Results from COG0201: A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Phase 2 Study to Evaluate the Safety and Efficacy of CT1812 in Subjects with Mild-to-Moderate Alzheimer's Disease

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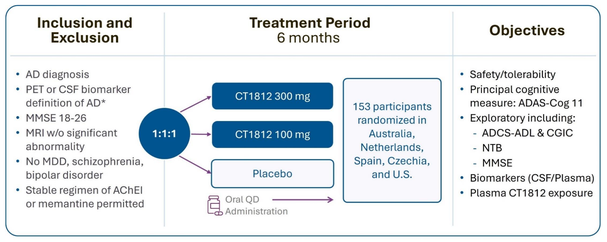
Consistent improvement in cognitive outcomes and favorable tolerability profile warrant further development of CT1812 in longer and larger clinical trials

Background

- CT1812 is an experimental, oral, small molecule, allosteric Aβ oligomer antagonist in clinical development for Alzheimer's disease (AD) and dementia with Lewy bodies (DLB)
- CT1812 is a sigma-2 receptor ligand that reduces the binding affinity of toxic amyloid beta oligomers[1,2]
- Reported here are the results of the first proof of concept Phase 2 study of CT1812 assessing safety, tolerability, cognition and biomarkers



* *Cut-offs from Clinical Neurochemistry Lab at Sahlgrenska University Hospital in Gothenburg, Sweden or study protocol*

Demographics & Baseline Characteristics (mITT)

	CT1812		Placebo	Total
	100mg (N=51)	300 mg (N=50)	(N=49)	(N=150)
Age - years				
Mean (SD)	72.4 (6.96)	74.1 (7.20)	71.6 (8.06)	72.7 (7.43)
Min, Max	53, 81	57, 85	51, 85	51, 85
Female sex - n (%)	34 (66.7%)	28 (56.0%)	28 (57.1%)	90 (60.0%)
Ethnicity - n (%)				
Hispanic or Latino	4 (7.8%)	6 (12.0%)	1 (2.0%)	11 (7.3%)
Not Hispanic or Latino	47(92.2%)	43 (86.0%)	48 (98.0%)	138 (92.0%)
Not reported	0	1 (2.0%)	0	1 (0.7%)
Race – n (%)				
Black or African-American	0	1 (2.0%)	2 (4.1%)	3 (2.0%)
Native Hawaiian or Other Pacific Islander	1 (2.0%)	0	0	1 (0.7%)
White	50 (98.0%)	48 (96.0%)	46 (93.9%)	144 (96.0%)
More than One Race	0	1 (2.0%)	1 (2.0%)	2 (1.3%)
Asian, American Indian, Alaska Native, Other	0	0	0	0
MMSE				
Mean (SD)	21.5 (3.38)	20.8 (3.48)	21.8 (3.03)	21.37 (3.31)
Min, Max	17.0, 29.0	13.0, 27.0	17.0, 29.0	13.0, 29.0
ApoE status – n (%)				
ApoE4 Pos. (homo/hetero)	30 (58.8%)	30 (60.0%)	31 (63.3%)	91 (60.7%)
Education level				
Grades through 11 – no. (%)	7 (13.7%)	8 (16.0%)	7 (14.3%)	22 (14.7%)

Adverse Events (Safety Population)

Subjects with:	CT 1812 100mg (N=51)	CT 1812 300 mg (N=51)	Placebo (N=50)	Total (N=152)
At least one TEAE	36 (70.6%)	42 (82.4%)	39 (78.0%)	117 (77.0%)
At least one TEAE related to treatment	11 (21.6%)	16 (31.4%)	7 (14.0%)	34 (22.4%)
At least on TEAEs leading to discontinuation	0	11 (21.6%)	3 (6.0%)	14 (9.2%)
AEs leading to death	0	0	1 (2.0%)	1 (0.7%)
At least one SAE	2 (3.9%)	3 (5.9%)	5 (10.0%)	10 (6.6%)
At least one SAE related to treatment	0	1 (2.0%)	0	1 (0.7%)
AE of Special Interest: LFT elevations ≥ 3xULN (AST or ALT)	0	9 (17.6%)	0	9 (6.0%)
At least one TEAE by maximum severity:				
Any	36 (70.6%)	42 (82.4%)	39 (78.0%)	117 (77.0%)
Mild	19 (37.3%)	22 (43.1%)	22 (44.0%)	63 (41.4%)
Moderate	16 (31.4%)	16 (31.4%)	14 (28.0%)	46 (30.3%)
Severe	1 (2.0%)	4 (7.8%)	3 (6.0%)	8 (5.3%)
Most common AE by System Organ Class and Preferred Term:				
Gastrointestinal disorders*	11 (21.6%)	7 (13.7%)	4 (8.0%)	22 (14.5%)
General disorders and administration site conditions*	2 (3.9%)	4 (7.8%)	2 (4.0%)	8 (5.3%)
Infections and infestations - Nasopharyngitis - Urinary tract infection	11 (21.6%) 0 3 (5.9%)	15 (29.4%) 3 (5.9%) 8 (15.7%)	15 (30.0%) 4 (8.0%) 5 (10.0%)	41 (27.0%) 7 (4.6%) 16 (10.5%)
Injury, poisoning and procedural complications - Fall - Post lumbar puncture syndrome - Skin laceration	14 (27.5%) 7 (13.7%) 2 (3.9%) 3 (5.9%)	4 (7.8%) 2 (3.9%) 0 0	13 (26.0%) 4 (8.0%) 4 (8.0%) 0	31 (20.4%) 13 (8.6%) 6 (3.9%) 3 (2.0%)
Investigations (see above LFT elevations)	5 (9.8%)	17 (33.3%)	7 (14.0%)	29 (19.1%)
Metabolism and nutrition disorders*	5 (9.8%)	1 (2.0%)	1 (2.0%)	7 (4.6%)
Musculoskeletal and connective tissue disorders - Arthralgia	8 (15.7%) 4 (7.8%)	4 (7.8%) 1 (2.0%)	6 (12.0%) 4 (8.0%)	18 (11.8%) 9 (5.9%)
Nervous system disorders - Headache	6 (11.8%) 4 (7.8%)	5 (9.8%) 0	12 (24.0%) 7 (14.0%)	23 (15.1%) 11 (7.2%)
Psychiatric disorders - Anxiety	2 (3.9%) 0	6 (11.8%) 3 (5.9%)	6 (12.0%) 2 (4.0%)	14 (9.2%) 5 (3.3%)
Skin and subcutaneous tissue disorders*	5 (9.8%)	3 (5.9%)	4 (8.0%)	12 (7.9%)

* *no individual sub-category within this preferred term exceeded 5%*

Methods

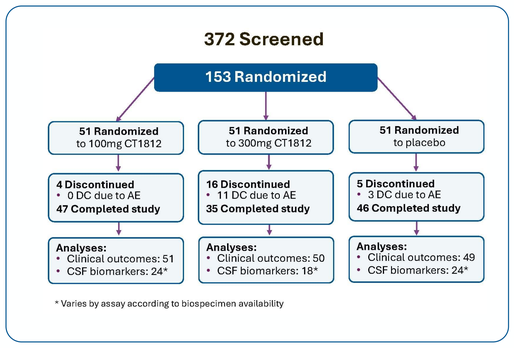
Cognitive, Functional and Biomarker Outcomes:

- Cognitive and functional assessments were performed at baseline and on study days 42, 98, 182
- CSF was drawn for biomarker assessment at screening, and at day 182 (optional)

Statistical Analysis:

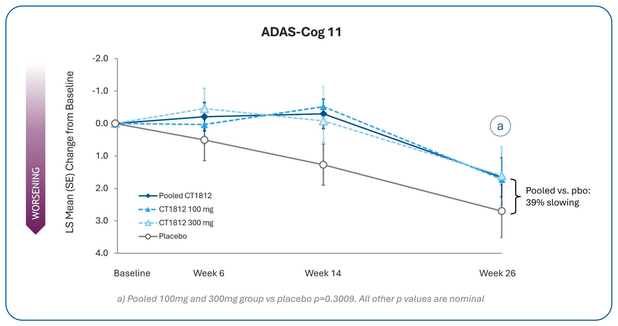
- Change from baseline in ADAS-Cog 11 of CT1812 treated (combined 300mg and 100mg) versus placebo was prespecified as the cognitive endpoint of interest
- For clinical measures, mean change from baseline was analyzed using a mixed-model for repeated measures (MMRM) with treatment as the main effect, visit, baseline score, and APOE ε4 (+ or -) status as covariates; and treatment by visit as an interaction term
- mITT population included all participants receiving study drug and at least one post-baseline ADAS-Cog11 assessment
- For biomarker measures, an ANCOVA model was used to assess treatment effects comparing change from baseline values of CT1812 vs placebo, with treatment as the main effect, baseline value and APOE ε4 (+ or -) status as covariates

Participant Disposition

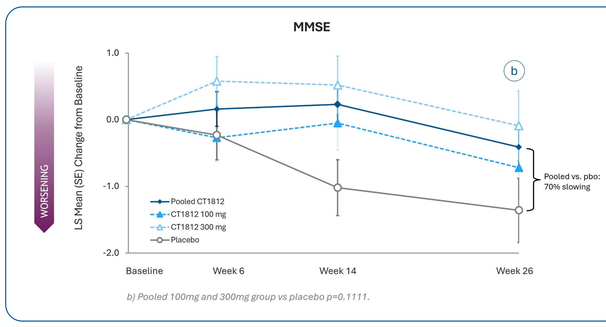


* Varies by assay according to biospecimen availability

Cognitive and Functional Results

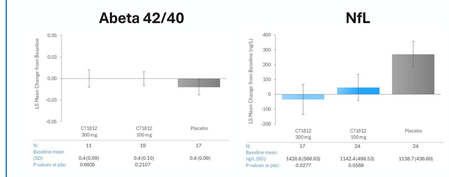


a) Pooled 100mg and 300mg group vs placebo p=0.3009. All other p values are nominal



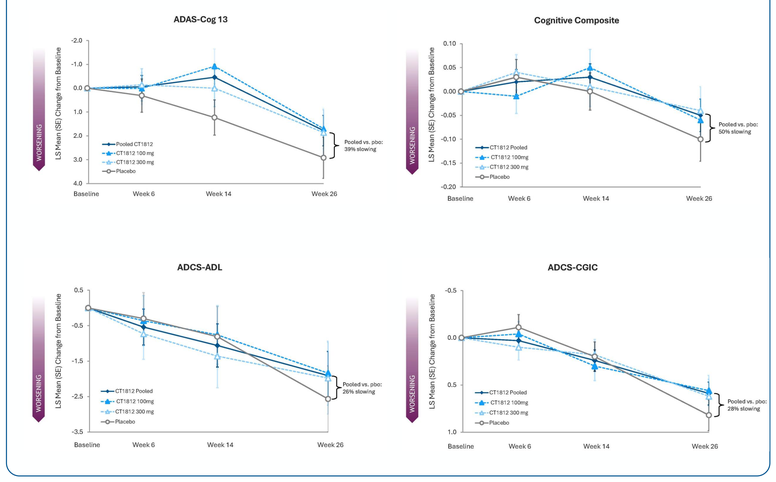
b) Pooled 100mg and 300mg group vs placebo p=0.1111.

Key CSF Biomarkers



Also measured:
neurogranin, synaptotagmin, SNAP25, pTau, total Tau and GFAP

See Poster Abstract ID #95767: *Top-Line CSF Biomarker Outcomes From The Phase 2 Clinical Trial SHINE In Alzheimer's Patients*



ADAS-Cog 11 Subscale	N CT1812	N Pcb	Value	95% CI	% Δ
Female	44	28	-0.68	-3.018, 1.659	30.8%
Male	31	14	-1.97	-5.61, 1.669	54.0%
MMSE 18-21	37	23	-1.28	-4.503, 1.948	32.0%
MMSE 22-26	38	19	-0.31	-2.707, 2.087	29.8%
Age <65	12	8	0.07	-4.044, 4.181	-3.2%
Age ≥65	63	34	-1.22	-3.524, 1.092	42.5%
ApoE4 - neg	29	15	-0.81	-4.406, 2.781	23.2%
ApoE4 - pos	46	27	-1.24	-3.666, 1.186	56.6%
Background med - no	26	18	-1.69	-4.781, 1.405	66.0%
Background med - yes	49	24	-0.71	-3.398, 1.98	25.0%

Summary

- CT1812 was exhibited a favorable safety profile with no discontinuations due to AEs in the 100mg dose
  - Most treatment-emergent AEs were mild to moderate in severity
  - LFT elevations (AST or ALT) were confined to the 300mg dose
  - SAEs were well balanced between CT1812 and placebo
- CT1812 treatment resulted in:
  - Consistent improvements in all cognitive outcomes and across subgroups compared to placebo
  - Reductions in CSF NfL, a marker of neurodegeneration measured; little change in the Aβ 40/42 ratio
- Limitations of the study include small group numbers and 6-months exposure

Acknowledgements

Cognition Therapeutics thanks the participants and their caregivers, as well as the study site investigators and staff. We also thank NIH / NIA for continued support of CT1812 development.

Conclusions

- This study provides evidence that CT1812 may slow cognitive decline in people with mild-to-moderate AD
- A dose range identified with evidence of cognitive benefits and favorable safety and tolerability profile
- Magnitude and durability of response will be investigated in larger, longer-duration clinical trials
- Early AD population is being studied in the ongoing 18-month COG0203 'START' study in 540 patients (NCT05531656)

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SHINE COG0201 study (NCT03507790) partially funded by $31M NIA grant (R01AG058660)
CT1812 is an investigational therapeutic that has not been approved for any use by the US Food and Drug Administration

References:
1. Izzo NJ, Yuede CM, LaBarbera KM, et al. *Alzheimer's Dement*. 2021 Aug; 17(8):1365-1382
2. LaBarbera, K.M., Sheline, Y.I., Izzo, N.J. et al. *Transl Neurodegener* 2023, 12(24)
3. Cut-offs from Clinical Neurochemistry Lab at Sahlgrenska University Hospital in Gothenburg, Sweden or study protocol