OC39 - Cognitive Improvement in Mild to Moderate Alzheimer’s Patients: Final Results of an Open Label, Phase 2A Study of T3D-959

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• Brain Matters Research, Delray Beach, FL. Dr. Mark Brody
Novel Approach: The Metabolic Hypothesis of AD

- Dysregulated Energy Homeostasis: Glucose Metabolism
- Dysregulated Lipid Homeostasis: Lipid Metabolism
- Beta Amyloid Plaques
- Tau Tangles
- Fat Deposits
- Inflammation
- Oxidative Stress
- Neurotransmitter Deficits

Massive Positive Feedback Loop Driving Neurodegeneration
Scientific Rationale: T3D-959 Breaking the Cycle – Disease Modification Potential

Dysregulated Energy Homeostasis: Glucose Metabolism

Dysregulated Lipid Homeostasis: Lipid Metabolism

Beta Amyloid Plaques
Tau Tangles
Fat Deposits
Inflammation
Oxidative Stress
Neurotransmitter Deficits

Massive Positive Feedback Loop Driving Neurodegeneration
Novel Approach: The Metabolic Hypothesis of AD

- Massive positive feedback loop of altered glucose/lipid metabolism alterations and pathological sequelae
- Metabolism function alterations (glucose and lipid) antedate structural change
- Decreased glucose metabolism inherent in neurodegeneration
- Aberrant lipid metabolism is a 3rd pathological hallmark of AD
- Intertwined molecular interactions – Abeta and Insulin
- Similarities of brain and peripheral insulin resistant diseases: AD and Type 2 Diabetes
  - Amyloid aggregation
  - Neural degeneration
  - Oxidative stress
  - Cognitive impairment
  - Inflammation
T3D-959: A PPAR δ/γ Dual Nuclear Receptor Agonist

**Glucose Energy Homeostasis**

**Lipid Homeostasis**

**PPARδ/γ (delta/gamma) dual agonist (activator)**

[PPARδ ED50=19nM, PPARγ ED50=297nM]

[central regulators of glucose and lipid metabolism via gene transcription]

### Actions:
- Insulin sensitivity/signaling
- Fatty acid oxidation/catabolism
- Cholesterol transport
- ↑ HDL
- Reduction in adiposity, ↓ TGs
- ↓ Inflammatory signaling
- Macrophage differentiation

### Actions:
- Insulin sensitivity/signaling
- Glycogen synthesis
- Adipogenesis
- Anti-oxidation
- ↓ Inflammatory signaling
- ↑ BDNF, NGF, Klotho

**Ubiquitous expression**
- High levels in the entorhinal cortex, hypothalamus, cerebellum, and hippocampus (dentate gyrus/CA1)
- Lower levels in the corpus callosum and caudate putamen-

**Restricted Regional Expression**
- Olfactory bulb
- Cortex
- Hippocampus CA3
Exploratory/Feasibility Phase 2a Study of T3D-959 in Mild to Moderate Alzheimer’s Disease Patients
Study Design – Main Study

**Patient population**
- MMSE 14-26
- CDR = 0.5 to 2.0
- Modified Hachinski ≤ 4
- Concomitant donepezil allowed (stable dose)
- No other psychoactive medication (4 week washout)
- No TZDs or insulin

**Treatment**
14 days to 6 months\(^{(1)}\)
- 3mg (n=9)
- 10mg (n=9)
- 30mg (n=9)
- 90mg (n=9)

**Endpoints**
- Cognitive function (ADAS-Cog11 and DSST)
- Glucose metabolism (FDG-PET)
- Hippocampal functional connectivity (BOLD fMRI)
- Safety / tolerability

\(^{(1)}\) Original main study protocol doses patients for 14 days. FDA subsequently allowed 26-week OLE – 4 patients 15mg q.d.
Data Collection

FDG-PET Imaging
BOLD fMRI Imaging
ADAS-cog11
DSST
Metabolome Profiling

Baseline | Dosing

Day -7 -5 1 14 21
## Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=34)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MMSE</strong></td>
<td></td>
</tr>
<tr>
<td>Average (range)</td>
<td>19.9 (14-26)</td>
</tr>
<tr>
<td>20-26 (mild)</td>
<td>N=17</td>
</tr>
<tr>
<td>14-19 (moderate)</td>
<td>N=17</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Average (range)</td>
<td>73.6 (57-90)</td>
</tr>
<tr>
<td><strong>Average fasting plasma glucose</strong></td>
<td>99.1mg/dL</td>
</tr>
<tr>
<td><strong>Concurrent AD medications</strong></td>
<td>N=28/34</td>
</tr>
<tr>
<td>Aricept</td>
<td>N=19</td>
</tr>
<tr>
<td>Namenda</td>
<td>N=15</td>
</tr>
<tr>
<td>Exelon</td>
<td>N=5</td>
</tr>
<tr>
<td>Multiple AD medications</td>
<td>N=14</td>
</tr>
<tr>
<td><strong>Region of Enrollment – All U.S.</strong></td>
<td></td>
</tr>
</tbody>
</table>
ADAS-cog11 Improvement After 14-Days Dosing

ADAS-cog11 mean change score on day 14 vs. day 1

All completers (n=32)

- # (%) of patients
- Average change in ADAS-cog11

1+ point improvement: 17/32 (53%)
2+ point improvement: 12/32 (38%)
3+ point improvement: 9/32 (28%)

Average change in ADAS-cog11: -5.89

-5.25
-4.1
ADAS-cog11 Improvement in Both Mild and Moderate AD subjects

ADAS-cog11 mean change score on day 14 vs. day 1
All completers (n=32)

- # (% of patients) - Average change in ADAS-cog11

1+ point improvement:
17/32 (53%)

2+ point improvement:
12/32 (38%)

3+ point improvement:
9/32 (28%)

Average improvement:
Moderate: -6.73 n=5/9
Mild: -4.84 n=4/9

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ADAS-cog11 Improvement Sustained Post-Dosing

*Improvement* sustained at 21 days
(7 days post discontinuation of dosing)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Day 14</th>
<th>Day 21</th>
<th>Difference Day 14 - Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>3mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>90mg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg all</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avg 3-30mg</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

-3.13 -3.41
-2.71 -4.10
-1.03 -1.40
-2.02 -2.69

n=7 n=8
n=8 n=9
n=8 n=9
n=32 n=34
n=24 n=26

-0.55 -0.62
1.97 2.80
ADAS-cog11 Improvement - Dose Response Association with ApoE Genotype

<table>
<thead>
<tr>
<th>Dose</th>
<th>ApoE4-</th>
<th>ApoE4+</th>
</tr>
</thead>
<tbody>
<tr>
<td>3mg</td>
<td>-3.72</td>
<td>-0.11</td>
</tr>
<tr>
<td>10mg</td>
<td>-4.34</td>
<td>-0.33</td>
</tr>
<tr>
<td>30mg</td>
<td>-4.5</td>
<td>0.53</td>
</tr>
<tr>
<td>90mg</td>
<td>-4.6</td>
<td>0.96</td>
</tr>
</tbody>
</table>

- **3mg ApoE4-**: n=5
- **10mg ApoE4-**: n=2
- **30mg ApoE4-**: n=5
- **90mg ApoE4-**: n=5
- **3mg ApoE4+**: n=3
- **10mg ApoE4+**: n=7
- **30mg ApoE4+**: n=4
- **90mg ApoE4+**: n=3

Dose Trend Analysis – Significant Genotype Effect p=0.004
DSST Improvement Sustained Post-Dosing

*Improvement* sustained at 21 days
(7 days post discontinuation of dosing)
FDG-PET Neuroimaging

Comparisons before and after 2-weeks dosing with T3D-959

- **Static** image analyses, not dynamic.
- **Relative** CMRgl values calculated, not absolute.
  
  A. Regional (sROI or ROI) to Whole Brain Ratio
  
  B. Regional to White Matter Ratio

- Relative values complicated by MOA that can increase CMRgl in reference regions

- **Calculations of Relative CMRgl:**

  \[
  \text{End of Treatment} \quad D14 \\
  \begin{array}{c}
  \text{Regional} \\
  \text{Whole Brain}
  \end{array}
  \quad \text{Minus} \quad \\
  \text{Baseline} \quad D0 \\
  \begin{array}{c}
  \text{Regional} \\
  \text{Whole Brain}
  \end{array}
  = \\
  \text{Glucose Metabolism Ratio Change}
  \]

  Or

  \[
  \text{End of Treatment} \quad D14 \\
  \begin{array}{c}
  \text{Regional} \\
  \text{White Matter}
  \end{array}
  \quad \text{Minus} \quad \\
  \text{Baseline} \quad D0 \\
  \begin{array}{c}
  \text{Regional} \\
  \text{White Matter}
  \end{array}
  = \\
  \text{Glucose Metabolism Ratio Change}
  \]

  Pos. = Increase in Ratio
  
  Neg. = Decrease in Ratio
FDG-PET Neuroimaging

Regional to **Whole Brain** Ratio: Significant CMRgl Changes

Conclusions:
- Brain target engagement
- Regional Specificity. Increased glucose metabolism ratio in brain regions critical to Alzheimer’s
FDG-PET Neuroimaging

Regional to *White Matter* Ratio – Significant CMRgl Changes

**Conclusions:**

- Dose dependency

- Regional Specificity. Changed glucose metabolism *ratio* in AD-vulnerable regions: temporal, parietal, frontal & occipital cortices.

- Changed regional glucose metabolism *ratio* with higher doses. *Either:*
  - ↑ *White Matter* CMRgl
  - ↓ Regional CMRgl

Composite of Trial Subjects by dose group (n=8-9)
Significant Change in Precuneous/White Matter Ratio by Dose Stratified by ApoE4 Genotype

Conclusions:
• Dose / ApoE genotype – dependent decrease in relative Precuneous CMRgl

[Precuneus CMRgl may be increasing, but White Matter CMRgl may be increasing more]

Overall dose trend p-value = 0.0068
Main Study – Placebo Effect? Commentary

If there was a placebo effect then:

1. All dose groups would respond the same (The 90mg cohort does not)

2. 7-days post dosing, when patients know they are not on drug, cognitive test scores should decrease (they actually maintain or increase)

3. There would be no genotype association with cognitive test improvements (association observed)

4. No FDG-PET differences between dose arms (differences observed)

5. A difference in ADAS-cog scores between mild and moderate subjects might be expected, given moderate subjects’ significantly lower propensity to exhibit ‘placebo effects’ (both mild and moderate subjects respond similarly)
Safety

• One drug-related AE*
  * First patient enrolled, subject 1001 (30mg) – Self-limited, resolved within 1-day
• No changes in clinical labs
• No changes in physical and neurological exams
• No changes in ECGs
• No respiratory rate or orthostatic blood pressure and heart rate changes
• No potential bone marrow effects as monitored with hematology testing
• No potential increases in plasma volume as assessed by the presence or absence of edema
• No weight gain
• No tolerability issues
Phase 2a – 26-week Open Label Extension

4 Subjects
(2 mild, 2 moderate)
All are ApoE4 Carriers
Monthly cognitive and safety assessments

At 22-weeks dosing (15mg q.d.):
• No AEs
• No tolerability issues
• CIBIC+ improvement in all subjects Group avg. = 2.75
Data Summary

1. Rapid durable improvement (2-3 weeks) in cognition: ADAS-cog11 & DSST

2. Both mild and moderate AD subjects show equivalent response

3. Dose-dependent changes in ADAS-cog11 stratified by ApoE genotype

4. ApoE genotype as future guide of optimal dosing

5. FDG-PET results:
   → brain penetration
   → dose-dependent target engagement (CMRgl changes)
   → CMRgl change / ApoE genotype association
   → CMRgl change – regional specificity

6. Short Term & Long Term Safety (in a limited number of patients)
T3D-959: Conclusions

1. Targeting AD neuro-metabolic dysfunction with T3D-959 is an attractive, and novel investigational approach

2. Results position T3D-959 as a potential disease-modifying drug therapy

3. T3D-959 will be investigated in future clinical trials as a monotherapy or combination therapy agent

4. Phase 2a study results indicate therapeutic activity in both mild and moderate severity patients

5. Results support future Phase 2b clinical testing
   A. High Safety/Tolerability √
   B. Cognitive Tests √
   C. FDG-PET √
   D. Unsolicited Caregiver Feedback √
   E. Clinical Investigator Impressions √
Appendix Slides
Metabolic Hypothesis and Plaque Hypothesis Congruence

Dysregulated Energy Homeostasis: Glucose Metabolism

Example - Plaques
- Insulin and IGF-1 Resistance
- Altered Cholesterol Metabolism
- Altered Sphingolipid Metabolism
- ↑ Aβ due to ↓ IDE activity
- ↑ Secretion of Aβ_{1-42}
- ↓ Removal of extracellular Aβ oligomers
- ↑ Ceramide > BACE > ↑ Aβ
- ↑ Cholesteryl esters > ↑ Secretion of Aβ
- ApoE4 & Aβ > toxic oligomers
- ApoE4 & Aβ > compete for LRP1 > ↓ Aβ removal
- ↓ HDL > ↑ Aβ oligomerization

Dysregulated Lipid Homeostasis: Lipid Metabolism

Example - Plaques
- Aβ binds to and blocks insulin degrading enzyme (IDE) > hyperinsulinemia > Insulin resistance
- BACE > Aβ production & insulin biogenesis > hyperinsulinemia > Insulin resistance
- Aβ binding to Insulin
- Aβ binding to Insulin Receptor
- Aβ42 increases Smase
- Aβ40 inhibition of HMG-CoA reductase
- APP regulation of cholesterol metabolism

Beta Amyloid Plaques
- Tau Tangles
- Fat Deposits
- Inflammation
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