CSF PROTEOMIC BIOMARKER ANALYSIS FROM PHASE 2 STUDY SHINE IDENTIFIED EFFECTS OF S2R MODULATOR CT1812 IN ALZHEIMER'S DISEASE

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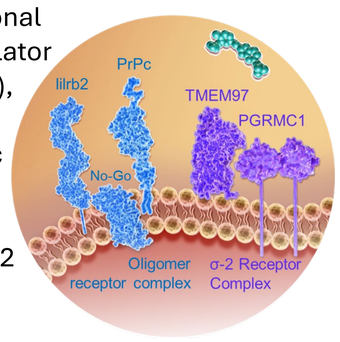
INTRODUCTION

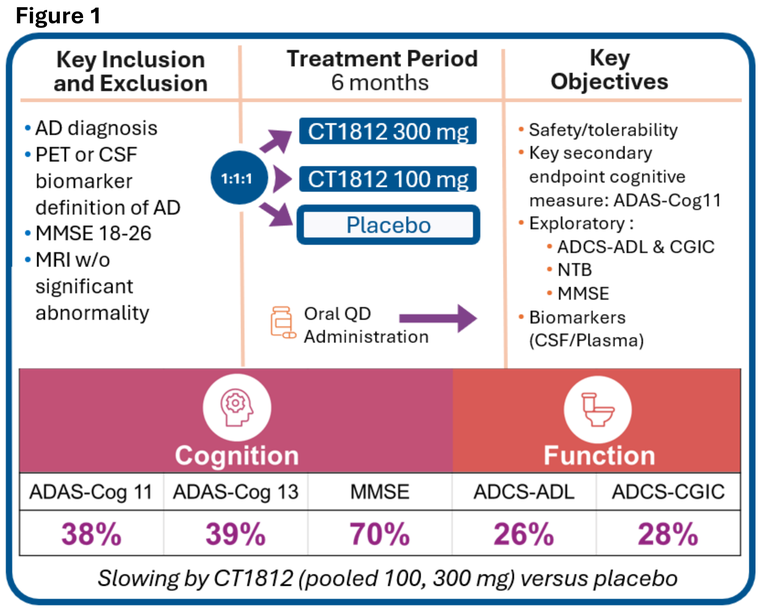
CT1812 (zervimesine) is an investigational brain-penetrant small molecule modulator of the sigma-2 receptor (S2R, *TMEM97*), that displaces Aβ oligomers bound to synapses[1] (*Schema 1*). In a post hoc analysis of Alzheimer's disease (AD) participants of the SHINE trial (NCT03507790), treatment with 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***).

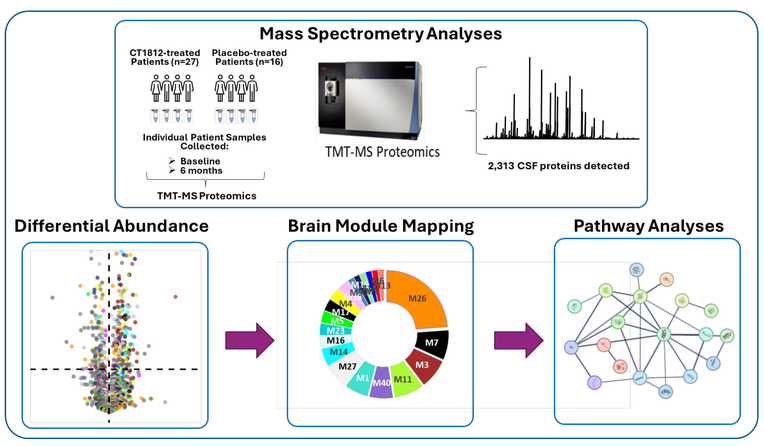
Figure 1



GOAL: Exploratory evaluation of CSF proteomes from SHINE to identify CT1812 pharmacodynamic biomarkers of target/pathway engagement and disease modification

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). Change from baseline was calculated, and differential abundance analysis (combined CT1812 doses vs placebo) was performed, followed by brain protein network and pathway analyses (STRING v12 and Metacore v24.3.71800, p≤0.05).



RESULTS

CSF Proteomic Analysis Identified Pharmacodynamic (PD) Biomarkers Impacted by CT1812

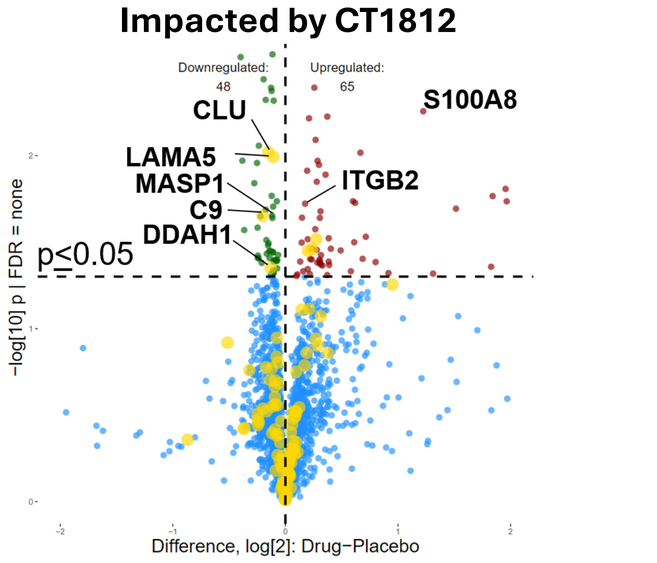


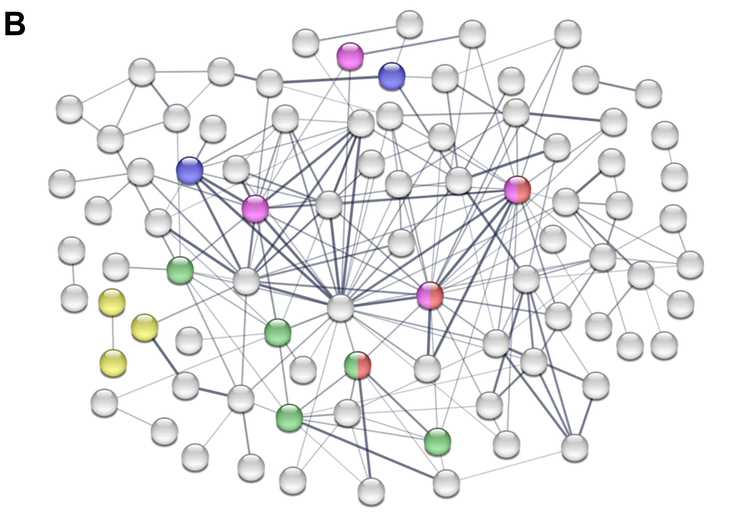
Fig 2. Volcano plot illustrates differentially abundant proteins (113 total; CT1812 vs Placebo, p≤0.05). Proteins of interest include AD priority biomarkers (yellow) clusterin (CLU, ApoJ), LAMA5, C9 and DDAH1, as well as inflammation-related proteins MASP1 and S100A8 .

Pathways Enriched by CT1812 Treatment Are Related to Synapses and Immune Response

A

Top MetaCore Pathway Maps (Drug-Placebo, 113 proteins p≤0.05)	p-value
Protein folding and maturation: Angiotensin system maturation	5.21E-10
Putative pathways of **activation of classical complement system** in major depressive disorder	6.95E-04
G-protein signaling: RhoA inhibition	1.44E-03
Development: TGF-beta-dependent induction of EMT via RhoA, PI3K and ILK	2.97E-03
Immune response: Lectin induced complement pathway	3.77E-03
Apoptosis and survival: Granzyme B signaling	3.77E-03
Immune response: Antigen presentation by MHC class I, classical pathway	4.68E-03
Cytoskeleton remodeling: Regulation of actin cytoskeleton organization by the kinase effectors of Rho GTPases	5.72E-03
Development: Regulation of cytoskeleton proteins in oligodendrocyte differentiation and myelination	6.00E-03
Oxidative stress: Role of Sirtuin1 and PGC1-alpha in activation of antioxidant defense system	6.29E-03

B



Biological Process
- Positive regulation of tau-protein kinase activity
- Synapse maturation
- Axon guidance

KEGG
- Complement and coagulation cascades
- Lysosome

GO Term ID	Term Description	Strength	FDR
GO:1902949	**Positive regulation of tau-protein kinase activity**	1.89	7.70E-03
GO:0015670	Carbon dioxide transport	1.71	2.70E-03
GO:0042744	Hydrogen peroxide catabolic process	1.55	1.20E-03
GO:0060074	**Synapse maturation**	1.50	3.61E-02
GO:0015671	Oxygen transport	1.50	3.61E-02

Fig 4. A) Differentially abundant proteins (113 total, p≤0.05) were analyzed for pathway enrichment using Metacore. **B)** STRING analysis illustrates the interconnectivity between proteins, with Protein-Protein enrichment p value of $1.0e^{-16}$. For visualization, disconnected nodes not shown. The top GO Biological Process terms are listed (sorted by strength) with False Discovery Rate (FDR) shown.

CSF PD Biomarkers of CT1812 Map to Disease-relevant Brain Networks

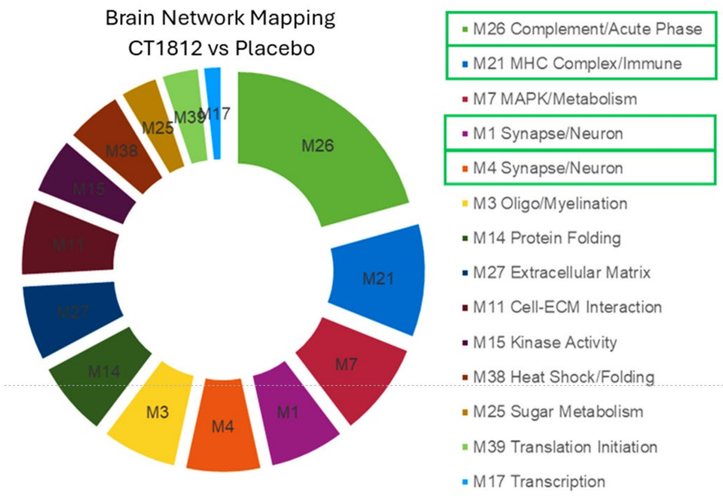


Fig 3. Differentially abundant proteins (113 total; CT1812 vs Placebo, p≤0.05) were mapped to 44 established protein co-expression network modules built from samples from healthy individuals, asymptomatic and symptomatic AD patients[3] (top 15 listed).

Candidate CSF Biomarkers Identified Include Novel and Replicated CT1812 PD Biomarkers

Protein Name	CT1812 vs Placebo (Log2 FC)	AD vs Ctrl[3] (Log2 FC)	Protein description
ATP6AP1[a,b]	↓ p<0.05	↓ p<0.0001	Important for vesicle/lysosome function
C4A	↓ p<0.05	↑ p<0.001	Involved in complement cascade; plasma levels increased in AD
CLU[a,b]	↓ p<0.05	↑ p<0.0001	Involved in immune response and amyloid biology, linked to AD
COL6A3[b,c]	↓ p<0.05	↑ p<0.0001	Genetically linked to movement disorders including PD
DDAH1[b]	↓ p<0.05	↑ p<0.0001	Regulates nitric oxide generation; AD CSF biomarker
SERPINA3	↓ p<0.01	↑ p<0.0001	Linked to amyloid oligomer toxicity, modulates neuroinflammation in AD
LAMA5	↓ p<0.05	↑ p<0.05	Increased in AD and MCI
MASP1	↓ p<0.05	↑ p<0.0001	Involved in lectin pathway of complement activation
ITGB2[a,b]	↑ p<0.05	↑ p<0.001	Involved in inflammation signaling; CSF levels increased in AD
S100A8[a,b]	↑ p<0.01	n.s	Regulates amyloid-beta aggregation; plasma levels increased in AD

Fig 5. PD biomarkers of interest. Replication with prior CT1812 exploratory proteomic biomarker analyses indicated (a. SHINE-A CSF proteomics, b. SHINE-A/SPARC CSF proteomics meta-analysis, c. SPARC CSF proteomics).

CONCLUSIONS

- Proteins significantly affected by CT1812 may support a role for CT1812 in immune response and synapse related pathways.
- CSF proteomic analysis of the completed SHINE trial corroborated previously identified pharmacodynamic biomarkers of CT1812 pathway engagement and disease modification and facilitated identification of novel biomarkers.
- These data further our understanding of the proteins and pathways CT1812 impacts and help support the observed synaptoprotective mechanism-of-action and advanced clinical development of CT1812 for AD.

Exploratory CSF biomarker findings support a biological impact of CT1812 (zervimesine) in Alzheimer's disease patients

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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 02-277 : 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. Lizama, K. Pandey, D. Duong, N. Seyfried, M. Grundman, 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.

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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