**Rapid Onset of Cognitive Improvements in a Subset of Mild and Moderate Alzheimer’s Patients**

**Treated with T3D-959: Interim Results of a Phase 2a Open Label Clinical Trial**

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### BACKGROUND

- Alzheimer’s disease is based on two fundamental discoveries:
  - Neurodegeneration may be linked to beta amyloid and tau protein accumulation in the brain.
  - Insulin resistance syndrome and Alzheimer’s disease: pathophysiologic mechanisms and therapeutic approaches.

- Alzheimer’s as a Neuro-Metabolic Disease
  - The organ with the highest level of energy metabolism in the brain. The adult male brain consumes 20% of the body’s total oxygen consumption, 25% of total body glucose in the resting state and receives 15% of the cardiac output. It accounts for nearly half of the oxygen used by the body.
  - Based on pre-clinical studies the Alzheimer’s disease process may start with decreased beta-cell function and reduced insulin and IGF-1 expression (insulin resistance growth factor-1), which cause diminished allocation of glucose metabolism. Microvascularization for the brain of the metabolic syndrome (ionized glutamate/DGAM) causes ischemia and insufficiency of the brain and Alzheimer’s disease patients. Ischemia is a familiar problem with brain atrophy through neurodegeneration of the brain. We believe that Alzheimer’s disease is not primary, but secondary to an altered brain metabolism.

- Insulin resistance in brain can account for most molecular, biochemical, neuroendocrine, and histopathological abnormalities in AD.

### METHODS - DESIGN

- **Randomized, parallel 4-arm design in subjects with mild to moderate Alzheimer's disease (DSST change endpoint).**

#### METHODS - PATIENTS

**Objectives:

- Enrollment: 40 participants (20 per arm).
- Safety and Tolerability.
- Cognitive testing results for ADAS-cog11 and DSST (Digit Symbol Substitution Test) for subjects completed.

#### METHODS - ENDPOINTS

- **Primary endpoint:** ADAS-cog11 response.
- **Secondary endpoints:**
  - Change from baseline to endpoint in DSST, ADAS-cog11, and other cognitive tests.
  - Safety and tolerability.

- **Resubmission date:** All other endpoints.

#### METHODS - TREATMENTS

- **Treatment arms:**
  - **Control:** Placebo
  - **T3D-959:** 3mg
  - **T3D-959:** 5mg
  - **T3D-959:** 10mg

### RESULTS

- **T3D-959: A Multi-Disciplinary Approach to Alzheimer’s Disease Treatment**

- **Phase 2a Clinical Trial**

#### T3D-959 Drug Properties and Development Stage

- PPAR gamma nuclear receptor agonist (Primary T3D-959).
- Small molecule studied as a once-a-day therapeutic.
- 2-3 h baseline.
- Phase 1 completed.
- Phase 1: completed.
- Phase 2a trial in Alzheimer's disease completed.
- LPLD: of high concordance of DSST with ADAS-cog11.
- Steen PPAR agonist: Nal, and Hoda Gabriel, PMP.

### CONCLUSIONS

- This is the first exposure to T3D-959 in Alzheimer’s patients. In this study the drug was well tolerated, produced no significant safety findings, and showed negative effects on cognition in patients with mild to moderate Alzheimer’s disease.

- Therapeutic treatment with the dual nuclear receptor agonist T3D-959 can improve cognitive function as measured by ADAS-cog11 and DSST, regardless of disease stage, t.i. mild or moderate.

- The robustness of observed cognitive improvements is likely linked to the neuro-metabolic mode of action of T3D-959.

- Targeting neuro-metabolic dysfunction in AD is a viable and attractive new avenue to developing effective AD therapeutics.

### ACKNOWLEDGEMENTS

T3D Therapeutics Inc. is currently supported by a major grant from the National Institute on Aging of the National Institutes of Health under Number N01-AG-6-2003, the financial and non-financial support of the North Carolina Biotechnology Center is acknowledged.

### REFERENCES