COGNITION™ Therapeutics

Adapted from AAIC 2022 Oral Presentation

CSF PROTEOMICS BIOMARKER ANALYSIS FROM THE SPARC CLINICAL TRIAL: TO ASSESS THE EFFECT OF THE SIGMA-2 RECEPTOR (S2R) MODULATOR CT1812 IN ALZHEIMER'S DISEASE PATIENTS

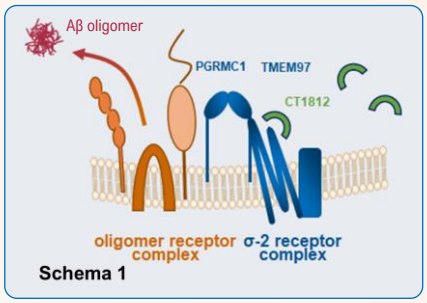
Pandey K[3], Waybright L[2], Duong DM[1], Malagise E[2], Blennow K[4], Zetterberg H[4], Mecca AP[5], van Dyck CH[5], Caggiano AO[2], Seyfried NT[1], Hamby ME[2]

[1] Emory University School of Medicine, Biochemistry, Atlanta, GA
[2] Cognition Therapeutics, Research, Pittsburgh, PA
[3] Emtherapro Inc, Systems Biology, Atlanta, GA
[4] Sahlgrenska Academy, University of Gothenburg, Göteborg, Sweden
[5] Yale University School of Medicine

INTRODUCTION

CT1812 is an investigational therapeutic that can displace toxic amyloid-beta oligomers (**Schema 1**) from neuronal receptors and is currently in development for Alzheimer's disease.

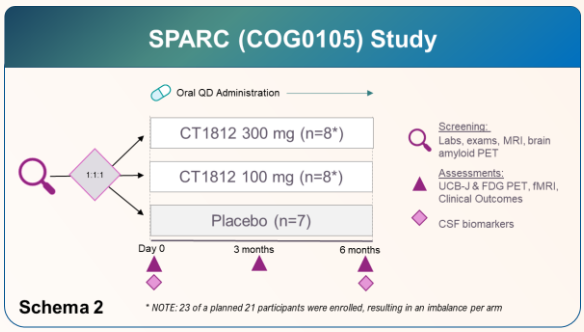
SPARC (COG0105; NCT03493282), was a randomized double-blinded placebo-controlled clinical trial designed to test the impact of the small molecule sigma-2 (σ-2) receptor modulator CT1812 on safety and synaptic density (**Schema 2**). Among study participants, CT1812 was found to be generally well tolerated, consistent with findings from prior studies. No significant treatment differences in synaptic density were observed in participants administered CT1812 or placebo, as measured by SV2a signal change compared to baseline. Exploratory analyses included discovery proteomics for pharmacodynamic biomarker identification and assessment of the impact of CT1812 on CSF proteins detected in mild-to-moderate Alzheimer's disease patients.



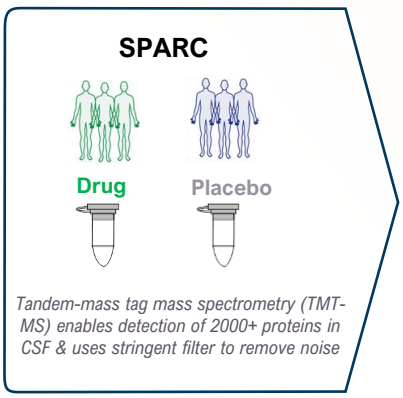
Schema 1

METHOD

Unbiased quantification using tandem-mass tag mass spectrometry (TMT-MS) of proteomes from Alzheimer's disease patients given the σ-2 receptor modulator CT1812 or placebo (n=18) was performed on baseline and end-of-study CSF to test two doses of CT1812 given once daily for 6 months in participants with mild-moderate Alzheimer's disease. Individual CSF proteomes were compared to pooled samples from SPARC participants and non-demented control CSF reference standards from the Emory Alzheimer's Disease Research Center to benchmark protein levels in SPARC participant CSF at baseline and to assess treatment effects via differential expression analysis (one-way ANOVA; p<0.05) and pathway analyses.

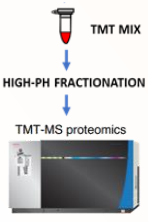


Schema 2



Tandem-mass tag mass spectrometry (TMT-MS) enables detection of 2000+ proteins in CSF & uses stringent filter to remove noise

Samples Balanced on Mass Spectrometer plex & by channel to minimize batch effects

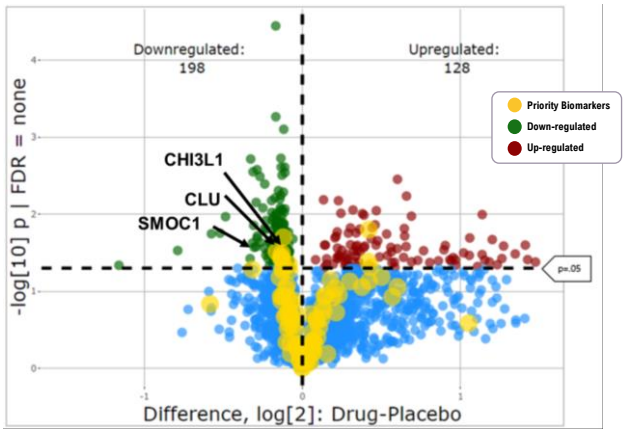


1. **Assessment of drug impact:** deep dive into profiles of individual biomarkers
2. **Biomarker differential expression analysis:** identification of significantly (p<0.05) differentially expressed proteins across drug vs. placebo cohort
3. **Correlation of biomarkers with external traits:** quantitative, clinical, etc.
4. **Summary level insights/ Assessment of drug MoA:** cluster and network analysis to identify summary insights into drug MoA

METHOD VALIDATION

This method was validated by looking at the degree of congruency between our proteomics data and validated assays in the laboratory of Kaj Blennow and Henrik Zetterberg at University of Gothenberg. It was determined that the two quantitative methods had a high degree of correlation (with Pearson correlation coefficient values between 0.83 and 0.90). This analysis validated the TMT-MS method as a reliable quantitative method with good construct validity to enable the identification of pharmacodynamic biomarkers using the proteomics method.

Differential Expression Analysis Identified 326 Differentially Abundant Proteins in CSF from CT1812 vs Placebo (N=18, p≤0.05)



CHI3L1 (YKL-40) = inflammatory protein ↑ in Alzheimer's disease
SMOC1 = Aβ plaque-associated protein ↑ in Alzheimer's disease
CLU = Alzheimer's disease genetic risk factor (clusterin; APOJ)

- CSF samples at six months and at baseline were available from 18 SPARC trial participants[4]
- Among CT1812-treated compared to placebo-treated individuals, 198 proteins were found to be downregulated and 128 upregulated
  - 14 (p<0.05) are previously well-characterized biomarkers of Alzheimer's disease, such as YKL-40 and SMOC1 (priority biomarkers)[1] and/or genetic risk factors for Alzheimer's disease such as clusterin[2]
- This analysis identified pharmacodynamic biomarkers of CT1812 that may reflect pathway engagement or disease modification

Pathway Analyses Point to Key Biological Processes Significantly Affected that may be Altered with CT1812 in Alzheimer's Disease Patients

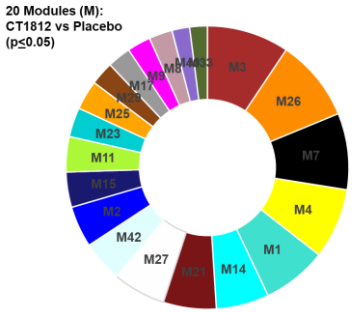
Pathway analysis using Metacore identified pathways that were altered in SPARC participants treated with CT1812 compared to placebo

- Those pathways that were statistically significantly altered include those related to inflammation and amyloid biology
- Of note: many of the pathways identified in this Metacore analysis that were found to be statistically significant in individuals with mild-to-moderate Alzheimer's disease who were treated with CT1812 in the ongoing Phase 2 SHINE study (interim analysis / n=24)
- An analysis comparing data from SPARC and interim data from SHINE is underway

CONCLUSIONS

- Pharmacodynamic biomarkers of CT1812 were identified, including 14 well-characterized biomarkers of Alzheimer's disease (priority biomarkers) and/or Alzheimer's disease genetic risk factors
- Pathway analysis and brain module association mapping illuminated key processes including inflammation and amyloid biology that may be affected by CT1812, supporting a synaptoprotective mechanism of action
- Biomarkers that are known to be disrupted in Alzheimer's disease were normalized towards control levels by CT1812
- Overall, data support targeting σ-2 receptor with CT1812 as a potentially promising therapeutic approach to Alzheimer's disease

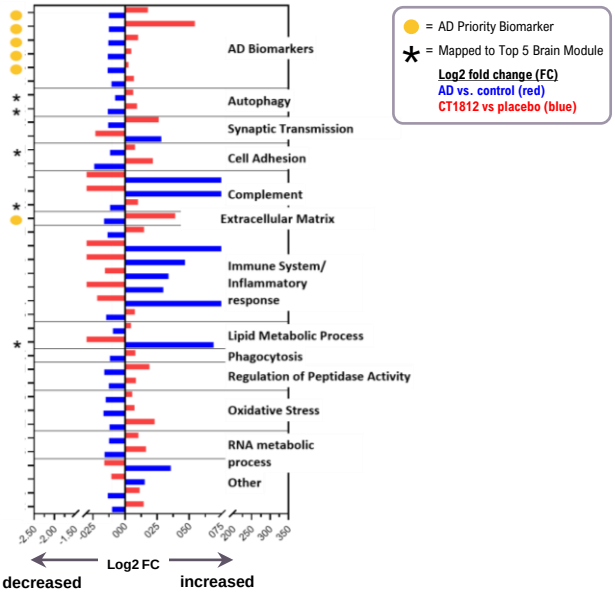
Mapping to the Brain Network Supports Role of CT1812 at Synapses



Previously, brain and CSF proteomics were analyzed and brain network mapping performed to assign proteins to a module associated with a given function[3]. We leveraged this dataset to understand what brain module functions the biomarkers that were altered by CT1812 vs placebo were involved in.

Two of the top five abundantly represented modules (highlighted in yellow) are associated with synaptic health and function. This supports synaptoprotective mechanism of CT1812.

CT1812 Normalizes Biomarkers Dysregulated in Alzheimer's Disease Towards Control Levels



Changes in protein levels in CT1812-treated vs placebo-treated SPARC participants were then compared to the changes observed in disease vs control reference standards

- 37 proteins identified in CSF are significantly (p<0.05) normalized towards levels observed in control reference samples with CT1812 compared to placebo
- These proteins are involved in key pathways disrupted in Alzheimer's disease including autophagy, inflammation, and synaptic function

REFERENCES & NOTES

1. Higginbotham L, Ping L, Dammer EB, et al. Integrated proteomics reveals brain-based cerebrospinal fluid biomarkers in asymptomatic and symptomatic Alzheimer's disease. *Sci Adv*. 2020;6(43):eaaz9360
2. AlzBiomarker AD vs Control: an interactive resource developed in collaboration with Henrik Zetterberg and colleagues at the University of Gothenburg. Downloaded 07/20/2022 from https://bityl.co/Dfo7
3. Johnson, E.C.B., Dammer, E.B., Duong, D.M. et al. Large-scale proteomic analysis of Alzheimer's disease brain and cerebrospinal fluid reveals early changes in energy metabolism associated with microglia and astrocyte activation. *Nat Med* 26, 769–780 (2020)
4. NOTE: 17 of the 23 individuals enrolled completed the six-mo SPARC study. An 18th participant discontinued due to elevated liver enzymes but had CSF drawn during their early termination visit on day 102.

CT1812 is an experimental candidate under clinical investigation for Alzheimer's disease and dementia with Lewy bodies; and has not been approved by the U.S. FDA or other regulatory agency