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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Note: Abstract content reflects only partial results as of the submission date. All other information/data in this poster are final preliminary results and should be reviewed.

ABSTRACT

Background: T3D-959 is a small molecule, orally-delivered, brain-penetrating PPARδ/γ dual nuclear receptor agonist acting to improve neuro-metabolic dysfunction in Alzheimer's disease (AD), an aspect of AD that is now recognized as a potential upstream driver of AD pathologies.

Methods: 36 subjects with mild-to-moderate AD (MMSE= 14-26), were randomized to receive 1 of 4 doses of T3D-959 q.d. for 14-days. Primary objectives were to evaluate; (1) changes in CMGgl measured by FDG-PET imaging; (2) changes in hippocampal functional connectivity (resting state default mode network activity) measured by BOLD fMRI; (3) changes in cognitive function (ADAS-cog11 and DSST testing) and (4) safety and tolerability. Cognitive testing was conducted four times; at baseline, pre-dosing day 1 of treatment (D1), day 14 end of treatment (D14), and at 7-days post-dosing followup (D21). FDG-PET and BOLD fMRI scans were administered at D1 and D14. Brain imaging results will be presented at a later time.

Results: Preliminary results from the first 18 evaluable patients (MMSE = 15-24) demonstrated that T3D-959 was well tolerated with lack of negative effects on cognition and no significant safety findings. Mean entire group ADAS-cog11 score improvement at D14 = 0.8 and at D21 = 1.6. Mean entire group DSST score improvement at D14 = 0.3 and at D21 = 3.6. Twelve of the 18 patients had improved ADAS-cog11 scores at D14, D21 or both ('responders'). Mean 'responder' ADAS-cog11 score improvement at D14 = 3.5 and at D21 = 3.8. An 83% concordance of ADAS-cog11 improvement with improvement in DSST testing was observed. Mean 'responder' DSST score improvement at D14 = 1.9 and at D21 = 5.8. Cognitive testing scores at D21 (7-days post-dosing) indicate potential long-acting pharmacodynamics of T3D-959. Mild and moderate severity patients had similar improvement in cognitive tests. Cognitive test results in additional patients will be presented.

Conclusions: These results provide evidence for targeting neuro-metabolic dysfunction in AD, provide a basis for longer term clinical trials of T3D-959 and, being aligned with pre-clinical disease reversal evidence, support the potential for disease modification. An FDA-approved 6-month extension study in a subset of study subject completers has been initiated.

BACKGROUND

A. Alzheimer's as a Neuro-Metabolic Disease

- The organ with the highest level of energy metabolism is the brain. The adult brain uses 20% of the body's total oxygen consumption, 25% of total body glucose in the resting awake state and receives 15% of the cardiac output. It only accounts for 2% of total body weight
- Based on pre-clinical studies the Alzheimer's disease process may start with likely metabolic 'triggers', insulin resistance and IGF-1 resistance (insulin-like growth factor-1), which cause diminished utilization of glucose (sugar) as an energy source for the brain, a condition described as Diminished Cerebral Glucose Metabolism (DCGM). DCGM causes a 'starvation' of the brain in Alzheimer's disease patients which precedes and is considered predictive of neurodegeneration of the brain. Hence, we believe that Alzheimer's disease is best approached and treated as a neuro-metabolic disorder.
- Insulin signaling modulates cell growth, cell survival, energy metabolism, acetylcholine production, neuronal plasticity, myelin maintenance, and inhibits oxidative stress and apoptosis in the brain.
- Brain insulin resistance can account for most molecular, biochemical, neurocognitive, and histopathological abnormalities in AD [4-17]
- Brain insulin resistance possibly promotes and triggers AD neurodegeneration.

B. A New Paradigm:

Regulating Neurometabolism with a Unique Nuclear Receptor Agonist – T3D-959

The Company's therapeutic approach to slow, stop or reverse the progression of Alzheimer's disease is based on two fundamental concepts:

1. Target 'upstream' defects found in Alzheimer's disease, as opposed to later-occurring, 'downstream' manifestations of the disease by addressing DCGM, which precedes and is predictive of cognitive decline.
2. Target multiple defects manifested by the disease, not one, with a single drug therapy.

C. T3D-959 Drug Properties and Development Stage

- PPARδ/γ dual nuclear receptor agonist (Primary target is PPARδ)
- Small molecule orally delivered as a once-a-day therapeutic
- Brain penetrating
- 20h+ T1/2 in humans
- Phase 1 completed – extremely high safety, no drug-related adverse events, no MTD reached
- Phase 2a trial in Alzheimer's disease completed, LPLD 5/11/16
- Phase 2a OL 6-month Extension Study, LPFD 6/8/16

D. T3D-959 Pre-Clinical Proof of Concept

i.c. Streptozotocin animal model of sporadic AD: i.c. administration of STZ, a pro-diabetes toxin, has been shown to impair spatial learning and memory and cause brain atrophy due to neurodegeneration with many AD-associated histopathological, molecular, and biochemical abnormalities[15]. Observed effects of T3D-959 treatment[1-3]:

- Decreased Ab
- Decreased pTau/Tau ratio
- Decreased oxidative stress
- Decreased inflammation
- Decreased neurotoxicity
- Increased brain insulin and IGF signaling
- Reversal of brain atrophy
- Reversal of brain cell loss
- Improved spatial learning and memory
- Improved motor function

PHASE 2A CLINICAL TRIAL

"Phase 2a Feasibility Study of T3D-959 in Subjects with Mild to Moderate Alzheimer's Disease"

ClinicalTrials.gov Identifier NCT02560753

STUDY OBJECTIVES

1. To evaluate changes in cerebral metabolic rate of glucose as measured by FDG-PET imaging for varying repeat doses of T3D-959.
2. To evaluate changes in hippocampal functional connectivity (resting state default mode network activity) as measured by BOLD fMRI for varying repeat doses of T3D-959.
3. To evaluate changes in cognitive functioning as measured by ADAS cog11 for varying repeat doses of T3-959.
4. To evaluate changes in cognitive functioning as measured by DSST for varying repeat doses of T3D-959.
5. To explore drug-induced changes in the metabolome as correlated with brain imaging changes
6. Safety and Tolerability

METHODS - DESIGN

Randomized, parallel, 4-dose design in subjects with mild-to-moderate Alzheimer's disease. Subjects randomized to one of 4 doses of T3D-959 (3, 10, 30, 90mg). T3D-959 taken orally once daily for 14 days. Subjects evaluated for changes from baseline in cerebral metabolic rate of glucose (FDG-PET imaging), functional connectivity of the hippocampus (BOLD-fMRI), and cognitive function.

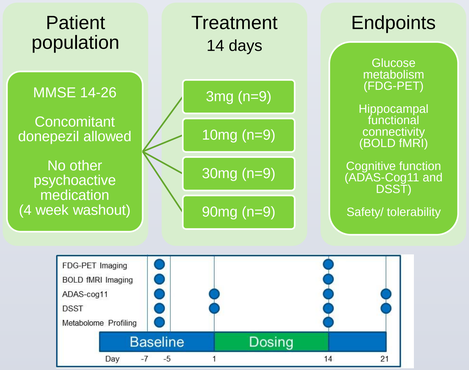
Cognitive testing results for ADAS-cog11 and DSST (Digit Symbol Substitution Test) scales for subjects completed:

- D1 = Baseline, day 1 of dosing (test done prior to dose)
- D14 = day 14 of dosing, last dose (test done post dose)
- D21 = follow-up 7 days after last dose

Cognitive tests administered 4 times [at baseline imaging, beginning of treatment (D1), end of treatment (D14), followup (D21)]

ADAS-cog11: higher negative number denotes improvement

DSST: higher positive number denotes improvement



RESULTS

IMPORTANT NOTE: THESE RESULTS ARE PRELIMINARY AND MAY BE SUBJECT TO CHANGE. DATABASE LOCK HAS NOT YET OCCURRED.

- Thirty four subjects completed the study. All 34 subjects will be included in the final intent to treat analysis for ADAS-cog11 (and therefore considered evaluable) for day 14 and end of treatment.
- Two subjects had documented issues with ADAS-cog11 testing at D14, thus in this preliminary analysis 32 subjects were evaluable at D14
- One subject refused DSST testing at D14.Thus 33 subjects were evaluable at D14 for DSST.
- Results demonstrated that T3D-959 was well tolerated with no significant safety findings and lack of negative effects on cognition.

GROUP	ADAS-cog11 D1 to D14	ADAS-cog11 D1 to D21	DSST D1 to D14	DSST D1 to D21
3mg	-3.23 (n=7)	-3.41 (n=8)	4.43 (n=7)	5.38 (n=8)
10mg	-0.55 (n=9)	-0.51 (n=9)	1.00 (n=8)	3.11 (n=9)
30mg	-2.96 (n=8)	-3.86 (n=9)	0.75 (n=8)	4.00 (n=9)
90mg	1.94 (n=8)	2.80 (n=8)	1.13 (n=8)	6.63 (n=8)
Avg. All Groups	-1.05 (n=32)	-1.27 (n=34)	1.72 (n=33)	4.71 (n=34)
Avg. 3 to 30mg groups	-2.05 (n=24)	-2.56 (n=26)	1.92 (n=24)	4.12 (n=26)
Avg. of ADAS-cog11 'responders' (3+ point improvement at D14)	-5.74 (n=10 of 32)	-6.03 (n=10)	3.00 (n=10)	9.27 (n=10)

Response Rates based on ADAS-cog11 at D14

'Responder' Definition	All cohorts	All cohorts (excluding 90mg cohort)
1+ point improvement	53% Avg Score -4.14 (17 of 32)	62% Avg Score -4.04 (15 of 24)
2+ point improvement	44% Avg Score -4.78 (14 of 32)	50% Avg Score -4.78 (12 of 24)
3+ point improvement	31% Avg Score -5.74 (10 of 32)	33% Avg Score -5.96 (8 of 24)

- **Durability of response - cognitive test improvements ADAS-cog11 and DSST sustained 7-days after dosing cessation**
- **Rapidity of cognitive test improvements – observed after two weeks dosing**
- **High concordance of DSST with ADAS-cog11 response**
- **Magnitude of response equivalent or better than marketed drugs**
- **No relationship between cognitive score improvements and disease severity - Both mild and moderate AD subjects show improvements in cognitive testing**

CONCLUSIONS

- This is the first exposure for T3D-959 in Alzheimer's patients. In this study the drug was well-tolerated, produced no significant safety findings and had no negative effects on cognitive function in patients with mild to moderate Alzheimer's disease.
- Therapeutic treatment with the dual nuclear receptor agonist T3D-959 can improve cognitive function in a number of patients as measured by ADAS-cog11 and DSST, regardless of disease stage, i.e. mild vs. moderate.
- The rapidity of observed cognitive test 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
- These results support future clinical testing of T3D-959 in a larger Phase 2b randomized, controlled trial

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