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

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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.

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.

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 Gothenburg. 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.

\textbf{SPARC}

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

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

- 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 synapticprotective 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 0-2 receptor with CT1812 as a potentially promising therapeutic approach to Alzheimer’s disease

REFERENCES & NOTES

2. Alzheimer biomarker 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
4. NOTE: 17 of the 23 individuals enrolled completed the six-month SPARC study. An 18th participant discontinued due to elevated liver enzymes but had CSF drawn during their early termination visit on day 102.