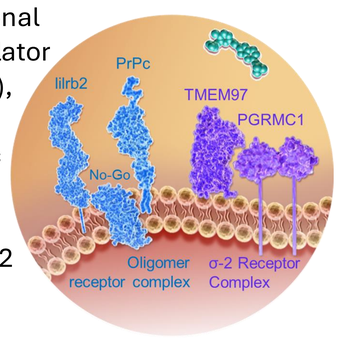
IDENTIFICATION OF CSF PROTEINS THAT CORRELATE WITH COGNITIVE OUTCOMES IN PARTICIPANTS OF PHASE 2 STUDY SHINE EVALUATING EFFECTS OF CT1812 IN PATIENTS WITH ALZHEIMER'S DISEASE

B.N. Lizama[1], K. Pandey[2], D. Duong[2,3], N. Seyfried[3], M. Grundman[4], A.O. Caggiano[1] , M,E. Hamby[1]

Affiliations: [1]Cognition Therapeutics, Research, Pittsburgh, PA, United States of America, [3]Emtherapro Inc, Systems Biology, Atlanta, GA, United States of America, [2]Emory University School of Medicine, Biochemistry, Atlanta, GA, United States of America, [5]Global R&D Partners, LLC and Department of Neurosciences, University of California, San Diego, CA, United States of America

INTRODUCTION

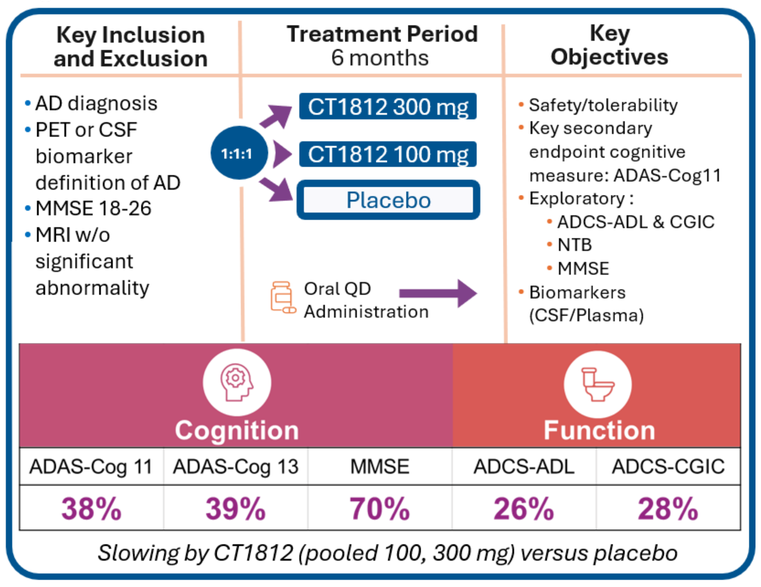
CT1812 (zervimesine) is an investigational brain-penetrant small molecule modulator of the sigma-2 receptor (S2R, *TMEM97*), that displaces Aβ oligomers bound to synapses[1] (*Schema 1*). In a post hoc analysis of Alzheimer's disease (AD) participants of the SHINE trial (NCT03507790), treatment with CT1812 slowed cognitive decline compared to placebo (ADAS-Cog11; 38% slowing in mITT population, 95% slowing in pre-specified p-Tau217 subgroup[2]).



Schema 1

SHINE was a randomized, double-blind, placebo-controlled Phase 2 clinical trial assessing safety and tolerability, exploratory cognitive and functional outcome measures, and exploratory biomarker effects of two CT1812 doses (100mg, 300mg; oral, once daily) in patients with mild to moderate AD (***Figure 1***).

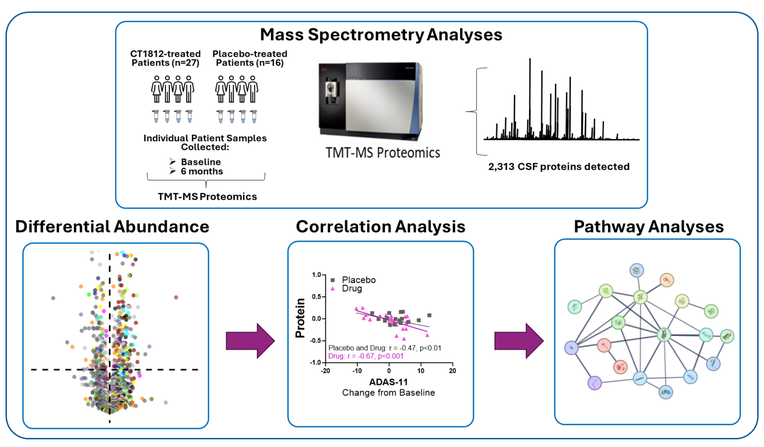
Figure 1



GOAL: Evaluate CSF proteomes from SHINE to identify CT1812 pharmacodynamic biomarkers of disease modification via correlation analysis with ADAS-Cog11

METHODS

A post hoc CSF proteomic sub-study of 45 participants was performed using tandem-mass tag mass spectrometry (TMT-MS) at baseline and end-of-study. CSF from treatment-compliant participants were analyzed (N=43; determined by CT1812 exposure levels). Pearson correlation analysis was performed on change from baseline (CFB) of protein levels to CFB in ADAS-Cog11 scores, followed by pathway analysis via STRING (v12).



RESULTS

CSF Proteomic Analysis Identified Biomarkers Correlated with ADAS-Cog11

Top 20 Most Significant			
Protein name	UniProt ID	p-value	r value
DLD	P09622	6.50E-06	-0.63
IGKV1-37	A0A075B6S9	4.16E-05	0.58
PAM	P19021	6.29E-05	-0.57
IGHV1-18	A0A0C4DH31	6.54E-05	0.57
IGHD	A0A087WUS7	1.38E-04	0.55
GAP43	P17677	1.40E-04	-0.55
SPARCL1	Q14515	1.53E-04	-0.55
GLG1	Q92896	1.63E-04	-0.54
IGKV1D-33	P01593	1.75E-04	0.54
OPCML	Q14982	1.77E-04	-0.54
NCAM1	H7BYX6	1.86E-04	-0.54
PIANP	F5H191	1.90E-04	-0.54
CDH2	P19022	2.14E-04	-0.54
LSAMP	H3BLU2	2.19E-04	-0.54
RAB14	P61106	2.37E-04	0.53
NRXN1	E7ERL8	2.39E-04	-0.53
NRXN2	Q9P2S2	2.60E-04	-0.53
BCAN	Q96GW7	2.62E-04	-0.53
PRNP	A2A2V1	3.06E-04	-0.52
SCG3	Q8WXD2	3.19E-04	-0.52

Fig 2. Table lists the top most significant (p≤0.05) proteins correlated with ADAS-Cog11 change from baseline. Proteins of interest indicated in bold.

Proteins Related to Amyloid Biology Are Correlated With ADAS-Cog11

A

Protein name	UniProt ID	Protein description	Placebo and Drug		Drug-treated Only	
			p-value	Pearson r value	p-value	Pearson r value
APLP1	P51693-2	Amyloid-like protein 1	1.67E-03	-0.47	1.47E-04	-0.67
APLP2	Q06481	Amyloid-like protein 2	5.14E-03	-0.42	1.66E-03	-0.58
APOE	P02649	Apolipoprotein E	6.35E-03	-0.41	1.54E-03	-0.58
APP	P05067	Amyloid-beta precursor protein	1.44E-03	-0.47	1.28E-04	-0.67
CLU	H0YC35	Clusterin/ApoJ	6.01E-03	0.44	9.33E-03	0.53
PGRMC1	O00264	Progesterone receptor membrane component 1; S2R component	3.28E-03	-0.44	1.13E-02	-0.48
PRNP	A2A2V1	Prion protein (PrPc); S2R-interacting protein	3.06E-04	-0.52	8.24E-04	-0.61

B

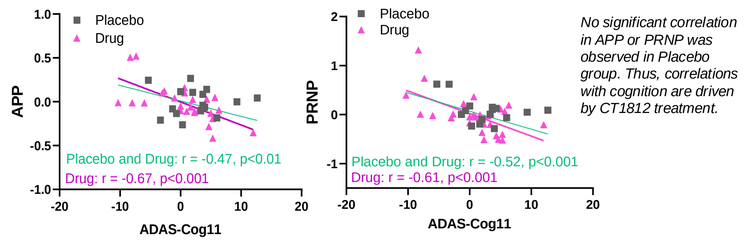
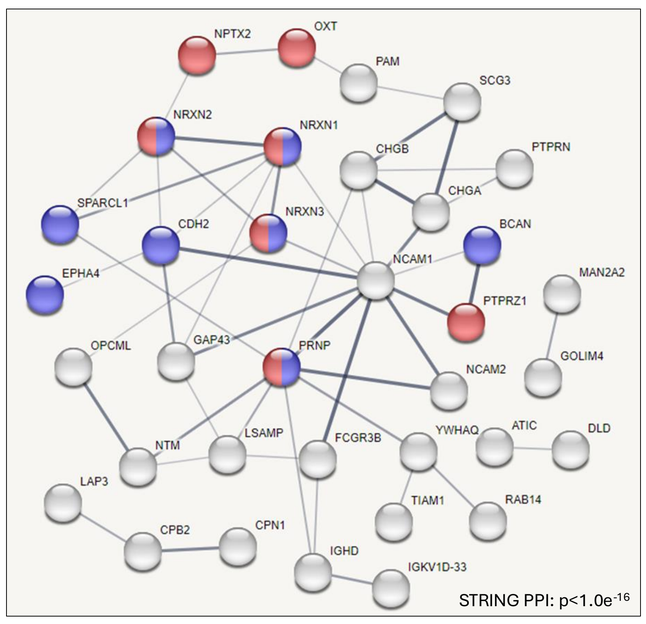


Fig 3. A) Significant (p≤0.05) correlates that relate to amyloid biology, as well as S2R interacting proteins. **B)** Scatterplots of APP and PRNP protein CFB and ADAS-Cog11 CFB show significant correlation with CT1812 treatment.

Proteins Correlated With ADAS-Cog11 Are Enriched In Synapse-related Pathways

A



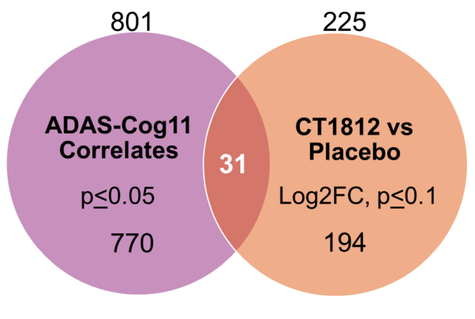
B

GO Term ID	Biological Process Term Description	Strength	FDR
GO:0007155	Cell adhesion	0.73	1.20E-03
GO:0007158	**Neuron cell-cell adhesion**	1.94	1.70E-03
GO:0008038	**Neuron recognition**	1.56	1.70E-03
GO:0050808	**Synapse organization**	1.02	1.70E-03
GO:0097118	**Neuroligin clustering involved in postsynaptic membrane assembly**	2.54	1.70E-03
GO:0008037	Cell recognition	1.15	1.39E-02
GO:0007399	**Nervous system development**	0.48	1.43E-02
GO:0007611	**Learning or memory**	0.95	2.30E-02
GO:0007416	**Synapse assembly**	1.20	2.64E-02
GO:0035176	Social behavior	1.42	2.67E-02

Fig 4: A) Proteins strongly correlated with ADAS-Cog11 (65 proteins, p≤0.05 and r≥|0.5|) were analyzed for pathway enrichment using STRING, illustrating the interconnectivity between proteins, with Protein-Protein enrichment p value of $1.0e^{-16}$. For visualization, disconnected nodes not shown. **B)** Top 10 Gene Ontology Biological Process terms (sorted by False Discovery Rate, FDR) are listed. Pathways of interest indicated in bold.

Candidate CSF Biomarkers of Favorable Direction With Cognition By CT1812 Identified

A



B

5 proteins changed in a favorable direction with cognition

Protein Name	CT1812 vs Placebo (Log2 FC)	AD vs Ctrl[3] (Log2 FC)	Correlation with ADAS-Cog11
CALB2	↓ p≤0.1	↑ p≤0.05	p≤0.05
CLU	↓ p≤0.05	↑ p≤0.0001	p≤0.01
LAMA5	↓ p≤0.05	↑ p≤0.05	p≤0.05
MASP1	↓ p≤0.05	↑ p≤0.0001	p≤0.05
SERPINA3	↓ p≤0.01	↑ p≤0.0001	p≤0.05

Fig 5. A) Venn diagram illustrates overlapping proteins correlated with ADAS-Cog11 (p≤0.05) and differentially abundant in CSF (CT1812 vs placebo (p≤0.1)). **B)** Overlapping trending (p≤0.1) or significant (p≤0.05) proteins changed with CT1812 vs placebo in a favorable direction with cognition.

CONCLUSIONS

- Proteins significantly correlated with cognition were consistent with the impact of CT1812 on synaptic protection and mechanisms in amyloid biology.
- These exploratory biomarker analyses, together with CT1812-associated trends in slowing cognitive decline, particularly in a pre-specified p-Tau217 subgroup, supports advanced clinical development of CT1812 for Alzheimer's disease.

Biomarker correlates with cognition identified in the SHINE trial studying effects of CT1812 (zervimesine) in Alzheimer's disease patients

Other Presentations on CT1812 by Cognition Therapeutics

Symposium Apr 1, at 14:45: POSITIVE IMPACT OF CT1812 TREATMENT ON PLASMA BIOMARKERS IN LOWER P-TAU217 SUBGROUP ALIGNS WITH CLINICAL BENEFITS IN MILD TO MODERATE AD PATIENTS
M. Hamby, S. Kavanagh, V. Di Caro, H. Zetterberg, K. Blennow, C. Teunissen, M. Grundman, A. Caggiano.

SHIFT 02-172: CSF PROTEOMIC BIOMARKER ANALYSIS FROM PHASE 2 STUDY SHINE IDENTIFIED EFFECTS OF S2R MODULATOR CT1812 IN ALZHEIMER'S DISEASE
B. Lizama, K. Pandey, D. Duong, N. Seyfried, E. Cho, M. Grundman, V. Di Caro, A. Caggiano, M. Hamby.

SHIFT 01-285: IDENTIFICATION OF MOLECULAR CORRELATES WITH CT1812 TREATMENT-RELATED DECREASE IN NFL CSF LEVELS CONNECTED TO SIGMA-2 RECEPTOR
V. Di Caro, E. Cho, B. Lizama, K. Pandey, D. Duong, N. Seyfried , K. Blennow, H. Zetterberg, M. Grundman , A. Caggiano, M. Hamby.

Visit cogrx.com for a complete list of publications and conference posters:

ClinicalTrials.gov: NCT03493282
Supported by National Institute on Aging: R01AG057553

Corresponding author: mhamby@cogrx.com

REFERENCES
1. Izzo, NJ, et al. Preclinical and clinical biomarker studies of CT1812: A novel approach to Alzheimer's disease modification. Alz & Dementia 2021.
2. Vijverberg EGB, et al. Results from COG0201: a Randomized, Placebo-controlled, Double-blind, International, Phase 2 Study to Evaluate the Safety and Efficacy of CT1812 in Adults with Mild-to-Moderate Alzheimer's Disease: Focus on Pre-specified Lower p-tau217 Subgroup. Slides presented at Clinical Trials on Alzheimer's Disease (CTAD) 2024; Madrid, Spain
3. Johnson ECB, et al. Large-scale deep multi-layer analysis of Alzheimer's disease brain reveals strong proteomic disease-related changes not observed at the RNA level. Nat. Neurosci. 2022