PHARMACODYNAMIC EFFECTS OF THE S2R MODULATOR CT1812 IN ALZHEIMER’S DISEASE (AD) PATIENTS OBSERVED IN A META-ANALYSIS OF CSF PROTEOMES FROM SPARC AND SHINE PART A

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BACKGROUND

The sigma-2 receptor (S2R) is encoded by TREM2, a four-domain transmembrane protein that forms a complex with the prototypical receptor molecule component 1 (PROM1C). CT1812 is a highly brain-penetrant small molecule modulator of S2R, that displaces all agonists bound to neuronal synapses (Scheme 1). In preclinical studies, CT1812 protects synapses, facilitates their restoration and improves cognitive performance in transgenic Alzheimer’s disease (AD) mice. CT1812 is in clinical development for AD. SHINE (NCT03507050), ongoing, and SPARC (NCT04326320), completed, are randomized double-blind placebo-controlled trials (Scheme 2).

Methods: Tandem mass tag mass spectrometry (TMT-MS) proteomics measurements on CSF from patients included in the interim analysis of the SHINE trial, SHINE-A, and in SPARC were previously performed and the findings presented.1,2 Although encouraging findings, replication in larger well-powered studies are needed. Towards this end, we performed a meta-analysis herein, leveraging the commonalities across trials: a) same treatment duration (6 mo), same patient population (old to moderate AD), and same CSF processing. Combining, for all patients from which we had a baseline and endpoint CSF draw and that were treatment compliant, the proteomic data from the two trials, increased the sample size from N=17 to N=30, resulting in an increased power for statistical analysis to identify pharmacodynamic biomarkers of CT1812 at treatment statistical significance across clinical trial cohorts (Scheme 3).

Following pre-processing to remove batch effects, treatment effects of CT1812 (CT1812 vs placebo, p<0.05) were assessed via differential expression comparative analyses and pathway analyses, using MetaCore and STRING, brain mapping, and weighted gene co-expression network analysis (WGCNA) to identify treatment related networks, or modules (Scheme 4).

Objective: A meta-analysis of CSF proteomes from Alzheimer’s disease (AD) patients from the SHINE and SPARC clinical trials was performed to identify pharmacodynamic biomarkers of the sigma-2 receptor (S2R) modulator CT1812.

Prioritization of AD Biomarkers Altered by CT1812, and Clear Separation Of Patients by Treatment (CT1812 vs Placebo)

Pathway Analysis of Differentially Abundant Proteins Implicates CT1812 in Regulating Synapses, Neuroinflammation, and Amyloid Biology

Comparative Analyses Illuminate Robust Candidate Pharmacodynamic Biomarkers that Replicate Across Independent Cohorts / Analyses

Network Analysis Identifies Treatment-Associated Networks, Hub Proteins Illuminating Mechanistic Insights of CT1812 in AD patients

CONCLUSIONS

This meta-analysis allowed for the identification of robust pharmacodynamic biomarkers of CT1812:

- 352 pharmacodynamic changes due to CT1812 identified
- 11 AD Priority biomarkers altered by CT1812 vs placebo
- 9 biomarkers showed replication across trials with similar directionality and degrees of change 19 additional robust biomarkers needing larger sample size to achieve significance discovered
- Brain network mapping and pathway analysis of differentially abundant proteins supports role of CT1812 in synaptic biology, neuroinflammation and amyloid biology
- Comparative analyses illuminate biomarkers that replicate across independent cohorts and analyses, and pathway analysis of these robust biomarkers highlight a prominent role of CT1812 in regulating synaptic and AD biology
- Network analysis identifies networks that are associated with CT1812 treatment, enabling further mechanistic understanding of how CT1812 may impact patients with Alzheimer’s disease

- Networks altered include Hub proteins Prion protein (PRNP) known to interact with S2R, and APOE known to be regulated by PRNP

Overall, data provide additional support of a synaptoprotective mechanism of action for CT1812, and support the continued clinical development of CT1812 for Alzheimer’s disease