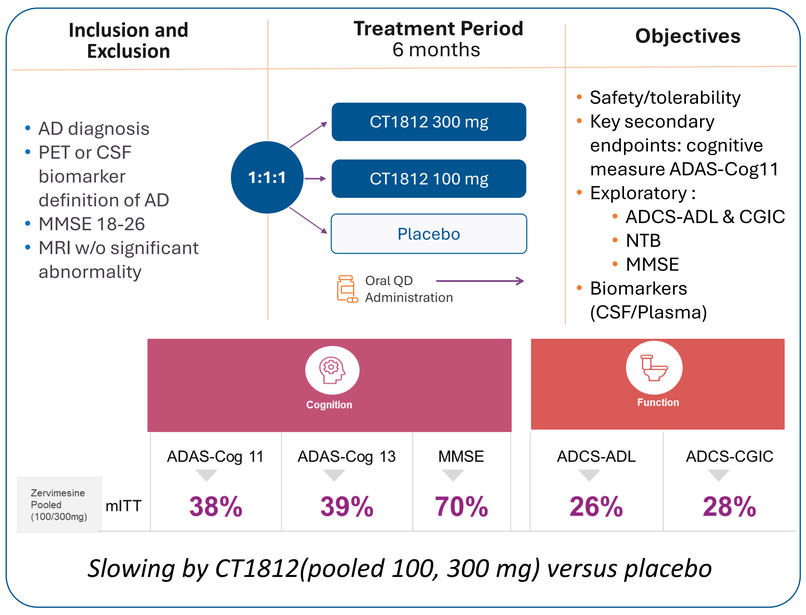
IDENTIFICATION OF MOLECULAR CORRELATES WITH CT1812 TREATMENT-RELATED DECREASE IN NfL CSF LEVELS CONNECTED TO SIGMA-2 RECEPTOR

Valentina Di Caro[1], Eunah Cho[1], Britney Lizama[1], Kiran Pandey[2], Duc Duong[2], Nicholas Seyfried[3], Kaj Blennow[4], Henrik Zetterberg[4], Michael Grundman[5], Anthony Caggiano[1], Mary Hamby[1]

1 Cognition Therapeutics, Inc, Pittsburgh, USA, 2 Emtherapro Inc, Atlanta, USA; 3 Emory University School of Medicine, Atlanta, USA , 4 Gothenburg University, Goteborg, Sweden; 5 Global R&D Partners, LLC and Department of Neurosciences U of CA, San Diego, CA, USA.

INTRODUCTION

Neurofilament light (NfL) is a recognized biomarker of neurodegeneration, in which CSF levels are elevated in multiple neurodegenerative disorders, including Alzheimer's disease (AD). Previously we reported a decrease in CSF NfL levels in AD patients treated with the sigma-2 receptor (S2R) modulator CT1812 (zervimesine) in the SHINE Ph2 trial relative to placebo (**Schema 1, Figure 1**). An exploratory proteomic biomarker analysis for SHINE was performed to identify proteins and pathways that correlated with changes in CSF NfL levels.



Schema 1: SHINE study design and overall clinical outcomes.

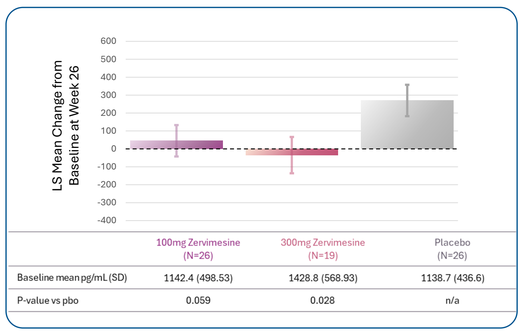
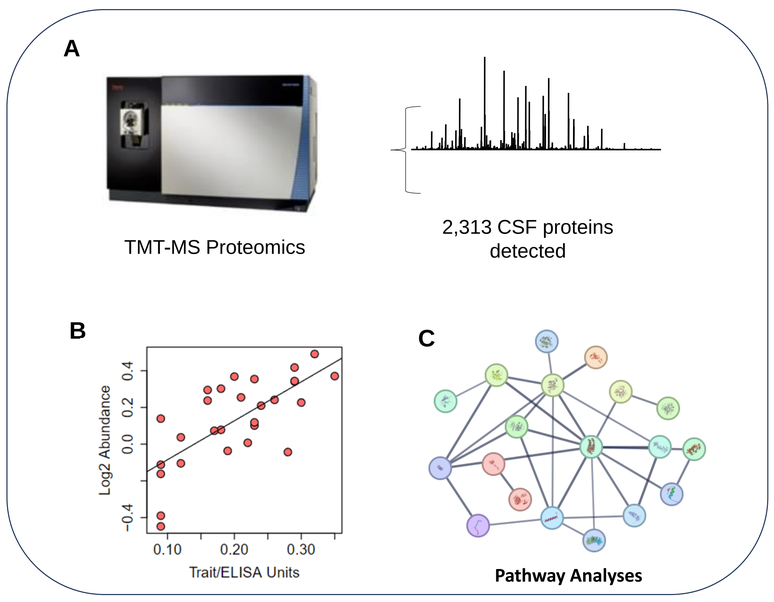


Figure 1: CT1812 decreases levels of NfL in CSF after 6 months of treatment.

METHODS

SHINE (COG0201) was a Phase 2 randomized, double-blind, placebo-controlled trial. Participants (N=150) received a daily oral dose of CT1812 (100 or 300 mg) or placebo for 6-months. NfL in CSF was measured by Lumipulse (N=68) at baseline and after 6 months of treatment and change from baseline (CFB) calculated. TMT-mass spectrometry proteomics (TMT-MS) was performed on CSF collected at the same time points in a subgroup of 45 participants. Pearson correlation analysis was performed between NfL CFB and CSF proteomes (N=41, mITT, treatment compliant participants, p≤0.05). Pathway analysis was performed using STRING (V12.0) and MetaCore (24.4.71900) using p value criterium p≤0.05.



Schema 2. Following CSF sample analysis via TMT-MS proteomics (A), Pearson correlation analysis was performed between NfL CFB and each protein in the CSF proteome (B). Identified correlates (p≤0.05) were subjected to pathway analysis (C).

RESULTS

Sets of Proteins Associated with NfL CSF levels

A

Protein	Protein ID	p-value	R-value
FABP3	P05413	1.17E-06	0.66
MPZ	E7EWP3	4.70E-06	0.63
S100B	P04271	3.61E-05	0.59
CADPS	H0YFP0	5.21E-05	0.69
OLFM3	Q96PB7	2.27E-04	-0.60
AKR1B1	P15121	2.40E-04	0.56
MBP	P02686	4.18E-04	0.51
IGHV3-64	A0A087WWF0	5.68E-04	-0.61
NEFM	E7ESP9	8.19E-04	0.49
NEFL/NfL	P07196	9.47E-04	0.51

B

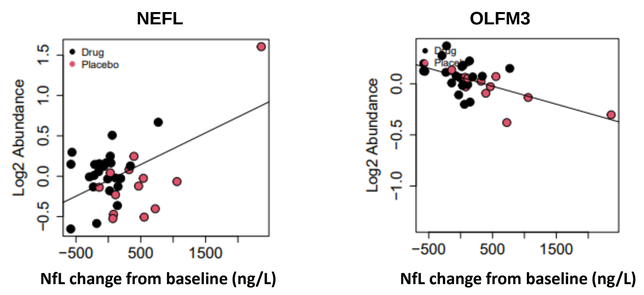


Figure 2: Top 10 most significant CSF proteins correlated to NfL are listed (p≤0.05). In bold protein associated to neurodegeneration (**A**); Representative scatter plots (**B**).

GO Terms Extracellular Space and Vesicle are Associated to NfL Correlates

A

GO Term ID	GO Component	Strength	p-value
0099160	Postsynaptic intermediate filament cytoskeleton	**2.37**	2.70E-02
0005615	Extracellular space	**0.48**	1.20E-03
0031410	Cytoplasmic vesicle	**0.45**	3.81E-02
0031982	Vesicle	**0.44**	1.20E-03
0005576	Extracellular region	**0.41**	1.40E-03
0005737	Cytoplasm	**0.17**	1.23E-02

B

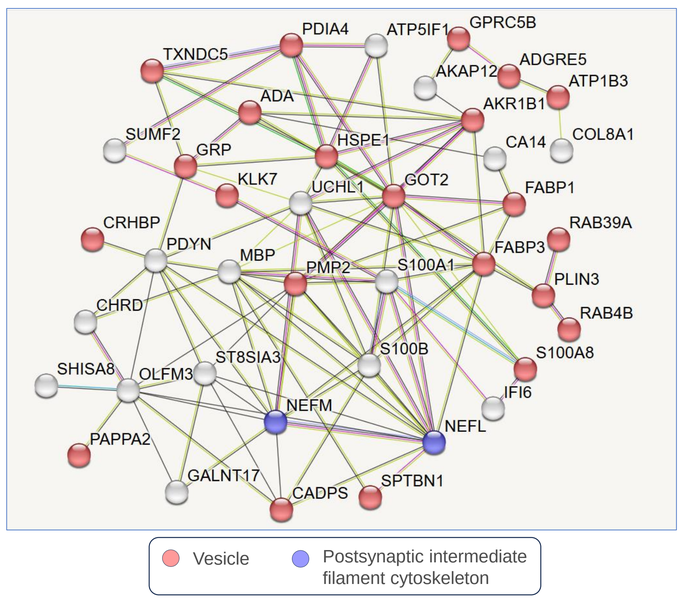


Figure 3: STRING pathway analysis of correlates to NfL CSF levels (p≤0.05). Gene ontology (GO) terms sorted by strength (**A**). Protein-protein interaction map of the 44 correlates to NfL CSF levels (p≤0.05). Low confidence, not connected proteins not shown (**B**).

Pathway Analyses Identify Protein Folding and Neuro System Development Pathways Significantly Associated to NfL Correlates

Top Metacore Pathway Maps, p≤0.05	p-value
Protein folding and maturation - Posttranslational processing of neuroendocrine peptides	**6.32E-09**
Neurophysiological process - Kappa-type opioid receptor signaling in the central nervous system	**3.93E-06**
Cytoskeleton remodeling - Neurofilaments in axon growth and synapses	**2.06E-03**
Development - Role of CDK5 in the nervous system	**2.70E-02**
Development - NOTCH signaling in the nervous system	**2.82E-02**

Figure 4: NfL-correlated proteins (p≤0.05) were analyzed for pathway enrichment using MetaCore. Top pathways are listed (non-relevant disease pathologies/organs excluded).

NfL Correlates are Connected to S2R Complex Components

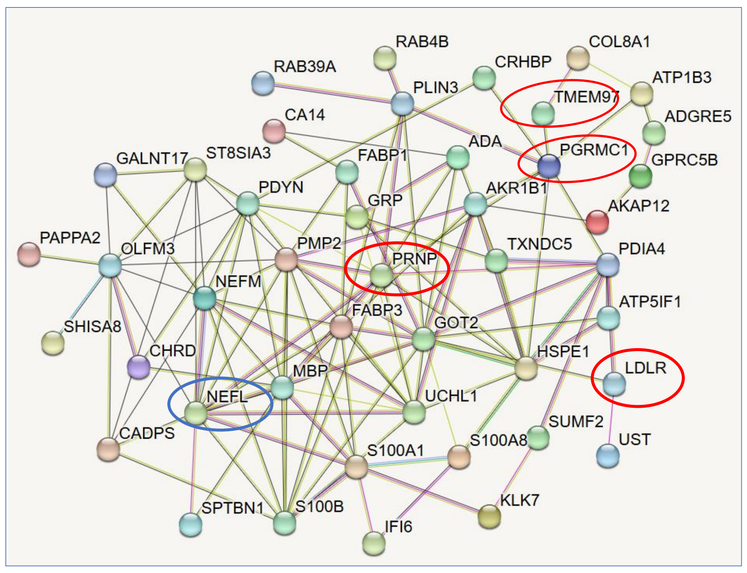


Figure 5: Protein-protein interaction map of the 44 correlates to NfL CSF levels (p≤0.05) with the S2R complex components (circled in red) added to this analysis to understand the relationship to CT1812's mechanism of action through S2R. Low confidence, not connected proteins not shown.

CONCLUSIONS

- **Molecular correlates identified related to changes in neurodegeneration given the robust associations to CSF NfL, including neurofilament light protein (NEFL), olfactomedin 3 (OLFM3), fatty acid-binding protein 3 (FABP3) and the astrocytic protein S100 calcium binding protein B (S100B).**
- **Correlates to CSF NfL levels are associated with pathways related to vesicle, protein folding and inflammation.**
- **Protein-protein interaction maps show a highly interconnected network with NEFL as a hub and illustrate the connectivity with S2R complex proteins.**

Findings are consistent with an impact of CT1812 on neurodegeneration through a S2R mechanism of action

SHINE COG0201

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 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.

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

CONTACT:
mhamby@ cogrx.com
vdicaro@cogrx.com

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