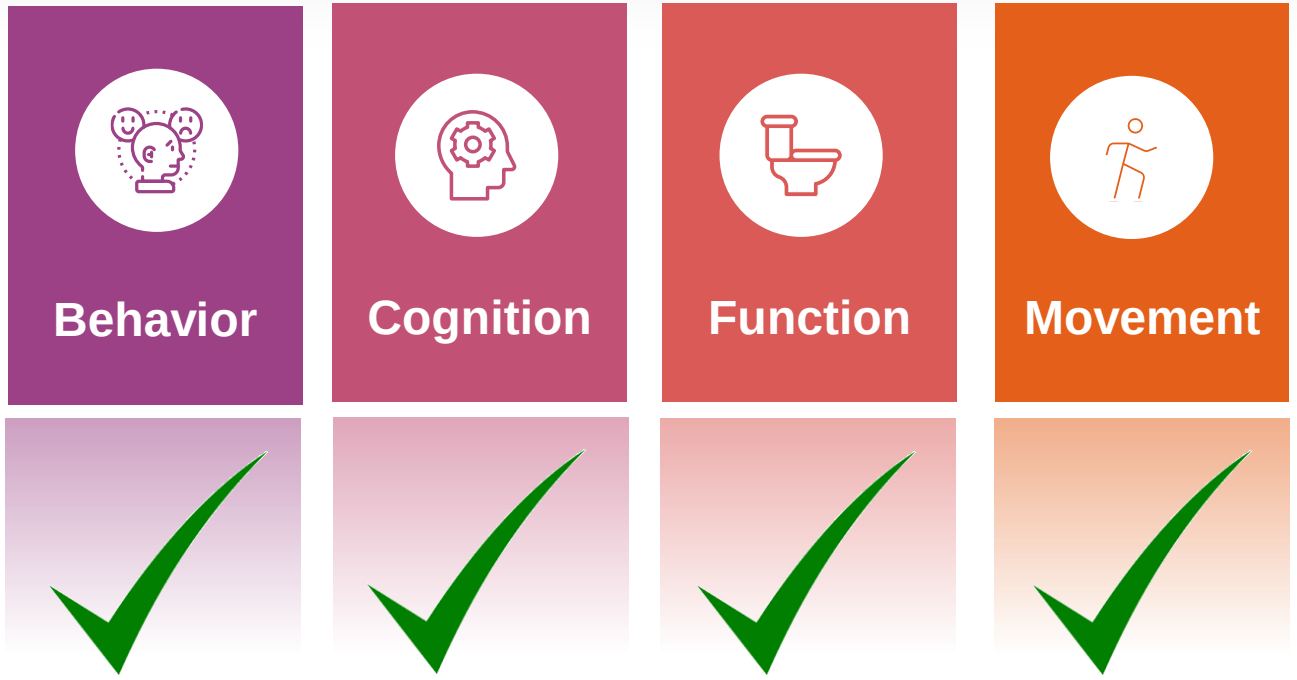
	Adverse Events	Serious AEs	Deaths†
CT1812	94.3%	10.3%	2 (2.2)%
Placebo	88.1%	19.0%	1 (2.4)%

* occurring in a CT1812 treatment group at a rate >10% and at a rate >2X the placebo rate
† not considered treatment related

Strong Early Data Supporting CT1812 for DLB

Safety and efficacy to be confirmed in phase 3 trials

- SHIMMER suggests CT1812 can slow progression in DLB
- Evidence across multiple endpoints
- Safe and well tolerated*
- Results support advancement of CT1812 into late-stage trials



*CT1812 has not been approved for any use by the FDA or other health authority; nor have regulators reviewed plans for subsequent clinical trials

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Acknowledgements

Cognition Therapeutics is grateful to everyone involved in the COG1201 SHIMMER Trial

Most importantly – each study participant and their care partners

University of Miami and Dr. James Galvin

Our collaborators at the Lewy Body Dementia Association and their Centers of Excellence

Site investigators and personnel

NIH and NIA for providing funding (R01AG071643)

Cognition colleagues and our CRO partners

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