Exploratory CSF Proteomics Biomarker Outcomes of The Phase 2 Clinical Trial SHINE to Assess The Effects of CT1812 in Alzheimer's Patients

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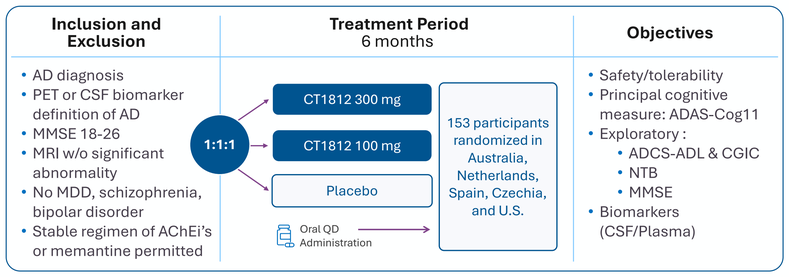
Key Takeaway: CSF biomarker findings of the SHINE trial shed light on potential CT1812 surrogate biomarkers such as CLU and SERPINA3 and biological pathways (e.g. vesicle trafficking) affected by CT1812.

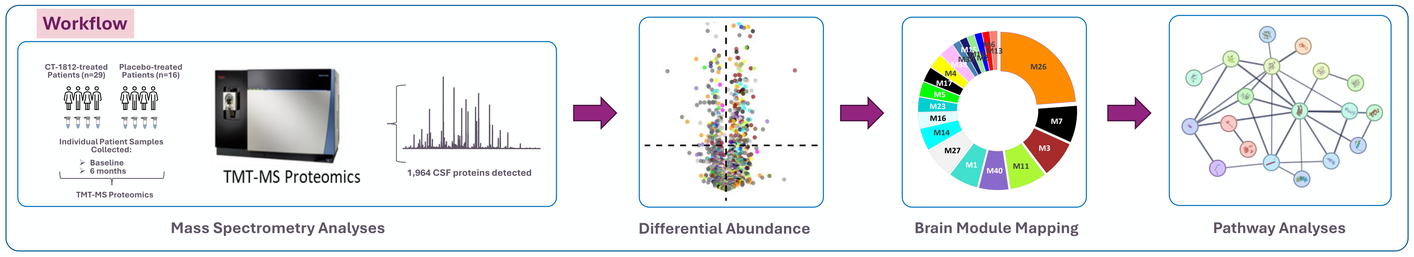
Background

SHINE (NCT03507790, COG0201) was a Phase 2 randomized, double-blind, placebo-controlled 6-month trial, conducted to study the effect of the experimental, sigma-2 receptor (S2R) modulator, CT1812, an Aβ oligomer antagonist, in patients with Alzheimer's (AD). An unbiased assessment of CSF proteomes from the patients that completed the SHINE trial was performed to identify pharmacodynamic (PD) biomarkers of target/pathway engagement and disease modification for CT1812.



Methods

- Tandem-mass tag mass spectrometry (TMT-MS) CSF proteomics was performed on baseline and end of study samples to test the effects of two doses of CT1812 compared to placebo in mild to moderate AD patients.
- Proteomic analysis from the first 24 participants was recently published[2]. Raw protein abundance data from all participants were combined, processed and normalized to remove batch effects before exploring effect of treatment.
- Change from baseline was calculated for participants for whom there were available CSF samples at the time of this analysis (N=45), and differential abundance analysis (CT1812 vs placebo) was performed to assess treatment effects followed by brain network mapping, Gene Ontology, and pathway analyses using STRING (v12.0) and MetaCore (24.2.71700) using p-value criterium p≤0.05.



Results

Brain Network Analysis Support Role for CT1812 Pharmacodynamic Biomarkers at Synapses

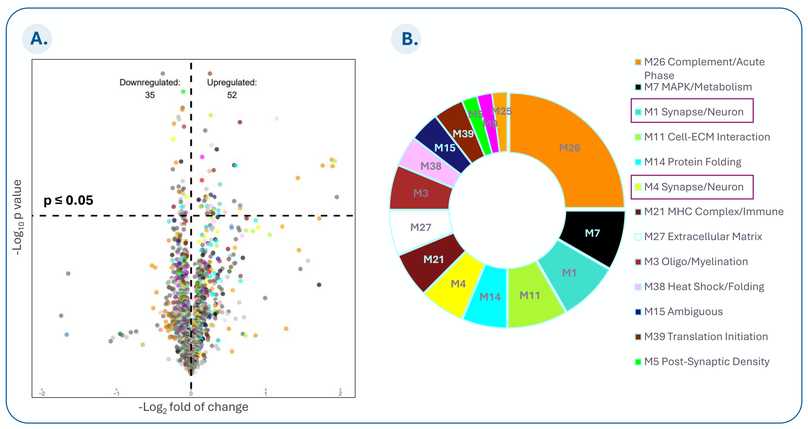


Figure 1. Differential abundant analysis of CSF from AD patients given CT1812 for 6 months vs placebo. **A)** Volcano plot illustrating the total of 87 differentially abundant proteins at p≤0.05. **B)** Differentially abundant proteins (CT1812 vs placebo; p≤0.05) were mapped to 44 previously established protein co-expression network modules built from samples from healthy individuals, asymptomatic and symptomatic AD patients[1] (top 15 shown here).

Pathway Analysis Identify Protein Folding, Immune Response and Oxidative Stress Pathways Significantly Altered in CSF

Top MetaCore Pathway Maps (CT1812 vs Placebo p ≤ 0.05)	p-value
Protein folding and maturation-Angiotensin system maturation	9.22E-11
G-protein signaling-RhoA inhibition	6.53E-04
Immune response -Antigen presentation by MHC class II	3.02E-03
Development-Regulation of cytoskeleton proteins in oligodendrocyte differentiation and myelination	3.32E-03
Oxidative stress -Role of Sirtuin1 and PGC1-alpha in activation of antioxidant defense system	3.48E-03
Signal transduction-Angiotensin II/AGTR1 signaling via Notch, Beta-catenin and NF-kB pathways	7.25E-03

N.B. non-relevant disease pathologies/organs excluded.

Figure 2. Differentially abundant proteins in CSF samples from AD patients given CT1812 vs placebo (p≤0.05) were analyzed for pathway enrichment using MetaCore.

GO Terms Vesicle and Secretory Granule are Associated with CT1812 Pharmacodynamic Biomarkers

A.

GO Terms	Term description	Strength	p-value
0070062	Extracellular exosome	0.74	6.82E-24
0005615	Extracellular space	0.60	1.82E-21
0031982	Vesicle	0.50	1.37E-15
0030141	Secretory granule	0.68	5.83E-06
0099503	Secretory vesicle	0.62	1.41E-05
0034774	Secretory granule lumen	0.90	2.43E-05
0030424	Axon	0.59	7.60E-03

N.B. Top 7 most relevant GO terms were selected.

B.

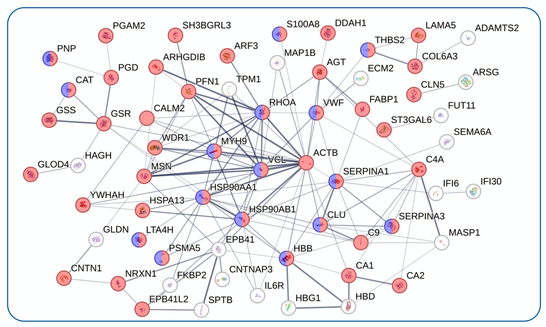
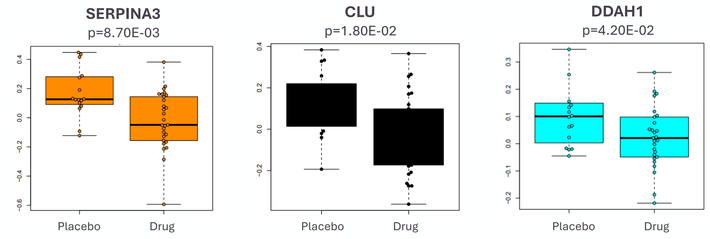


Figure 3. Differentially abundant proteins in CSF samples from CT1812 vs placebo (p≤0.05) were analyzed for **A)** gene ontology (GO) cellular components analysis using STRING (GO terms sorted by p-value). **B)** STRING protein-protein interaction map to show protein associated with GO terms: "vesicle", in red, and "secretory granule", in blue (medium confidence; proteins not connected not visualized).

A.



B.

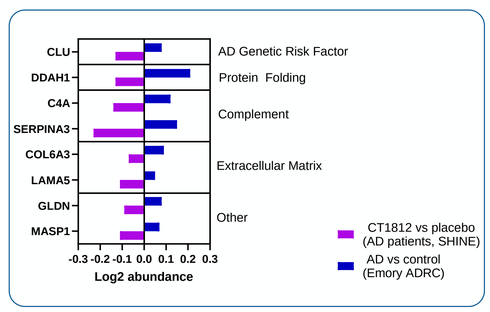


Figure 4. Within-study comparisons to CSF protein levels in reference standards (Emory ADRC AD and control) enabled comparison of the SHINE AD cohort to well-characterized AD and non-demented control CSF. **A)** Representative box plots to illustrate proteins significantly increased in AD compared to control CSF that are significantly downregulated in CT1812 vs placebo. **B)** 8 proteins are significantly (p≤0.05) normalized towards control with CT1812 (log2 change in abundance in AD vs control (blue) and CT1812 vs placebo (purple)).

Conclusions

- Pharmacodynamic biomarkers of CT1812 are identified, such as CLU, DDAH and SERPINA3, which may reflect improvement in disease dysregulation.
- Brain network mapping and pathway analysis of differentially abundant proteins supports role of CT1812 in synaptic biology, immune response, oxidative stress and vesicle trafficking.
- Comparative analysis to reference CSF standards identifies proteins disrupted in, or genetically linked to, AD that positively change towards normalization by 6 months treatment with CT1812.
- This data extends our knowledge from previously reported analysis[2] on how CT1812 can effectively change the patient proteome and provides evidence that the S2R modulator, CT1812 may be a promising disease modifying approach to AD.

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CT1812 is an investigational therapeutic that has not been approved for any use by the US Food and Drug Administration

References:
1. Johnson, E.C.B., et al.. Nat Neurosci 25, 213–225 (2022)
2. Lizama BN, et al. Neurobiol Dis. 2024 Jun 22;199:106575.

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