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

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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:

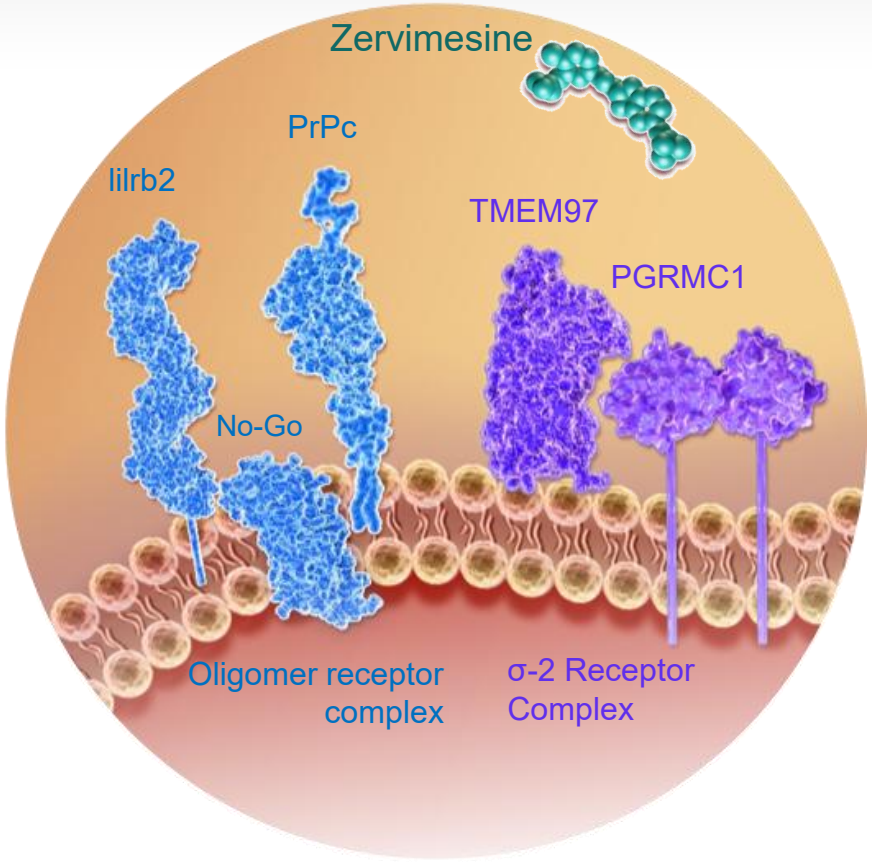
- CT1812 (zervimesine*) is an investigational therapeutic that has not been approved for any use by the US Food and Drug Administration or other health authority
- Plans for subsequent clinical trials have not yet been reviewed by FDA or EMA

*CT1812 assigned USAN name: zervimesine

Zervimesine – CT1812

Lead product candidate in development for Dementia with Lewy bodies and Alzheimer's Dz

- BBB-penetrant small molecule oligomer antagonist that displaces BOTH Aβ and α-synuclein oligomers[2]
- Distinct MoA: ligand of TMEM97 (sigma-2) receptor
- Oral, once-daily dosing; favorable safety profile
- DLB and Alzheimer's disease rationale
  - 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]



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

BBB: blood brain barrier; PoC: proof of concept

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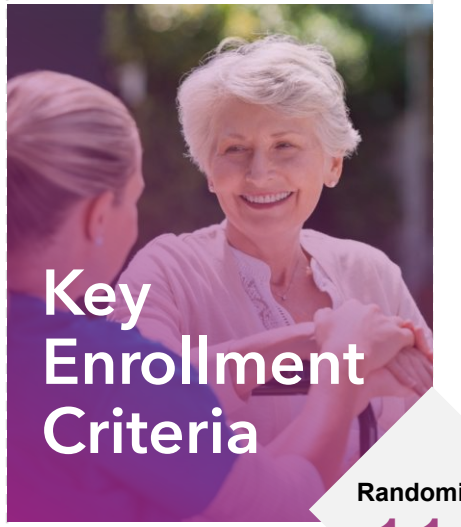
SHIMMER Study Designed to Assess Multifactorial Burden

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



- ☑ Age 50-85
- ☑ 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 : ADCS-CGIC
- Biomarkers

Study Objectives

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

Disposition

- 293 Screened
- 130 Randomized
- 130 in ITT Population
- 129 in Safety Population

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

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	80.6[a]
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

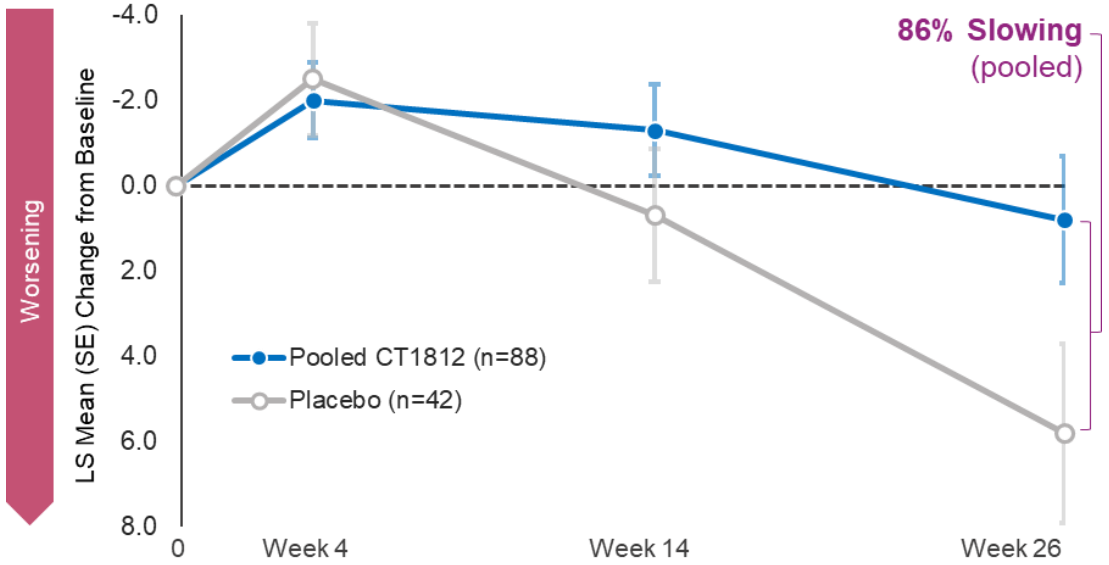
*Means (SD)

[a] Four converted from negative to positive; five not assessed

CT1812 Showed 86% Impact on Neuropsychiatric Measures

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

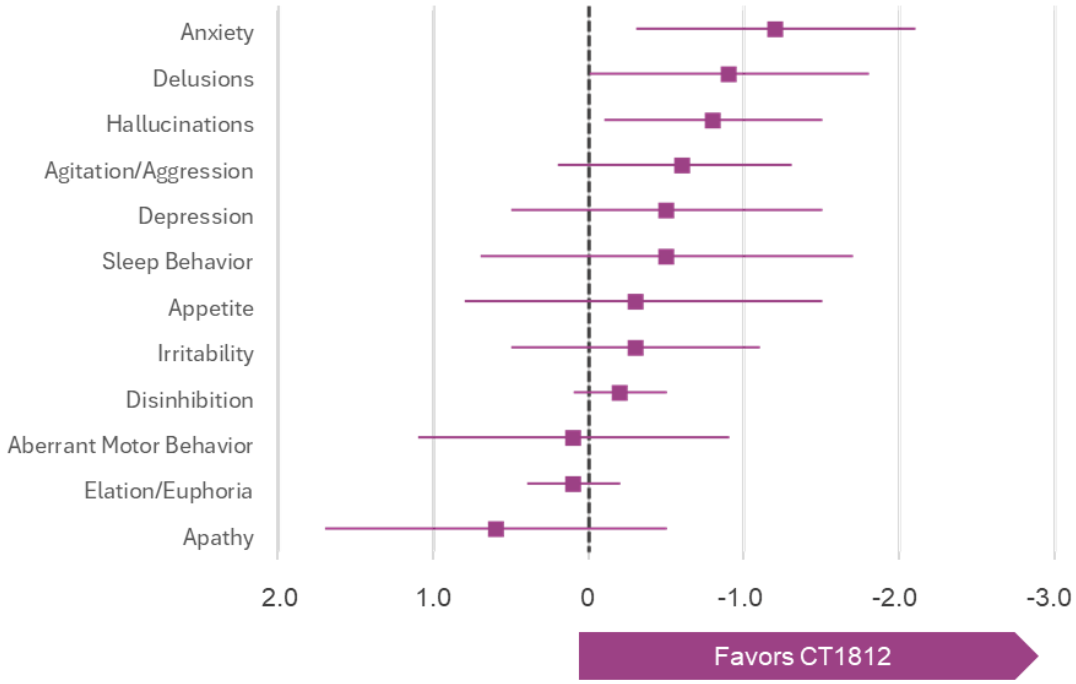
NPI-12



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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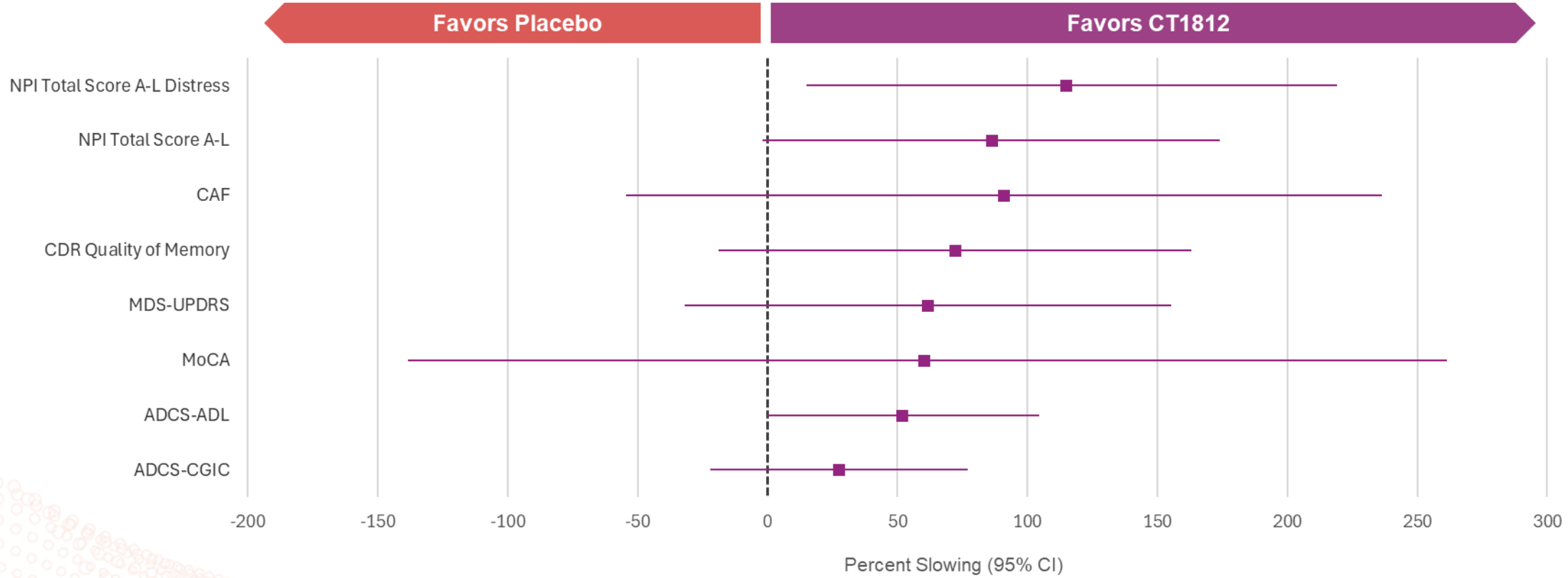
Percent Slowing at Day 182 for Exploratory Efficacy Endpoints of Interest

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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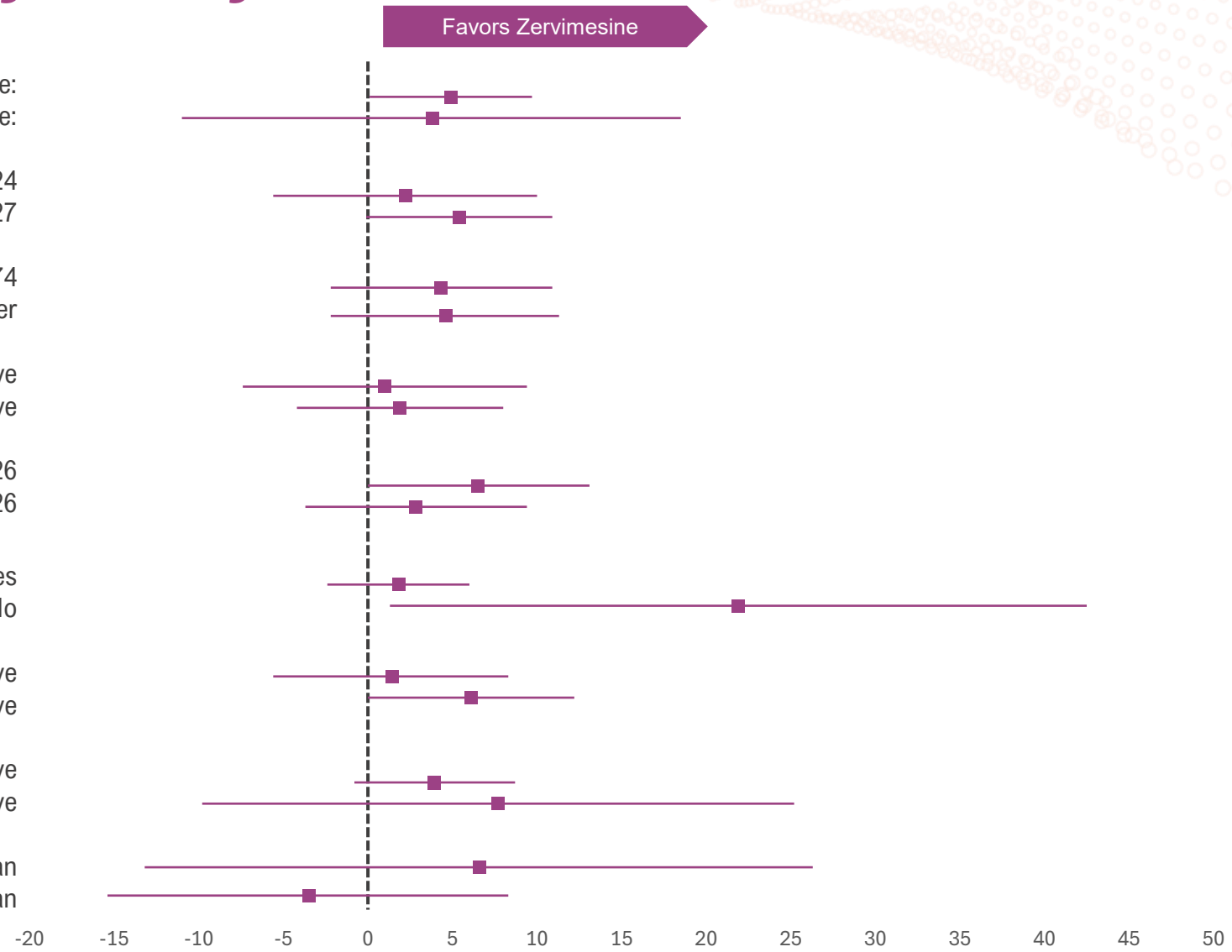
Subgroup / Sensitivity Analysis - ADL

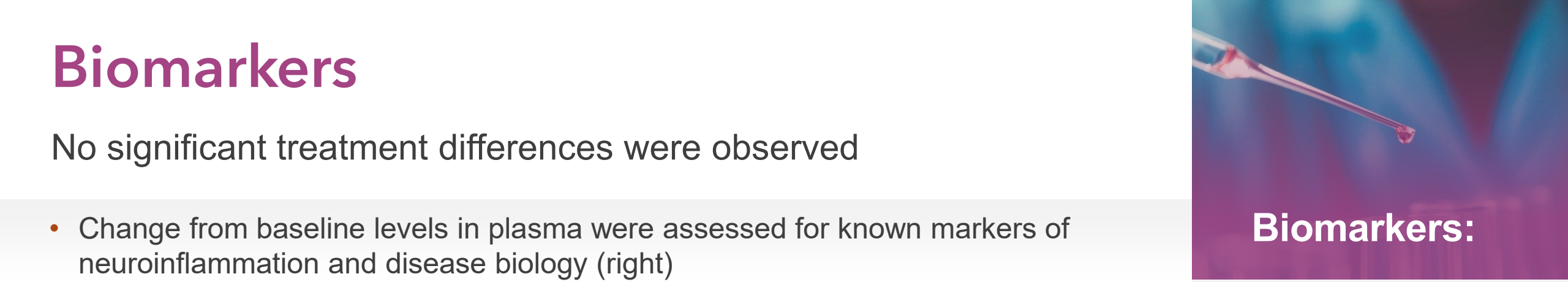
(n) CT1812	Pbo		
73	33	Sex	Male:
15	9		Female:
38	23	MMSE at baseline	Low 18-24
49	19		High 25-27
46	16	Age	Below 74
42	26		74 or older
23	15	Amyloid positivity	C2N positive
44	18		C2N negative
42	19	Parkinsonian features	UPDRS <26
45	23		UPDRS ≥26
72	35	AChEi or memantine	Yes
16	7		No
38	16	ApoE4 (hereo/homozygous)	Positive
46	25		Negative
73	31	Skin Biopsy CND	Positive
11	9		Negative
10	9	pTau217 Ratio	Below median
13	6		Above median



Biomarkers

No significant treatment differences were observed

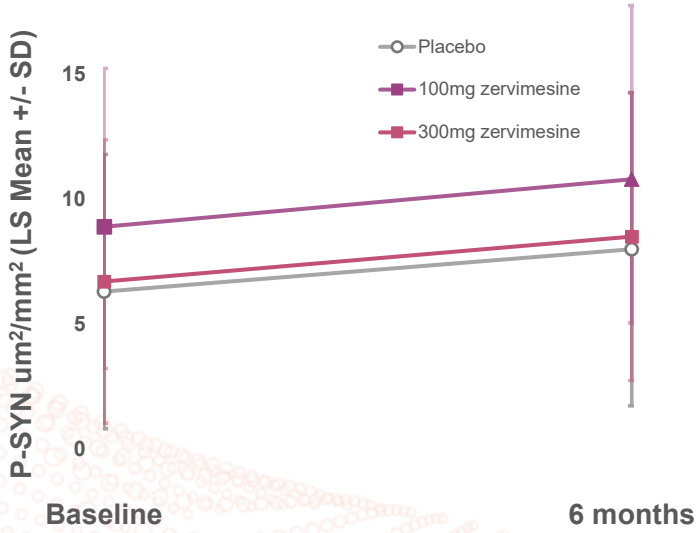
- Change from baseline levels in plasma were assessed for known markers of neuroinflammation and disease biology (right)
- Reduction in NfL (p>0.10) observed with CT1812 treatment similar to COG0201 in mild-to-moderate AD



Biomarkers:

- 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

Skin phosphorylated alpha-synuclein



- Phospho-synuclein was assessed at baseline and at 60 months using the ***CND Syn-One Test***
- All groups showed a significant (p<0.01) change from baseline
  - Placebo: 27%
  - 100mg CT1812: 21%
  - 300mg CT1812: 27%

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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

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

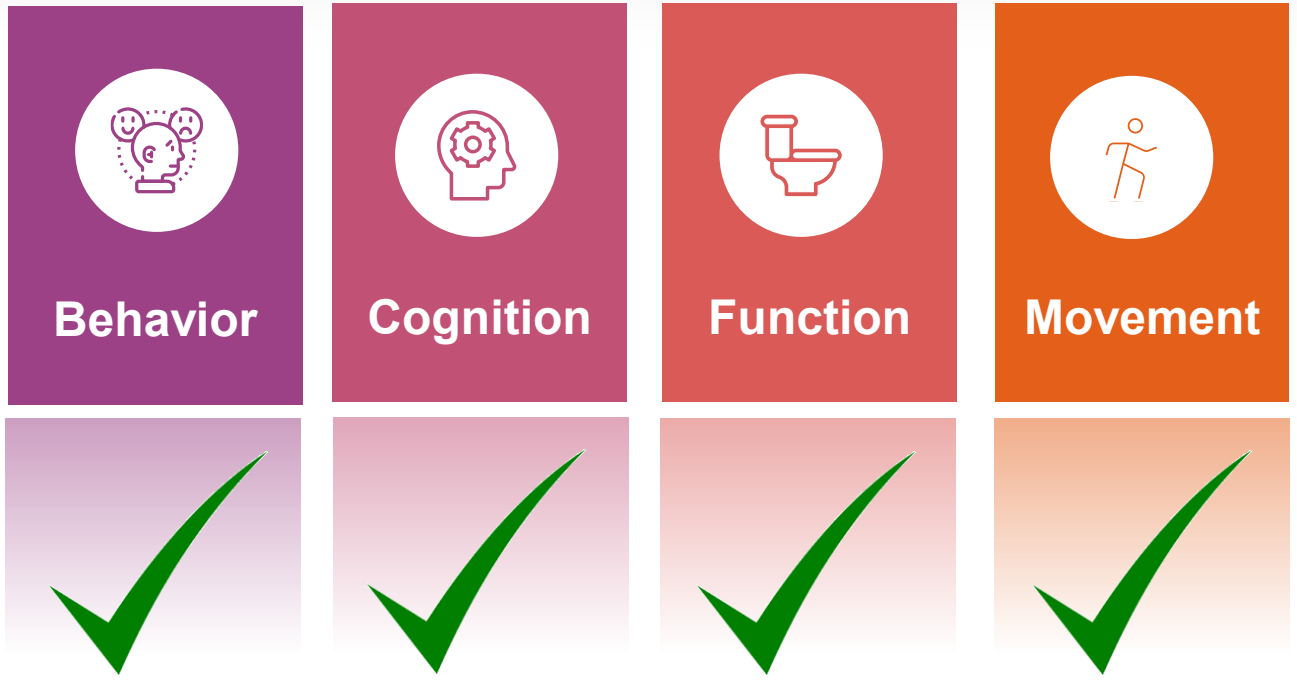
	Adverse Events	Serious AEs	Deaths†
CT1812	94.3%	10.3%	2 (2.2)%
Placebo	88.1%	19.0%	1 (2.4)%

* 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

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Cognition colleagues and our CRO partners

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