A Neuroimaging Approach to Treating Alzheimer’s Disease: Hypothesis Testing in a Phase 2a Exploratory Clinical Trial with the New Chemical Entity T3D-959

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ABSTRACT

A major test of the neuroimaging hypothesis of Alzheimer’s disease pathogenesis is a dysfunctional glucose and lipid metabolism being key drivers of disease pathogenesis (3). In a Phase I clinical trial of the PPAR gamma agonist T3D-959, we obtained a statistically significant change in cerebral glucose metabolism in a brain region known to have increased glucose utilization in Alzheimer’s disease. The Phase I trial demonstrated that T3D-959 is safe, well-tolerated, and efficacious in increasing cerebral glucose metabolism. To test the hypothesis in Alzheimer’s disease, we conducted a Phase 2a clinical trial in which we evaluated T3D-959’s efficacy in increasing brain glucose metabolism and the potential for disease modification in AD patients.

The Phase 2a clinical trial was a multicenter, double-blind, placebo-controlled, randomized, parallel-group study designed to assess the efficacy of T3D-959 in increasing brain glucose metabolism in mild-to-moderate AD patients. Subjects were randomized to one of four doses of T3D-959 (3, 10, 30, or 90 mg) or placebo. The primary endpoint was the change in cerebral glucose metabolism from baseline to 12 months in a predefined brain region known to be abnormal in AD patients. The secondary endpoints included changes in cognitive function, clinical chemistry, and safety and tolerability measures.

The results of the Phase 2a trial demonstrated statistically significant increases in cerebral glucose metabolism in multiple brain regions, with the 90 mg dose showing the most robust effects. These findings support the hypothesis that T3D-959 has the potential to modify the disease process in AD patients.

Metabolism Analysis Demonstrates Systemic Exposure and Possible Brain Effects

T3D-959 is a small molecule agonist of PPAR (peroxisome proliferator-activated receptor) that has been shown to increase glucose metabolism in preclinical studies. The Phase 2a trial was designed to evaluate the systemic exposure and potential brain effects of T3D-959 in AD patients.

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FDG-PET Data from Voxel Wise Analysis and sROI Analysis

FDG PET images were obtained at baseline and after completion of dosing for each dose group: 3 mg, 10 mg, 30 mg, or 90 mg. The analyses were performed using voxel-wise and statistical region-of-interest (sROI) approaches.

Voxel-wise analysis showed dose-dependent effects in the spatial extent of positive regional increases in cerebral glucose metabolism. The highest increases were observed in the 90 mg dose group. As expected, these effects were more pronounced in the T3D-959-treated subjects compared to placebo. The spatial extent of these increases was dependent on the reference region used.

sROI analysis showed greater increases in glucose metabolism in the T3D-959-treated subjects compared to placebo. The sROI analysis also revealed that the increases were more pronounced in the T3D-959-treated subjects compared to placebo. The sROI analysis also revealed that the increases were more pronounced in the T3D-959-treated subjects compared to placebo.

FDG PET Data from Voxel Wise Analysis

FDG-PET analysis showed dose-dependent effects in the spatial extent of positive ROSDs (regions of statistically significant differences) in cerebral glucose metabolism. The highest increases were observed in the 30 mg and 90 mg dose groups. These findings support the hypothesis that T3D-959 has the potential to modify the disease process in AD patients.

FDG PET Results for Pre-specified Anatomical ROIs

FDG-PET analysis of pre-specified anatomical ROIs showed dose-dependent increases in glucose metabolism in multiple brain regions, including the hippocampus, the amygdala, the entorhinal cortex, and the temporal lobe.

CONCLUSIONS FROM FDG-PET RESULTS

The Phase 2a trial suggests that T3D-959 has the potential to modify the disease process in AD patients. The results support the hypothesis that T3D-959 has the potential to modify the disease process in AD patients. The results also suggest that T3D-959 is well tolerated and has a favorable therapeutic index.

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References

