Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

T3D-959

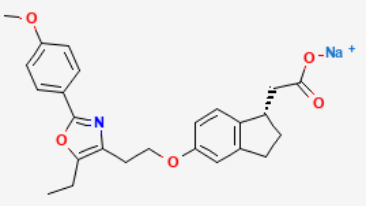
Evidence Summary

This PPAR modulator may improve peripheral and central metabolic function while avoiding the side effects associated with existing PPAR-targeted drugs. Clinical trials are ongoing.

Neuroprotective Benefit: It may mitigate cognitive decline related to cerebral metabolic dysfunction by improving brain metabolism and reducing neuroinflammation.

Aging and related health concerns: It may favorably modulate the peripheral metabolic profile. It shows anti-diabetic activity in preclinical models.

Safety: It has been generally safe and well-tolerated in clinical trials, thus far. Possible side effects include muscle weakness and cramps, but were low frequency.

Availability: In clinical trials	**Dose**: Not established	**Chemical formula:** $C_{25}H_{26}NNaO_5$ **MW**: 443.5 g/mol
Half-life: 14.8-19.9 hours	**BBB**: Penetrant	
Clinical trials: Tested in Phase 1 in healthy volunteers (n=96), and Phase 2 in Alzheimer's disease (n=34, 256)	**Observational studies**: None	Source: PubChem

What is it?

T3D-959 is a dual peroxisome proliferator-activated receptor (PPAR) agonist, which acts on PPARδ and PPARγ. It is a biased agonist, which is 15 times more potent toward PPARδ (human ED_{50} = 19 nM), relative to PPARγ (human ED_{50} = 297 nM) [1]. PPARs are involved in the regulation of metabolic homeostasis, particularly lipid metabolism. A class of PPARγ modulators called thiazolidinediones have been used as anti-diabetic agents, and this dual agonist was originally being developed for diabetes and dyslipidemia by Dara Therapeutics under the name DB959. In 2013, T3D Therapeutics licensed DB959 from Dara (Press release), and pivoted clinical development toward Alzheimer's disease.

Neuroprotective Benefit: It may mitigate cognitive decline related to cerebral metabolic dysfunction by improving brain metabolism and reducing neuroinflammation.

Types of evidence:

- 2 clinical trials
- 3 laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

PPARs are metabolic regulators and are involved in lipid metabolism in the CNS. PPARγ activity has also been associated with a variety of neuroprotective effects, including the induction of brain derived neurotrophic factor (BDNF). Although they are not ideal for CNS indications due to their limited

bioavailability in the brain and side effect profile [2], the use of thiazolidinediones, also called glitazones, the class of anti-diabetics which primarily act as PPARγ agonists, has been associated with a reduced incidence of dementia in some populations [3; 4]. The protective effects are likely mediated by an improvement in bioenergetics in the brain, as cerebral hypometabolism is a risk factor and feature of cognitive decline.

Human research to suggest benefits to patients with dementia:

The results of clinical trials testing thiazolidinediones in Alzheimer's disease (AD) were mixed, such that meta-analyses indicate a lack of consistent clinically meaningful cognitive benefit in this population [5]. The overall data suggest that PPARγ is a reasonable target, however, thiazolidinediones are not the optimal PPARγ modulators for this population. Furthermore, the PPAR family contains three members, α, δ, and γ, which have overlapping and intertwined roles in the regulation of metabolism. Due to the complex regulatory networks amongst the PPARs, it may be necessary to modulate multiple family members to meaningfully impact brain metabolism and influence cognitive trajectories [6]. The bias of T3D-959 for PPARδ may offer a better therapeutic profile.

T3D-959, the mixed PPARδ/PPARγ agonist, was tested in an exploratory Phase 1/2 clinical trial in patients with mild to moderate AD (n=34) (NCT02560753) [7]. This study tested T3D-959 at oral doses of 3, 10, 30, or 90 mg per day for 14 days, and focused primarily on safety, pharmacokinetics, and pharmacodynamics. Treatment led to dose-dependent changes in the plasma metabolomics profile, including decreases in the branched chain amino acids, isoleucine, leucine, and valine, which are associated with insulin resistance. The ratio of glycine levels (EOT/BL), another measure of insulin resistance, was also increased at the highest dose, consistent with the ability of T3D-959 to improve insulin sensitivity. FDG-PET analyses also indicated dose-dependent regional changes in glucose utilization in the brain in response to treatment. In terms of the lipid profile, there was a decrease in several ceramides, and an increase in fatty acid oxidation. Underpowered exploratory aims assessing cognitive function found that T3D-959 treatment was associated with improvement on the ADAS-Cog11 and the Digit Symbol Substitution Tests (DSST), however, there was no placebo comparator group.

A placebo-controlled, double-blind 24-week Phase 2 RCT (PIONEER) (NCT04251182) testing T3D-959 at 15, 30, and 45 mg in 256 participants with mild to moderate AD is ongoing. The primary endpoints are cognition with the ADAS-Cog11, function with the ADCS-CGIC, as well as safety and tolerability. The study will also measure exploratory biomarkers, including proteomics, metabolomics, and lipidomics. Results from the completed trial are projected for Q1 2023.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Alzheimer's disease

T3D-959 has primarily been tested in a metabolic model of AD, where, as a metabolic modulator, it would be expected to be most efficacious. The positive effects in this model suggest that T3D-939 may be most effective in AD patients with co-existing metabolic disease, and/or cerebral hypometabolism, as well as those with an inflammatory endophenotype. Ongoing clinical studies may offer better insight into whether this therapy is beneficial for patients with a variety of AD subtypes, or only those with a particular metabolic/inflammatory profile.

In the rat streptozotocin-induced model of AD, T3D-959 (1 mg/kg/day by oral gavage), improved motor performance on the rotarod test and spatial learning and memory on the Morris water maze, toward control levels [1; 8; 9]. These behavioral effects coincided with the preservation of cortical and white matter structure, consistent with decreased neuronal loss. Levels of oxidative stress, Aβ, and phosphorylated tau were also reduced with treatment. T3D-959 also restored insulin/IGF signaling and reduced neuroinflammation in this model. The dosing used a therapeutic regimen, with treatment starting at one or seven days following intracerebral streptozotocin, suggesting that T39-959 may benefit patients in early stages of the disease. Delayed treatment (starting at seven days), appeared to show more benefit in this model, particularly with respect to its effects on the neuroinflammatory profile. Both conditions stimulated anti-inflammatory mediators, such as IL-10, IL-7, and VEGF, but only delayed treatment also suppressed pro-inflammatory mediators, including IFN-γ, M-CSF, MCP-1, and RANTES.

APOE4 interactions: Based on exploratory outcome data for the Phase 1/2 clinical trial in patients with mild to moderate AD, ApoE genotype may influence the efficacy of T3D-959. In a study of plasma metabolomics, the ApoE4 carriers treated with the highest dose (90 mg) were the only ones to show significant changes in the long-chain fatty acid profile (AAIC Presentation 2018). The cognitive outcomes, based on ADAS-Cog11, were also influenced by ApoE4 genotype, but due to the small numbers, it is not clear if the differences are clinically meaningful. Since T3D-959 is primarily geared toward improving both peripheral and central metabolism, it is likely to be most effective in patients with cerebral hypometabolism. Since ApoE is a lipid carrier and influences lipid levels, a lipid metabolism modulating therapy, like T3D-959, may be particularly beneficial in ApoE4 carriers, but more studies are needed.

Aging and related health concerns: It may favorably modulate the peripheral metabolic profile. It shows anti-diabetic activity in preclinical models.

Types of evidence:

- 1 clinical trial
- Several laboratory studies

Diabetes: POTENTIAL BENEFIT

Before it was acquired by T3D Therapeutics, the dual PPARδ/PPARγ T3D-959 agonist was being developed for Type 2 diabetes by Dara Therapeutics under the name DB959. In the preclinical diabetes models, the db/db mouse, the Zucker Diabetic Fatty rat, and the Zucker Fatty fa/fa rat, DB959 (10 mg/kg/day) improved insulin sensitivity and reduced plasma glucose by 48 to 63%. Fat-fed DIO mice treated with DB959 gained a similar level of weight relative to vehicle-treated mice (7% vs 5%), which was lower than those treated with the thiazolidinedione, rosiglitazone (11%). In the hApo-A1 mouse model of hypercholesteremia, treatment with DB959 led to a 38% reduction in plasma triglycerides and 53% increase in HDL-c. Similar effects were seen in fat-fed hamsters. DB959 dose dependently increased fatty acid β-oxidation in skeletal muscle cells, and increased cholesterol transport in macrophages.

In the exploratory Phase 1/2 study in AD patients (NCT02560753), peripheral metabolic parameters were assessed (AAIC Presentation 2018). Based on a plasma metabolomics study, there was a shift in lipid metabolism consistent with increased beta oxidation of fatty acids. This included an increase of fatty acid-derived acylcarnitine species. There were also decreases in certain ceramide species which are implicated in metabolic disease, at doses of 30 and 90 mg. The branch-chained amino acids, leucine, isoleucine, and valine, as well as some of their major metabolites, which are implicated in insulin resistance, were decreased at the 90 mg dose.

These studies suggest that T3D-959 has anti-diabetic properties, and may regulate metabolic homeostasis in the periphery as well as the CNS. T3D-959 may also be investigated for non-alcoholic fatty liver disease (NAFLD)/ non-alcoholic steatohepatitis (NASH) (T3D Therapeutics website).

Safety: It has been generally safe and well-tolerated in clinical trials, thus far. Possible side effects include muscle weakness and cramps, but were low frequency.

Types of evidence:

- 3 clinical trials
- Several laboratory studies

In a Phase 1 single ascending dose (SAD) (100-fold dose range) study in healthy volunteers (n=76), T3D-959 was well-tolerated at doses up to at least 200 mg. Similarly, in a Phase 1b multiple ascending dose (MAD) study in healthy volunteers (n=32), it was well-tolerated throughout the 40-fold dose range tested (Press release, T3D Therapeutics website).

In an open-label Phase 2a trial (NCT02560753) in patients with mild to moderate AD, T3D-959 up to 90 mg for 14 days was generally safe and well-tolerated [7]. The drug showed dose-dependent exposure. Of the 4/34 patients who experienced adverse events, only one was deemed to be treatment-related, which was muscular weakness. There were no abnormalities on clinical laboratory tests or vital signs in the four patients who participated in an 18-week extension study (15 mg QD). There were no treatment-related serious adverse events or high frequency adverse events of any type. Unlike thiazolidinediones, T3D-959 has not been associated with weight gain.

Drug interactions: Interactions for T3D-959 have not yet been established, but due to its PPARγ agonist activity, some of the interactions may be similar as for thiazolidinediones. It may also have interactions with anti-diabetics.

Sources and dosing:

T3D-959 is not currently approved for use in humans outside of clinical trials. A safe and effective dose has not yet been established for any condition. It is being developed by T3D Therapeutics for Alzheimer's disease, and is currently being tested at doses of 15, 30, and 45 mg per day, orally.

Research underway:

According to Clincaltrial.gov, there is currently one active clinical trial for T3D-959, which is the Phase 2 PIONEER RCT (NCT04251182) in mild to moderate AD. The estimated study completion date is in the summer of 2022.

Search terms:

Pubmed, Google: T3D-959

- Alzheimer's disease, diabetes, clinical trials, safety

Websites visited for T3D-959:

- Clinicaltrials.gov
- PubChem
- Cafepharma

References:

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