Exploratory CSF proteomic analysis of a pre-specified pTau217 subgroup from the SHINE clinical trial identifies biomarkers correlated with cognition improvement in Alzheimer's disease patients treated with zervimesine

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Key takeaway: Candidate CSF biomarkers correlated with cognition were identified in a subgroup exhibiting the greatest benefit with zervimesine (CT1812) treatment.

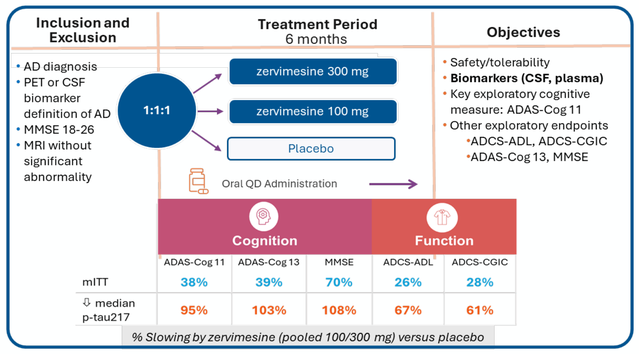
Background

The sigma-2 receptor (S2R) modulator zervimesine (CT1812) is an allosteric Aβ oligomer antagonist currently in Phase 2 clinical trials[1] for Alzheimer's disease (AD) and dementia with Lewy bodies[2]. Preclinical and clinical studies have shown that zervimesine displaces Aβ and α-synuclein oligomers from neurons[3], preserving synapses and restoring cognitive performance in a transgenic mouse model of AD[4].

Participants with AD treated with zervimesine exhibited 38% slowing of cognitive decline (ADAS-Cog11) compared to placebo in the mITT cohort of the SHINE trial (NCT03507790, COG0201) (*Schema 1*). However, in the pre-specified below-median p-tau217 subgroup a more robust, 95% slowing of cognitive decline was observed with zervimesine[5]. Given favorable clinical outcomes in the below-median p-tau217 subgroup (hereafter referred to as the low p-tau217 group), correlation analysis of the CSF proteome with ADAS-Cog11 was performed to elucidate mechanisms of zervimesine-mediated preservation of cognition.

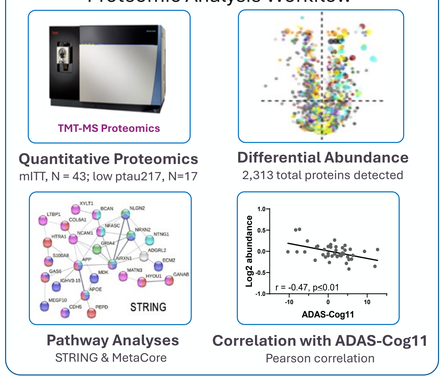
An exploratory CSF proteomic sub-study was conducted for the first 43 participants of SHINE with available CSF samples at baseline and 6 months, who were also actively taking their treatment, as indicated by bioanalysis of drug exposure levels (*Schema 2*). Pearson correlation analysis was performed on change from baseline (CFB) of protein levels to CFB in ADAS-Cog11 scores, followed by pathway analyses.

Trial Design: a Phase 2 Safety and Efficacy Study in Adults with Mild-to-Moderate AD



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 zervimesine doses (100mg, 300mg; oral, once daily) in patients with mild-to-moderate AD. Topline results show positive signals in zervimesine-treated participants versus placebo for cognitive and functional measures, from the full trial cohort (mITT, N=150 participants) and from the prespecified subgroup defined by below-median (1 pg/mL) baseline levels of plasma pTau217 (N=69 participants).

Proteomic Analysis Workflow

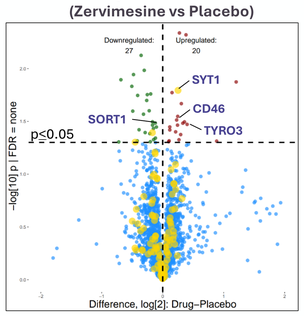


Schema 2. Overview of TMT-MS proteomics approach to quantify the change from baseline protein differential abundance (drug vs placebo) and downstream analyses to identify proteins correlated with ADAS-Cog11 and biological pathways associated with these proteins.

Results

Pharmacodynamic biomarkers of zervimesine identified in low p-tau217 group

A. Differentially abundant CSF proteins (Zervimesine vs Placebo)



B. Top significantly decreased (Zervimesine vs Placebo)

Protein	Log2FC	p-value
EMILIN1	-0.69	1.27E-02
NAPA	-0.51	1.47E-02
IGHV1OR15-1	-0.48	1.14E-02
GAS1	-0.41	1.79E-02
SPESP1	-0.35	7.49E-03
EDN3	-0.30	1.04E-02
ATP6AP1	-0.26	2.00E-02
RNF130	-0.25	1.76E-02
ITM2A	-0.22	2.51E-02
HSPE1	-0.20	1.74E-02

Top significantly increased (Zervimesine vs Placebo)

Protein	Log2FC	p-value
CSTA	1.20	1.34E-02
TGFBR1	0.38	4.79E-03
TYRO3	0.36	3.20E-02
SH3BGRL	0.33	3.29E-02
CRIM1	0.31	2.15E-02
UBE2D2	0.27	4.60E-03
SYT1	0.25	1.61E-02
SH3BGRL3	0.25	2.84E-02
CD46	0.23	3.07E-02
ST6GALNAC1	0.15	1.69E-02

C.

Top MetaCore Pathway Maps (Low p-tau217; Zervimesine vs Placebo, p≤0.05)	p-value
O-glycan biosynthesis	4.20E-04
Neurophysiological process_Synaptic vesicle fusion and recycling in nerve terminals	6.54E-03
Development_Keratinocyte differentiation	7.30E-03
G-protein signaling_RhoB activation	8.09E-03
Proteolysis_Ubiquitination pathway	9.77E-03
Immune response_IL-6 signaling via JAK/STAT	1.19E-02
Immune response_IL-6 signaling via MEK/ERK and PI3K/AKT cascades	1.29E-02
Alzheimer disease: synaptic dysfunction	1.43E-02
Development_Role of CDK5 in the nervous system	1.75E-02
Tau pathology in Alzheimer disease	2.11E-02
Signal transduction_BMP signaling via ALK-4 and TGF-beta receptor type I	4.36E-02
Development_TGF-beta-induction of EMT via ROS	4.58E-02

Figure 1. (A) Volcano plot of differential abundance of proteins altered by zervimesine vs placebo in low p-tau217 subgroup. Each data point in the scatter plot represents a protein (47 proteins p≤0.05 ; green: decreased, red: increased, yellow: AD priority biomarker[6,7]). **(B)** Topmost significant proteins increased (*top*) or decreased (*bottom*) in CSF samples from participants in the low p-tau217 group (sorted by log2 fold change). **(C)** MetaCore (version 24.4.71900) (sorted by p-value) pathway analyses of proteins p≤0.05. Pathways of interest related to AD pathology or S2R biology are indicated in bold. *N.B.* Top pathway maps exclude non-relevant tissues or diseases.

CSF protein correlates (106) with ADAS-Cog11 identified in low p-tau217 group

A.

Term ID	GO Biological Process Terms	strength	FDR
GO:0051919	Positive regulation of fibrinolysis	2.29	4.90E-03
GO:0051917	Regulation of fibrinolysis	1.77	4.90E-03
GO:0099560	**Synaptic membrane adhesion**	1.66	5.50E-03
GO:0042730	Fibrinolysis	1.62	3.53E-02
GO:0031102	**Neuron projection regeneration**	1.53	1.10E-02
GO:0072378	Blood coagulation, fibrin clot formation	1.52	4.94E-02
GO:0006956	**Complement activation**	1.42	9.60E-04
GO:0006958	**Complement activation, classical pathway**	1.42	1.91E-02
GO:0030195	Negative regulation of blood coagulation	1.36	2.60E-02
GO:0006911	**Phagocytosis**, engulfment	1.31	2.93E-02

B.

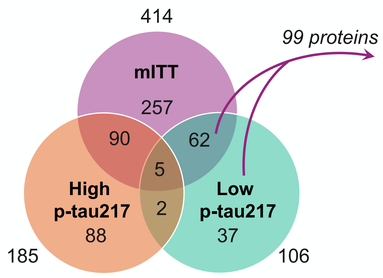
C.

Top MetaCore Pathway Maps	p-value
Signal transduction_Anti-inflammatory and cardioprotective Adiponectin signaling	3.99E-04
Gamma-Secretase regulation of neuronal cell development and function	1.52E-03
G-protein signaling_Rac1 activation	3.21E-03
Gamma-secretase proteolytic targets	4.01E-03
Development_Role of CDK5 in the nervous system	5.07E-03
LRRK2 in neurons in Parkinson's disease	7.67E-03
The complement system and macrophages in neuropathic pain	1.20E-02
Immune response_Lectin induced complement pathway	1.70E-02
Protein folding and maturation_Posttranslational processing of neuroendocrine peptides	1.70E-02
Neurophysiological process_Synaptic vesicle fusion and recycling in nerve terminals	1.84E-02

Figure 2. Analysis of 106 CSF proteins with log2 abundance change from baseline (CFB) that correlate with ADAS-Cog11 CFB (p≤0.01) in low p-tau217 group (zervimesine and placebo). **(A)** Top STRING (sorted by strength) GO biological process terms and **(B)** STRING PPI map of proteins in low p-tau217 group, at confidence threshold 0.400. **(C)** MetaCore (version 24.4.71900) (sorted by p-value) pathway analyses of protein correlates. Pathways of interest related to AD pathology or S2R biology are indicated in bold. Pathways associated with amyloid biology, complement activation, immune response, and synapse to be most altered pathways with zervimesine treatment compared to placebo-treated controls.

CSF protein correlates (99) with ADAS-Cog11 selective to the low, but not high, p-tau217 group identified

A.



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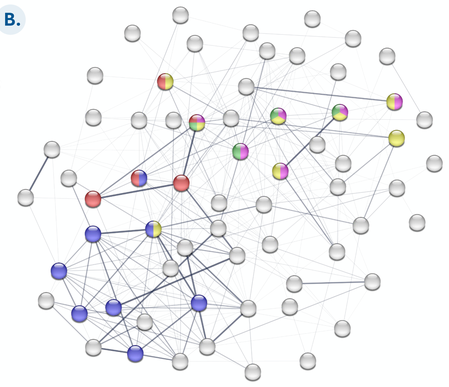


Pathways of Interest
- Complement and coagulation cascades (*KEGG*)
- Phagosome (*KEGG*)
- Glutamatergic synapse (*GO Component*)
- Integral component of presynaptic membrane (*GO Component*)
- Integral component of postsynaptic membrane (*GO Component*)

Figure 3. CSF proteins with log2 abundance change from baseline (CFB) that correlate with ADAS-Cog11 CFB (p<0.01) in zervimesine and placebo treated participants. **(A)** Venn diagram to show common correlates (p≤0.01). **(B)** Proteins correlated with ADAS-Cog11 in the low p-tau217 group, excluding the proteins in common with the high p-tau217 group (99 total, indicated with arrows), were used for STRING analysis. The STRING PPI map illustrates the connectivity of proteins correlated with ADAS-Cog11 (confidence threshold 0.150; unconnected nodes hidden), with pathways of interest indicated (FDR≤0.05).

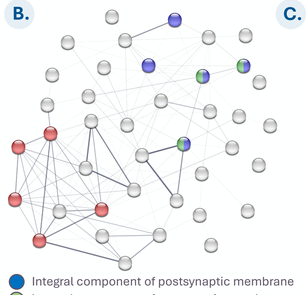
ADAS-Cog11 correlates (62) identified in both mITT and low p-tau217 groups relate to immune response and synapses

A.

Term ID	GO Component Term	strength	FDR
GO:0042824	**MHC class I peptide loading complex**	2.04	1.66E-02
GO:0042571	Immunoglobulin complex, circulating	1.91	2.23E-02
GO:0099059	**Integral component of presynaptic active zone membrane**	1.79	3.15E-02
GO:0019814	Immunoglobulin complex	1.77	3.60E-03
GO:0071556	Integral component of lumenal side of endoplasmic reticulum membrane	1.75	3.60E-03
GO:1905370	Serine-type endopeptidase complex	1.75	3.60E-03
GO:0072562	Blood microparticle	1.32	9.80E-04
GO:0099055	**Integral component of postsynaptic membrane**	1.32	9.80E-04
GO:0099056	**Integral component of presynaptic membrane**	1.29	2.89E-02
GO:0005791	Rough endoplasmic reticulum	1.26	3.35E-02

Term ID	KEGG Pathway Term	strength	FDR
hsa04610	**Complement and coagulation cascades**	1.48	2.90E-04

B.



C.

Top MetaCore Pathway Maps	p-value
Gamma-Secretase regulation of neuronal cell development and function	2.82E-04
Gamma-secretase proteolytic targets	7.65E-04
Immune response_CD40 signaling in B cells	9.13E-04
Transcription_HIF-1 targets	1.26E-03
Protein folding and maturation_Bradykinin / Kallidin maturation	2.36E-03
Immune response_Lectin induced complement pathway	5.68E-03
Protein folding and maturation_Posttranslational processing of neuroendocrine peptides	5.68E-03
Immune response_Antigen presentation by MHC class I, classical pathway	6.59E-03
Immune response_Classical complement pathway	7.32E-03
Immune response_IL-4-responsive genes in type 2 immunity	1.00E-02
G-protein signaling_Rac1 activation	1.21E-02
Signal transduction_Anti-inflammatory and cardioprotective Adiponectin signaling	1.65E-02
The complement system and macrophages in neuropathic pain	2.96E-02
Putative pathways of MHC class I-dependent postsynaptic long-term depression in major depressive disorder	4.65E-02
Immune response_Oncostatin M signaling via JAK-STAT	4.87E-02

Figure 4. The 62 proteins significantly correlated with ADAS-Cog11 in both the mITT and low p-tau217 group, excluding those also correlated in the high p-tau217 group (Figure 3A), which may represent the robust biomarkers of cognition, were analyzed using **(A)** STRING pathway analysis, **(B)** STRING PPI map (confidence threshold 0.150; all nodes shown) and **(C)** MetaCore pathway analysis. Pathways of interest related to AD pathology or S2R biology are indicated in bold. *N.B.* Top pathway maps exclude non-relevant tissues or diseases.

Conclusions

- **CSF pharmacodynamic biomarkers of zervimesine (CT1812) were identified by proteomic differential abundance analysis from a biomarker-defined patient population that exhibited the greatest benefit from zervimesine treatment**
- **Protein correlates of cognition were identified in a biomarker-defined patient population, which highlight a role for immune response and synapse-related biology in improved cognition by zervimesine**
- **The CSF biomarker findings are in alignment with the pronounced favorable clinical outcome in the biomarker-defined patient population and support further clinical development of zervimesine for AD**

Other Presentations by Cognition Therapeutics at AAIC 2025

Poster #106858, Sunday July 27: Zervimesine (CT1812) Treatment Benefits Patients with Lower Baseline Plasma p-tau217 Across the Mild-to-Moderate AD Spectrum

Poster #107075, Monday July 28: Plasma proteomic analysis of a biomarker-defined subpopulation in the SHINE Ph2 trial to identify molecular correlates to the favorable decrease in the neuroinflammatory marker GFAP with zervimesine in Alzheimer's disease participants

Featured Research Session, Tuesday July 29, 8:00-8:45AM: Baseline Characteristics and Results of the Phase 2 COG1201 SHIMMER Study of Zervimesine (CT1812)

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CT1812 is an investigational therapeutic that has not been approved for any use by the US Food and Drug Administration. The USAN Council has adopted zervimesine as the United States Adopted Name (USAN) for CT1812.

References: 1. Clinical trials NCT03493282, NCT03507790, 2. Clinical trial NCT05225415, 3. Lizama BN, et al. *Int J Mol Sci*. 2023 Mar 26;24(7):6251., 4. Izzo NJ et al., *PLoS One*. 2014 Nov 12;9(11):e111898. 5. Hamby ME et al., AD/PD 2025 Podium Presentation, ID 3184. 6.Higginbotham L et al. *Sci Adv*. 2020 Oct 21;6(43):eaaz9360. 7. Johnson ECB et al. *Nat Neurosci*. 2022 Feb;25(2):213-225.

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