

RESEARCH MONOGRAPH . COMPOUND PROFILE

T3D-959

A non-thiazolidinedione dual nuclear receptor agonist originally developed for metabolic disease and repositioned as a first-in-class brain insulin-sensitizing therapy for Alzheimer's disease, distinguished by concurrent PPARD and PPARγ activation, high central nervous system penetrance, and Phase 2 evidence of disease-modifying effects on cognition and amyloid biomarkers.

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ABSTRACT

T3D-959 (DB-959, DB-959Na as the sodium salt) is an orally bioavailable, brain-penetrant, non-thiazolidinedione dual agonist of peroxisome proliferator-activated receptor delta (PPAR δ ; human ED₅₀ 19 nM) and peroxisome proliferator-activated receptor gamma (PPAR γ ; human ED₅₀ 297 nM), conferring approximately 15-fold selectivity for the delta isoform. The compound was originally synthesized by Bayer and advanced through Phase 1 clinical trials for dyslipidemia and type 2 diabetes by DARA BioSciences before being acquired in 2013 by T3D Therapeutics and repositioned as a disease-modifying candidate for Alzheimer's disease (AD) on the basis of the "type 3 diabetes" hypothesis, which posits that sporadic AD is driven by progressive brain insulin resistance, deficient insulin and insulin-like growth factor signaling, and consequent neurometabolic dysfunction. T3D-959 is the first PPAR δ -activating compound to enter clinical development for AD and represents a mechanistically distinct approach from the anti-amyloid antibody and cholinesterase inhibitor classes that dominate the current AD therapeutic landscape. Preclinical characterization in the intracerebral streptozotocin (i.c. STZ) rat model of sporadic AD, conducted principally by the de la Monte laboratory at Brown University, demonstrated that oral T3D-959 at doses of 0.3 to 3.0 mg/kg/day preserved spatial learning and memory in the Morris water maze, prevented brain weight loss, normalized phosphorylated tau and amyloid precursor protein-amyloid beta 42 (A β PP-A β 42) levels, reduced markers of oxidative stress, and partially restored cholinergic enzyme expression and white matter integrity. Therapeutic effects were observed even when treatment was

delayed seven days after the STZ insult, suggesting relevance to mild and moderate disease stages. A separate preclinical study demonstrated that T3D-959 at 1.0 mg/kg/day improved motor function and prevented cerebellar white matter atrophy in the same model. An exploratory Phase 2a clinical trial in 36 subjects with mild to moderate AD (Chamberlain et al. 2020)

demonstrated safety and tolerability at oral doses of 3, 10, 30, and 90 mg daily for 14 days, with no serious adverse events.

Pharmacokinetic analysis confirmed dose-dependent systemic exposure exceeding the PPARD ED50 at all doses tested. Plasma metabolomics showed dose-dependent reductions in branched-chain amino acids and ceramides and increases in acylcarnitines, consistent with improved insulin sensitivity and enhanced fatty acid beta-oxidation. FDG-PET neuroimaging demonstrated dose-dependent increases in regional cerebral glucose metabolism, with the strongest effects in the putamen, anterior cingulate, insula, and orbital frontal cortex. Cognitive assessments showed improvements on the ADAS-Cog11 at 30 mg and on the Digit Symbol Substitution Test at all doses, with a delayed improvement pattern consistent with a transcriptional regulatory mechanism of action and an apparent ApoE4 genotype interaction. The Phase 2 PIONEER trial, a 24-week multicenter randomized double-blind placebo-controlled study in 250 patients with mild to moderate AD, reported positive top-line results in November 2023 at the 16th Clinical Trials on Alzheimer's Disease (CTAD) conference. In the modified intent-to-treat population (n=141), the 30 mg group showed improvement on ADAS-Cog11 (0.73 versus 2.70 on placebo; p=0.073), and the 15 mg group showed improvement on ADCS-CGIC (0.39 versus 0.86 on placebo; p=0.060). Plasma amyloid beta 42/40 ratio improved significantly in the 30 mg (p=0.011) and 45 mg (p=0.033) groups, and the neurodegeneration

marker neurogranin improved significantly in the 30 mg group ($p=0.035$). The compound was well tolerated, with adverse event rates similar between active and placebo arms (37.3% versus 43.1%) and no treatment-related serious adverse events. A Phase 2b/3 trial (NCT06964230) at 30 mg daily for 78 weeks in approximately 376 patients with biomarker-validated mild to moderate AD is planned to initiate in 2026. T3D-959 is not approved for any indication in any jurisdiction. This monograph reviews the chemistry, dual-receptor pharmacology, preclinical evidence base, clinical development program, pharmacokinetics, sourcing, reconstitution, stack interactions, adverse-event signal, and a comparative assessment of five alternative PPAR-targeting and insulin-sensitizing candidates against T3D-959 on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Proposed International Nonproprietary Name: T3D-959.

Development codes: DB-959 (DARA BioSciences); DB-959Na (sodium salt formulation used in clinical development); T3D-959 (T3D Therapeutics).

Chemical Abstracts Service registry number: 1258076-66-2 (free acid).

PubChem Compound Identifier: CID 49839871 (sodium salt).

Synonyms: DB959, DB 959, T3D 959.

1.2 Structural class and chemistry

T3D-959 is a non-thiazolidinedione dual nuclear receptor agonist of the peroxisome proliferator-activated receptor (PPAR) family, specifically targeting the PPAR δ (PPAR β /delta) and PPAR γ isoforms. The compound is structurally distinct from the thiazolidinedione class of PPAR γ agonists (pioglitazone, rosiglitazone), which is significant because the thiazolidinedione scaffold is associated with peripheral edema, weight gain, congestive heart failure risk, and bone fracture risk that have limited the clinical utility of those agents [1, 2].

Molecular formula: C₂₅H₂₇NO₅ (free acid); C₂₅H₂₆NNaO₅ (sodium salt).

Molecular weight: Approximately 421.49 g/mol (free acid); approximately 445.47 g/mol (sodium salt).

Physical properties: The compound is supplied as the sodium salt (DB-959Na) for clinical and research use. It is a small molecule with physicochemical properties consistent with oral bioavailability and blood-brain barrier penetration, including moderate molecular weight and lipophilicity.

Stereochemistry: The compound does not contain a thiazolidinedione ring. Specific stereochemical details beyond the published molecular formula have not been fully disclosed in the peer-reviewed literature.

1.3 Synthesis

The synthetic route for T3D-959 has not been published in detail in the peer-reviewed literature. The compound was originally synthesized at Bayer as part of a medicinal chemistry program exploring non-thiazolidinedione PPAR agonists for metabolic disease applications [3]. The sodium salt formulation (DB-959Na) is the clinical-grade material used in all reported human studies. Industrial synthesis details remain proprietary to T3D Therapeutics. Investigators acquiring research-grade material should confirm identity and purity by high-performance liquid chromatography and mass spectrometry against the published molecular formula and CAS registry number.

2. Abstract

T3D-959 (DB-959) is a brain-penetrant, orally active, non-thiazolidinedione dual agonist of the peroxisome proliferator-activated nuclear receptors delta and gamma, with approximately 15-fold selectivity for PPAR δ (human ED₅₀ 19 nM) over PPAR γ (human ED₅₀ 297 nM). The compound was first developed by Bayer for metabolic indications and was repositioned for Alzheimer's disease (AD) by T3D Therapeutics following the recognition that sporadic AD involves progressive brain insulin resistance, impaired brain glucose and lipid metabolism, and neuroinflammation, collectively a neurometabolic dysfunction state sometimes termed "type 3 diabetes" [4, 5].

The mechanistic rationale positions T3D-959 as a transcriptional regulator that, through PPAR δ and PPAR γ heterodimerization with retinoid X receptors and subsequent DNA promoter binding, restores expression of genes governing glucose utilization, lipid metabolism, insulin signaling, and anti-inflammatory pathways in the central nervous system [6]. This mechanism is fundamentally distinct from the amyloid-targeting (anti-amyloid antibodies, secretase inhibitors), cholinergic (acetylcholinesterase inhibitors), and glutamatergic (memantine) strategies that constitute the majority of the AD therapeutic pipeline.

Preclinical studies in the intracerebral streptozotocin rat model of sporadic AD demonstrated that T3D-959 reversed cognitive deficits, restored brain insulin and insulin-like growth factor signaling, normalized tau phosphorylation and amyloid-beta markers, reduced neuroinflammation and oxidative stress, and preserved white matter integrity at oral doses of 0.3 to 3.0 mg/kg/day [6, 7, 8]. These effects were observed with both early (one day post-insult) and delayed (seven days post-insult) treatment initiation, supporting the therapeutic window for application in mild to moderate human disease.

An exploratory Phase 2a trial (Chamberlain et al. 2020) in 36 subjects with mild to moderate AD confirmed safety, demonstrated dose-dependent systemic pharmacology consistent with insulin sensitization (reduced branched-chain amino acids, reduced ceramides, increased fatty acid beta-oxidation markers), showed dose-dependent increases in regional cerebral glucose metabolism on FDG-PET, and provided preliminary signals of cognitive improvement at 30 mg daily [9]. The Phase 2

PIONEER trial (n=250, 24 weeks) subsequently reported in 2023 that the 30 mg dose produced improvement on ADAS-Cog11 and significant improvement in plasma amyloid-beta 42/40 ratio and neurogranin biomarkers, with excellent tolerability and no treatment-related serious adverse events [10, 11]. A Phase 2b/3 trial at 30 mg daily for 78 weeks (NCT06964230) is planned.

The compound is not approved for any indication in any jurisdiction. It is an investigational new drug under active clinical development by T3D Therapeutics.

3. Discovery and Development History

3.1 Origin

T3D-959 was synthesized at Bayer as part of a medicinal chemistry program directed at non-thiazolidinedione PPAR agonists for the treatment of metabolic syndrome, dyslipidemia, and type 2 diabetes [3, 12]. The compound was designed to avoid the thiazolidinedione scaffold and its associated adverse effects (peripheral edema, weight gain, congestive heart failure, bone density loss) while retaining potent PPAR agonist activity with a novel selectivity profile favoring PPAR δ over PPAR γ .

3.2 Metabolic disease development (DARA BioSciences)

DARA BioSciences acquired worldwide rights to DB-959 from Bayer and conducted Phase 1 clinical trials in healthy volunteers for dyslipidemia and type 2 diabetes in 2010 and 2011. These Phase 1 studies enrolled 96 normal subjects dosed for up to 7 days and demonstrated no drug-related adverse events, with a maximum tolerated dose greater than 200 mg (more than twice the highest dose subsequently tested in the Phase 2a AD trial) [9, 12]. DARA BioSciences subsequently shifted its corporate focus to oncology care products and did not advance DB-959 into Phase 2 metabolic disease trials.

3.3 Repositioning for Alzheimer's disease (T3D Therapeutics)

In 2013, T3D Therapeutics, founded by John Didsbury, acquired DB-959 from DARA BioSciences with the specific intent of repositioning the compound as a disease-modifying therapy for Alzheimer's disease [3, 12]. The repositioning was based on the convergence of three lines of evidence: (a) the growing epidemiological and molecular evidence that type 2 diabetes is a significant risk factor for AD; (b) the de la Monte laboratory's characterization of sporadic AD as a "type 3 diabetes" involving progressive brain insulin resistance, deficient insulin and insulin-like growth factor signaling, and downstream neurodegeneration [4, 5]; and (c) the preclinical

demonstration that PPAR agonists, particularly those targeting PPARD, were neuroprotective in models of neurodegeneration and that PPARD activation was more neuroprotective than PPARG activation alone in the streptozotocin AD model [6, 13].

3.4 Preclinical development

The preclinical program was conducted principally at Brown University in collaboration with the de la Monte laboratory. Three published reports (Tong et al. 2016a, Tong et al. 2016b, de la Monte et al. 2017) established the efficacy of T3D-959 in the i.c. STZ rat model across multiple disease-relevant endpoints [6, 7, 8]. A subsequent publication (de la Monte et al. 2019) demonstrated that dual PPARD/g activation with T3D-959 produced greater therapeutic benefit than selective activation of either receptor alone, providing mechanistic support for the dual-agonist design [13].

3.5 Clinical development

The Phase 2a exploratory trial was conducted in 2016 at multiple United States sites, with results published in 2020 (Chamberlain et al., Journal of Alzheimer's Disease) [9]. The Phase 2 PIONEER trial was initiated in February 2020, enrolled 250 patients at multiple United States sites, and reported top-line results at the 16th CTAD conference in November 2023 [10, 11]. Additional analyses were presented at the 2024 Alzheimer's Association International Conference (AAIC) [14]. A Phase 2b/3 randomized double-blind placebo-controlled trial (NCT06964230) at 30 mg daily for 78 weeks is planned to initiate in 2026.

4. Mechanism of Action

T3D-959 is a dual nuclear receptor agonist. Its principal molecular activities are activation of the peroxisome proliferator-activated receptor delta (PPAR δ) and peroxisome proliferator-activated receptor gamma (PPAR γ), two ligand-dependent transcription factors of the nuclear receptor superfamily that regulate gene expression by heterodimerizing with retinoid X receptors (RXR) and binding to PPAR response elements in DNA promoter regions [6, 15].

4.1 PPAR delta activation

PPAR δ (also designated PPARbeta/delta) is a nuclear receptor expressed widely in the brain, skeletal muscle, heart, adipose tissue, and immune cells. In the central nervous system, PPAR δ is expressed at high levels in cortical and hippocampal neurons, astrocytes, and oligodendrocytes [15, 16]. Activation of PPAR δ promotes fatty acid beta-oxidation, mitochondrial biogenesis, glucose utilization, and anti-inflammatory gene programs. In neurons, PPAR δ activation enhances mitochondrial function, reduces oxidative stress, promotes myelination, and suppresses proinflammatory cytokine production through inhibition of NF-kappaB signaling [16, 17].

T3D-959 activates human PPAR δ with an ED₅₀ of 19 nM, which is the primary pharmacological target [6]. The potency for rat PPAR δ is approximately 3-fold lower than for rat PPAR γ , reflecting species-specific differences in receptor pharmacology that are important for the interpretation of preclinical dose-response data [6].

4.2 PPAR gamma activation

PPAR γ is the molecular target of the thiazolidinedione class of insulin sensitizers (pioglitazone, rosiglitazone) and is expressed in adipose tissue, immune cells, and at lower levels in neurons and glia. PPAR γ activation promotes insulin sensitization through transcriptional upregulation of glucose transporter expression, adiponectin secretion, and anti-inflammatory gene programs [1, 2, 15]. In the brain,

PPARg activation reduces neuroinflammation, modulates microglial polarization toward anti-inflammatory phenotypes, and has been associated with reduction of amyloid-beta production through transcriptional downregulation of BACE1 [18].

T3D-959 activates human PPARg with an ED50 of 297 nM, approximately 15-fold less potent than its PPARd activity [6]. This secondary PPARg activation may provide additive or synergistic neuroprotective effects through complementary insulin-sensitizing and anti-inflammatory pathways. De la Monte et al. (2019) demonstrated that dual PPARd/g activation with T3D-959 produced greater therapeutic benefit than selective activation of either receptor alone in the i.c. STZ rat model, supporting the pharmacological rationale for the dual-agonist design [13].

4.3 Brain insulin sensitization

The overarching mechanistic hypothesis for T3D-959 in AD is that the compound corrects the neurometabolic dysfunction that characterizes sporadic AD. The "type 3 diabetes" hypothesis, developed principally by de la Monte and colleagues, holds that sporadic AD involves progressive brain insulin resistance and deficient insulin and insulin-like growth factor (IGF) signaling, leading to impaired brain glucose utilization, dysregulated lipid metabolism, increased oxidative stress, tau hyperphosphorylation, amyloid-beta accumulation, neuroinflammation, and neuronal loss [4, 5]. By activating PPARd and PPARg, T3D-959 restores the expression of genes governing insulin receptor substrate signaling, glucose transporter expression, and lipid metabolic enzymes, thereby addressing multiple downstream pathological processes through a single upstream transcriptional mechanism.

4.4 Downstream pathological effects

The preclinical evidence demonstrates that the transcriptional effects of T3D-959 translate to normalization of multiple AD-relevant pathological markers: reduced phosphorylated tau (at S396 and T205 epitopes), reduced AbPP-Ab42 levels, restored choline acetyltransferase expression, reduced ubiquitin (indicating decreased unfolded protein response), reduced glucose-6-phosphate dehydrogenase release (indicating reduced cytotoxicity), and partial restoration of myelin-associated glycoprotein expression [6, 7, 8]. These effects position the compound as a pleiotropic disease-modifying agent rather than a single-target symptomatic therapy.

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

T3D-959 is well absorbed after oral administration. Pharmacokinetic analysis in the Phase 2a trial confirmed dose-dependent systemic exposure with once-daily oral dosing [9]. Single-point pharmacokinetic analysis at the approximate T_{max} (4 hours post-dose) showed the following mean plasma concentrations:

3 mg: 86.5 ng/mL (3.6 times the PPAR α ED₅₀). 10 mg: 290 ng/mL (12.0 times the PPAR α ED₅₀). 30 mg: 763 ng/mL (31.7 times the PPAR α ED₅₀). 90 mg: 2,765 ng/mL (114.9 times the PPAR α ED₅₀).

Even at the lowest clinical dose of 3 mg, plasma concentrations exceeded the PPAR α ED₅₀, confirming target engagement at all tested doses [9].

5.2 Distribution

T3D-959 demonstrates a high degree of central nervous system penetrance, a critical pharmacological feature that distinguishes it from the thiazolidinedione PPAR γ agonists (pioglitazone, rosiglitazone), which have limited blood-brain barrier permeability [1, 6, 18]. Preclinical studies estimated a brain-to-plasma ratio of approximately 35%, and the Phase 2a FDG-PET data confirmed dose-dependent effects on regional cerebral glucose metabolism, providing functional evidence of brain penetration in humans [9]. Calculated brain concentrations at all clinical doses exceeded the PPAR α ED₅₀.

5.3 Metabolism

Detailed human metabolic pathway characterization has not been published in the peer-reviewed literature. The pharmacokinetic profile supports once-daily oral dosing, consistent with a moderate elimination half-life. Phase 1 studies demonstrated dose-proportional exposure up to at least 200 mg without saturation of absorption or first-pass metabolism [9, 12].

5.4 Elimination

Specific renal and hepatic elimination parameters have not been published. The compound is predominantly eliminated through hepatic metabolism based on its physicochemical properties and the absence of significant unchanged drug in pre-clinical urinary excretion studies.

5.5 Routes of administration

T3D-959 is administered exclusively by the oral route in all clinical studies. The compound is formulated as the sodium salt (DB-959Na) in capsule form for once-daily oral administration. No intravenous, intramuscular, or subcutaneous formulations have been reported.

5.6 Special populations

Specific pharmacokinetic studies in renal impairment, hepatic impairment, or pediatric populations have not been published. The Phase 2a trial enrolled subjects aged 57 to 90 years (mean 75 years), and the pharmacokinetic and safety data in this elderly AD population are the principal clinical pharmacokinetic reference [9]. The Phase 2 PIONEER trial enrolled subjects with mild to moderate AD; subgroup pharmacokinetic data by age, renal function, or hepatic function have not been reported.

6. Preclinical Pharmacology

6.1 Intracerebral streptozotocin model

The principal preclinical evidence for T3D-959 in AD was generated in the intracerebral streptozotocin (i.c. STZ) model in adult Long Evans rats. This model, established by the de la Monte laboratory, replicates the full range of neurometabolic abnormalities observed in sporadic AD, including brain insulin resistance, deficient insulin and IGF signaling, tau hyperphosphorylation, amyloid-beta accumulation, neuroinflammation, oxidative stress, white matter degeneration, cholinergic deficits, and progressive cognitive impairment [4, 5, 6].

6.2 Cognitive and motor outcomes

T3D-959 at oral doses of 0.3 to 3.0 mg/kg/day significantly improved spatial learning and memory in the Morris water maze in i.c. STZ-treated rats [6, 7]. Early treatment (initiated one day post-STZ) produced complete normalization of spatial learning at 3.0 mg/kg. Delayed treatment (initiated seven days post-STZ) produced complete normalization at 0.7 to 1.0 mg/kg, with protective effects observed even at the lowest tested dose of 0.3 mg/kg [6]. In a separate study, T3D-959 at 1.0 mg/kg/day improved motor function on rotarod testing, with the most pronounced effects at intermediate difficulty levels [8].

6.3 Neuropathological outcomes

T3D-959 treatment abrogated the i.c. STZ-associated reduction in brain weight across all treatment groups [6]. Molecular biomarker analysis demonstrated normalization of phosphorylated tau (at S396 and T205 epitopes), reduction of AbPP-Aβ42 levels to control values, partial restoration of choline acetyltransferase expression, reduction of ubiquitin and glucose-6-phosphate dehydrogenase release (markers of unfolded protein response and cytotoxicity, respectively), and partial restoration of myelin-associated glycoprotein (MAG-1) expression [6, 7].

6.4 Brain insulin and IGF signaling

De la Monte et al. (2017) demonstrated that T3D-959 improved brain insulin and IGF signaling pathways and reduced neuroinflammation in the i.c. STZ model [7]. The compound restored expression of insulin receptor substrate proteins and downstream signaling mediators, consistent with its proposed mechanism as a brain insulin sensitizer.

6.5 Cerebellar pathology

A separate preclinical study assessed T3D-959 at 1.0 mg/kg/day on cerebellar pathology in the i.c. STZ model [8]. T3D-959 prevented white matter atrophy in the cerebellum, with delayed treatment (7 days post-STZ) producing values approximating control. Semi-quantitative histopathology demonstrated restoration of molecular layer thickness, Purkinje cell layer cellularity, and granule cell layer integrity.

6.6 Dual versus selective PPAR activation

De la Monte et al. (2019) compared the therapeutic effects of dual PPAR α /g activation (T3D-959) with selective PPAR α or PPAR γ activation in the i.c. STZ model [13]. The dual agonist produced greater therapeutic benefit across multiple endpoints than either selective agonist alone, providing mechanistic support for the dual-target design of T3D-959 and suggesting that the concurrent activation of both PPAR isoforms produces additive or synergistic neuroprotective effects.

6.7 ALS and other neurodegenerative models

T3D-959 was evaluated in two preclinical models of amyotrophic lateral sclerosis (ALS): an AAV-mediated C9orf72 G4C2-repeat expansion model and a TDP-43 Q331K transgenic mouse model [19]. Comprehensive analyses revealed that T3D-959 did not rescue hallmark disease phenotypes in either ALS model, suggesting that the neuroprotective effects of the compound are specific to the metabolic dysfunction phenotype characteristic of AD rather than broadly applicable across neurodegenerative diseases.

7. Clinical Evidence Base

7.1 Phase 1 (healthy volunteers)

Phase 1 clinical trials conducted by DARA BioSciences in 2010 and 2011 enrolled 96 healthy subjects in single and multiple ascending dose studies with oral T3D-959 (as DB-959Na) for up to 7 days [9, 12]. No drug-related adverse events were observed. The maximum tolerated dose was greater than 200 mg, providing a substantial safety margin above the subsequently identified optimal efficacy dose of 30 mg. Pharmacokinetics demonstrated dose-proportional exposure and supported once-daily oral dosing.

7.2 Phase 2a exploratory trial (Chamberlain et al. 2020)

The Phase 2a study was a randomized, parallel-group, open-label, exploratory trial of T3D-959 in 36 subjects (34 completing) with mild to moderate AD, conducted at multiple United States sites [9].

Study design: Four dose groups received once-daily oral T3D-959 for 14 days: 3 mg (n=9), 10 mg (n=9), 30 mg (n=10), and 90 mg (n=8). Subjects were stratified by ApoE4 status (17 ApoE4-positive, 17 ApoE4-negative). Follow-up assessment occurred at day 21 (7 days post-treatment discontinuation). There was no placebo control group.

Safety: Only 4 subjects (11%) experienced 8 adverse events, none serious or severe. One adverse event was classified as treatment-related (muscular weakness, resolved within one day). No clinically significant ECG abnormalities, laboratory abnormalities, or vital sign changes were observed.

Metabolomics: Plasma metabolomic profiling of 821 metabolites demonstrated dose-dependent systemic pharmacology consistent with insulin sensitization. All three branched-chain amino acids (leucine, isoleucine, valine) were significantly decreased ($p < 0.05$) in the 90 mg group, a finding consistent with improved insulin sensitivity given that elevated branched-chain amino acids are a biomarker of insulin resistance. Seven of ten ceramide species decreased significantly at 30 and 90 mg doses, including N-palmitoyl sphingosine (C16:0). Acylcarnitine species in-

creased dose-dependently, indicating enhanced fatty acid beta-oxidation. Glycine levels increased at 90 mg, and six of eleven measured plasmalogens increased (plasmalogen deficiency is implicated in AD pathology).

FDG-PET neuroimaging: FDG-PET demonstrated dose-dependent increases in regional cerebral glucose metabolism. Statistical parametric mapping showed a significant dose-response trend in the number of positively changed voxels: 10 mg (70 voxels), 30 mg (518 voxels), 90 mg (2,136 voxels; R-squared=0.998, p=0.026). Brain regions with the strongest responses included bilateral putamen, bilateral anterior cingulate, bilateral insula, and orbital frontal cortex.

Cognitive assessments: ADAS-Cog11 showed the most consistent improvements in the 30 mg group, with a follow-up-to-baseline change of negative 3.97 points (p=0.006). ApoE4-negative subjects showed a delayed improvement pattern, with all ApoE4-negative subjects in the 3, 10, and 30 mg groups showing improved scores at follow-up (average negative 5.02 points). The Digit Symbol Substitution Test (DSST) showed a dose-dependent improvement trend from 3 mg to 90 mg at follow-up (R-squared=0.957), with the across-subject follow-up-to-end-of-treatment change (+3.5 points) significantly different from the screening-to-baseline change (p=0.005).

Pharmacodynamic lag: The pattern of minimal change at end-of-treatment but significant improvement at the one-week follow-up suggested a delayed pharmacodynamic effect consistent with the transcriptional regulatory mechanism of action, which requires time for gene expression changes to translate to functional protein and cellular effects.

7.3 Phase 2 PIONEER trial

The PIONEER study was a multicenter, randomized, double-blind, placebo-controlled Phase 2 trial of T3D-959 in patients with mild to moderate AD diagnosed by NIA-AA criteria [10, 11, 14].

Study design: 250 patients were randomized to placebo, 15 mg, 30 mg, or 45 mg of T3D-959 once daily for 24 weeks. The modified intent-to-treat (mITT) population comprised 141 patients after exclusion of sites with data irregularities: placebo (n=32), 15 mg (n=38), 30 mg (n=39), 45 mg (n=32).

Primary endpoints: The study met its coprimary endpoints per protocol. On ADAS-Cog11, the 30 mg group showed improvement relative to placebo (0.73 versus 2.70; p=0.073). On ADCS-CGIC (Alzheimer's Disease Cooperative Study, Clinician's

Global Impression of Change), the 15 mg group showed improvement relative to placebo (0.39 versus 0.86; $p=0.060$).

Biomarker results: Plasma amyloid-beta 42/40 ratio improved significantly in the 30 mg group ($p=0.011$) and the 45 mg group ($p=0.033$), with effect magnitude reported as comparable to that observed for anti-amyloid antibodies (lecanemab) at 6 months. The neurodegeneration marker neurogranin improved significantly in the 30 mg group ($p=0.035$) and approached significance in the 45 mg group ($p=0.051$). Proteomic analysis documented changes in markers of inflammation, oxidative stress, and metabolic function. A high pTau-217/non-pTau-217 ratio in blood was identified as defining a subpopulation particularly responsive to T3D-959 therapy, with the high pTau-217 ratio group dosed at 30 mg ($n=30$) exhibiting an improvement of 2 points versus placebo on ADAS-Cog11.

Safety: T3D-959 was safe and well tolerated. Adverse event rates were similar between active treatment and placebo groups (37.3% versus 43.1%), with no treatment-related serious adverse events. There were no drug-related adverse events related to stroke and no clinical signs of amyloid-related imaging abnormalities (ARIA), which is notable given that ARIA is a significant safety concern with anti-amyloid antibody therapies. One discontinuation was attributed to drug-related mild peripheral edema.

Dose selection: The 30 mg once-daily dose was identified as providing optimal safety and efficacy for further investigation.

7.4 Planned Phase 2b/3 trial

A Phase 2b/3 randomized, double-blind, placebo-controlled trial (NCT06964230) is planned to evaluate T3D-959 at 30 mg daily for 78 weeks in approximately 376 patients with biomarker-validated mild to moderate AD [10]. The trial is scheduled to initiate in 2026.

8. Sourcing and Quality Verification

T3D-959 is an investigational compound under active clinical development by T3D Therapeutics. Pharmaceutical-grade material (DB-959Na, sodium salt) is controlled by T3D Therapeutics and is not commercially available for general research use through the sponsor.

Research-grade T3D-959 (free acid or sodium salt) is available from specialized chemical and pharmaceutical research suppliers (Probechem Biochemicals, MedChemExpress, and other specialty vendors) at greater than 95 percent purity by HPLC. Supply is typically in milligram quantities. The CAS registry number (1258076-66-2 for the free acid) and PubChem CID (49839871 for the sodium salt) serve as unambiguous identifiers for procurement.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography area-percent purity, ideally greater than 95 percent
- Mass spectrometry confirmation of molecular weight (consistent with C₂₅H₂₇NO₅ for the free acid or C₂₅H₂₆NNaO₅ for the sodium salt)
- Nuclear magnetic resonance spectroscopy for structural confirmation
- Karl Fischer or loss-on-drying analysis for residual water content

The research-grade T3D-959 market is small relative to more established research compounds, and batch-to-batch variability may be observed from specialty suppliers. On-receipt analytical confirmation is strongly recommended for any investigation where dose-response precision is important. Third-party analytical laboratories can provide independent verification of vendor certificates of analysis.

9. Reconstitution and Handling

T3D-959 sodium salt is supplied as a solid powder for research applications. The compound is soluble in dimethyl sulfoxide (DMSO) for in vitro applications. For cell culture experiments, concentrated stock solutions in DMSO (typically 10 to 50 mM) should be prepared and diluted into culture media to achieve the desired final concentration, with DMSO vehicle controls included in all experiments.

Storage of the solid compound at negative 20 degrees Celsius under desiccated conditions is recommended by research suppliers. Stock solutions in DMSO should be stored in single-use aliquots at negative 20 degrees Celsius to avoid freeze-thaw cycles.

For in vivo research applications, the compound can be formulated in standard oral dosing vehicles (methylcellulose suspensions, polyethylene glycol solutions) consistent with the published preclinical studies, which used oral gavage as the route of administration [6, 7, 8].

The clinical formulation (DB-959Na capsules) is controlled by T3D Therapeutics and is available only through the clinical trial program. Investigators conducting research outside the clinical trial program should use research-grade material with appropriate analytical verification.

10. Stack Interactions and Combinations

T3D-959 interacts with several drug classes through its PPAR agonist pharmacology and through potential pharmacokinetic interactions. Investigators conducting research with T3D-959 should consider:

Thiazolidinedione PPARg agonists (pioglitazone, rosiglitazone): Concurrent use would produce additive PPARg activation and potentially increase the risk of PPARg-mediated adverse effects (peripheral edema, weight gain, fluid retention). The combination is pharmacologically redundant for the PPARg component. T3D-959 was designed to minimize PPARg overactivation through its 15-fold PPARD selectivity; adding a full PPARg agonist would negate this design advantage.

Fibrates (bezafibrate, fenofibrate, gemfibrozil): Fibrates are PPARalpha agonists with variable PPARD activity. Concurrent use could produce additive PPAR activation across multiple isoforms. Pharmacokinetic interactions through shared hepatic metabolism pathways are possible. The combination has not been studied.

Anti-amyloid antibodies (lecanemab, donanemab, aducanumab): T3D-959 operates through a mechanistically distinct pathway from anti-amyloid antibodies. The PIONEER trial demonstrated improvement in amyloid biomarkers without ARIA, suggesting that the combination could be complementary. However, the combination has not been studied in clinical trials and the potential for additive effects on amyloid clearance or for unexpected interactions is unknown.

Cholinesterase inhibitors (donepezil, rivastigmine, galantamine): The Phase 2a and PIONEER trials permitted concurrent cholinesterase inhibitor use as standard of care. No specific interaction was identified. The combination is pharmacologically rational, as T3D-959 addresses upstream metabolic dysfunction while cholinesterase inhibitors provide symptomatic relief through cholinergic augmentation.

Memantine: Similarly, concurrent memantine use was permitted in the clinical trials. No specific interaction was identified. The glutamatergic mechanism of memantine is orthogonal to the PPAR-mediated mechanism of T3D-959.

Insulin and insulin sensitizers (metformin, sulfonylureas): The insulin-sensitizing activity of T3D-959 could produce additive effects on systemic glucose metabolism when combined with antidiabetic agents. Investigators studying T3D-959 in patients with concurrent type 2 diabetes should monitor for hypoglycemia, although no hypoglycemic events were reported in the Phase 2a or PIONEER trials.

CYP enzyme substrates and inhibitors: Detailed cytochrome P450 interaction data for T3D-959 have not been published. Investigators should exercise caution with concurrent strong CYP inhibitors or inducers until formal drug-drug interaction studies are available.

11. Adverse Events and Safety

11.1 Phase 1 safety

Phase 1 trials in 96 healthy subjects at doses up to at least 200 mg for up to 7 days demonstrated no drug-related adverse events [9, 12]. The maximum tolerated dose exceeded 200 mg.

11.2 Phase 2a safety

In the Phase 2a trial (n=36, 14 days, doses 3 to 90 mg), only 4 subjects (11%) experienced 8 adverse events, none serious or severe [9]. One event was classified as treatment-related: muscular weakness that resolved within one day. No clinically significant ECG abnormalities were observed. One subject had transient QTc prolongation (419 to 458 ms) that resolved by follow-up. No laboratory abnormalities or vital sign changes were noted. An 18-week extension substudy in 4 subjects showed no tolerability concerns.

11.3 Phase 2 PIONEER safety

In the PIONEER trial (n=250, 24 weeks, doses 15 to 45 mg), adverse event rates were similar between T3D-959 (37.3%) and placebo (43.1%) groups [10, 11]. No treatment-related serious adverse events were reported. One subject discontinued due to drug-related mild peripheral edema. Reported possible side effects at low frequency included muscle weakness and cramps. There were no drug-related adverse events related to stroke and no clinical signs of ARIA.

11.4 Comparison to thiazolidinedione safety profile

The safety profile of T3D-959 is notably favorable relative to the thiazolidinedione PPAR γ agonists. Pioglitazone and rosiglitazone are associated with peripheral edema (incidence 5 to 15%), weight gain (2 to 4 kg over 6 to 12 months), congestive heart failure exacerbation, bone fracture risk (particularly in postmenopausal women), and bladder cancer concern (pioglitazone) [1, 2]. The non-thiazolidine-

dione structure and PPARD-preferential selectivity of T3D-959 appear to confer a substantially lower risk of these PPARG-mediated adverse effects, although longer-duration and larger-sample-size studies are needed to confirm this advantage.

11.5 ARIA absence

The absence of ARIA in the PIONEER trial is clinically significant. ARIA (amyloid-related imaging abnormalities, including ARIA-E edema and ARIA-H hemorrhage) is a major safety concern with anti-amyloid antibody therapies, occurring in 10 to 35% of patients treated with lecanemab or donanemab and requiring MRI monitoring [10]. The mechanistically distinct approach of T3D-959 avoids this class-specific toxicity, which is a practical advantage for clinical implementation if efficacy is confirmed in Phase 3.

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative PPAR-targeting and insulin-sensitizing candidates against T3D-959, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five comparators were selected as the principal compounds with clinical or advanced preclinical evidence for PPAR-mediated or insulin-sensitizing mechanisms in neurodegenerative disease, with priority on those that share T3D-959's mechanistic or therapeutic positioning.

12.1 Pioglitazone (Actos)

Mechanism: Selective PPARG agonist of the thiazolidinedione class, with weak PPARalpha activity. Approved for type 2 diabetes. Brain penetration is limited relative to T3D-959 [1, 18].

Development trajectory: Multiple epidemiological studies suggested that pioglitazone use in type 2 diabetes patients was associated with reduced AD risk. The TOMMORROW trial (Takeda/Zinfandel Pharmaceuticals), a large Phase 3 prevention trial in cognitively normal at-risk subjects identified by a genetic biomarker algorithm, was terminated in 2018 for futility after an interim analysis [20]. A smaller Phase 2 trial in mild to moderate AD patients showed no significant cognitive benefit. Pioglitazone remains available as a generic diabetic medicine but is not in active development for AD.

Novelty: Low. The PPARG agonist mechanism is well established and the thiazolidinedione class has been extensively studied.

Effect size: Null in the TOMMORROW Phase 3 prevention trial. Small and inconsistent in Phase 2 AD treatment trials. Preclinical effects are robust in rodent models but have not translated to clinical efficacy.

Promising potential: Low. Phase 3 futility in the TOMMORROW trial has substantially reduced enthusiasm for selective PPAR γ agonism as a monotherapy strategy in AD.

Side-effect profile: Peripheral edema (5 to 15%), weight gain, congestive heart failure exacerbation, bone fracture risk, bladder cancer concern. The safety profile limits chronic dosing in elderly AD populations, which are the target population for any AD therapy.

Overall validation: Low to moderate. Extensive epidemiological and preclinical support, but the clinical translation has failed at Phase 3. The mechanism hypothesis (PPAR γ -mediated insulin sensitization in the brain) remains plausible but is confounded by the limited brain penetration of pioglitazone.

Comparison to T3D-959: T3D-959 has substantially higher brain penetration, preferential PPAR δ activation (which preclinical data suggest is more neuroprotective than PPAR γ activation alone), a non-thiazolidinedione structure avoiding the class-specific adverse-effect profile, and positive Phase 2 clinical signals. The pioglitazone TOMMORROW failure may reflect the limitations of selective PPAR γ agonism and/or inadequate brain exposure rather than the invalidity of the PPAR mechanism itself.

12.2 Rosiglitazone (Avandia)

Mechanism: Selective PPAR γ agonist of the thiazolidinedione class. Approved for type 2 diabetes but subject to severe prescribing restrictions due to cardiovascular safety concerns [2].

Development trajectory: GlaxoSmithKline conducted a Phase 2 program (REFLECT trials) evaluating rosiglitazone as an adjunct to cholinesterase inhibitor therapy in mild to moderate AD. The trials (Risner et al. 2006, Gold et al. 2010) showed no overall cognitive benefit, although post-hoc analyses suggested a possible benefit in ApoE4-negative patients [21, 22]. The cardiovascular safety concerns (myocardial infarction risk increase on meta-analysis) and the negative Phase 2 results terminated further AD development.

Novelty: Low. Mechanism is identical to pioglitazone (selective PPAR γ agonism).

Effect size: Null overall in Phase 2 AD trials. Possible small effect in ApoE4-negative subgroup, which is interesting in light of the ApoE4-genotype interaction observed with T3D-959 in the Phase 2a trial.

Promising potential: Very low. Cardiovascular safety concerns and negative clinical results have terminated development.

Side-effect profile: Peripheral edema, weight gain, congestive heart failure, cardiovascular risk (myocardial infarction signal on meta-analysis), bone fracture risk. The safety profile is the worst of the comparator panel.

Overall validation: Low. Negative Phase 2 with serious safety concerns.

Comparison to T3D-959: T3D-959 avoids the cardiovascular safety concerns, has superior brain penetration, and offers dual PPAR α /g activation rather than selective PPAR γ agonism. The ApoE4 interaction observed with rosiglitazone (possible benefit in ApoE4-negative patients) parallels observations in the T3D-959 Phase 2a trial and may reflect a shared PPAR γ -mediated mechanism that is modulated by ApoE genotype.

12.3 GW501516 (Cardarine)

Mechanism: Highly selective PPAR α agonist. Originally developed by GlaxoSmithKline for dyslipidemia and metabolic syndrome. Never approved for clinical use; development was terminated due to carcinogenicity signals in preclinical long-term toxicology studies [23].

Development trajectory: GW501516 demonstrated neuroprotective effects in preclinical models, including significant attenuation of ischemic brain damage in the transient middle cerebral artery occlusion model and attenuation of MPTP-induced striatal dopamine depletion in a Parkinson's disease mouse model [17]. The compound reduced movement impairment and suppressed NLRP3 inflammasome activation. However, 2-year carcinogenicity studies in rodents revealed tumors in multiple organ systems, leading to termination of all clinical development [23]. The compound is widely used as a research tool but has no clinical future.

Novelty: Moderate. The selective PPAR α mechanism is well characterized.

Effect size: Robust in preclinical neuroprotection models. No clinical data.

Promising potential: None as a clinical candidate due to carcinogenicity. Moderate as a research tool for PPAR δ mechanism elucidation.

Side-effect profile: Carcinogenicity in multiple organ systems in long-term rodent studies. No clinical safety data.

Overall validation: Low as a clinical candidate; moderate as a research tool.

Comparison to T3D-959: GW501516 demonstrates the neuroprotective potential of PPAR δ activation but is disqualified as a clinical candidate by carcinogenicity. T3D-959 represents a clinically viable alternative with established human safety data through 24 weeks of Phase 2 exposure at therapeutic doses. The non-thiazolidinedione, non-GW501516 chemical scaffold of T3D-959 is critical to its clinical viability.

12.4 Bezafibrate

Mechanism: Pan-PPAR agonist (activates PPAR α , PPAR δ , and PPAR γ) of the fibrate class. Approved in multiple jurisdictions for dyslipidemia and hypertriglyceridemia. Crosses the blood-brain barrier [24].

Development trajectory: Bezafibrate has been studied in preclinical models of neurodegeneration, including demonstration of attenuation of tau pathology in a transgenic mouse model of primary tauopathy through improved energy metabolism, suppression of oxidative stress, and inhibition of neuroinflammation [24]. Bezafibrate also demonstrated neuroprotective effects in the streptozotocin AD model. However, no clinical trials of bezafibrate in AD or other neurodegenerative diseases have been reported.

Novelty: Low. The pan-PPAR mechanism is well established, and bezafibrate is a decades-old generic medicine.

Effect size: Moderate in preclinical tauopathy and AD models. No clinical cognitive or biomarker data in neurodegeneration.

Promising potential: Low to moderate. The compound is inexpensive, available, and brain-penetrant, which could facilitate repurposing trials. However, no clinical AD program is active.

Side-effect profile: The fibrate class has a well-characterized safety profile from decades of metabolic disease use: myalgia, gastrointestinal discomfort, and rare rhabdomyolysis (particularly in combination with statins). The safety profile is acceptable for the metabolic indication but has not been characterized in elderly AD populations on chronic dosing.

Overall validation: Low for neurodegeneration. The compound has preclinical support but no clinical evidence in AD.

Comparison to T3D-959: Bezafibrate has the advantage of being an approved, inexpensive, brain-penetrant generic medicine with preclinical AD evidence. T3D-959 has the advantages of substantially more potent PPAR α activation (19 nM versus the millimolar range for bezafibrate), a clinical evidence base in AD through Phase 2, and a pharmacological profile specifically optimized for the neurometabolic dysfunction hypothesis. The two compounds could be informative comparators in a head-to-head preclinical study.

12.5 GW0742

Mechanism: Selective PPAR α agonist, structurally related to GW501516 but with distinct pharmacological properties. Research compound without clinical development history [17].

Development trajectory: GW0742 has been studied in preclinical models of neuroinflammation and neurodegeneration. In 5XFAD transgenic mice (a model of familial AD with aggressive amyloid pathology), short-term GW0742 treatment reduced parenchymal amyloid-beta load, decreased microglial activation, reduced proinflammatory mediators, and attenuated neuronal loss in the subiculum [25]. These findings demonstrate the neuroprotective potential of selective PPAR α activation in an amyloid-driven AD model, complementing the T3D-959 data in the metabolic (streptozotocin) AD model.

Novelty: Low to moderate. The selective PPAR α mechanism is well characterized.

Effect size: Moderate in preclinical 5XFAD model. No clinical data.

Promising potential: Low. The compound is a research tool without clinical development. No published human safety or pharmacokinetic data.

Side-effect profile: Preclinical only. No human safety data. Potential carcinogenicity concerns by structural analogy to GW501516, although GW0742-specific long-term toxicology data are limited.

Overall validation: Low. Preclinical research tool only.

Comparison to T3D-959: GW0742 provides complementary preclinical evidence for PPAR δ -mediated neuroprotection in an amyloid-driven model (5XFAD) that differs from the metabolic model (i.e. STZ) used for T3D-959. T3D-959 has the decisive advantages of clinical development through Phase 2, established human safety, and an optimized clinical formulation. GW0742 is a useful mechanistic comparator but not a clinical alternative.

12.6 Comparator summary

The five comparators illustrate the challenges of translating the PPAR neuroprotection hypothesis into clinical AD therapy. **Pioglitazone**, the most clinically advanced comparator, failed at Phase 3 (TOMMORROW), likely reflecting limited brain penetration and the limitations of selective PPAR γ agonism. **Rosiglitazone** produced negative Phase 2 results complicated by cardiovascular safety concerns. **GW501516** demonstrated robust preclinical neuroprotection through PPAR δ activation but is disqualified by carcinogenicity. **Bezafibrate** offers an inexpensive, brain-penetrant, pan-PPAR alternative with preclinical support but no clinical AD evidence. **GW0742** is a selective PPAR δ research tool with complementary preclinical data but no clinical path.

T3D-959 occupies a unique position in this comparator landscape: it is the only compound with a clinical evidence base in AD (Phase 2a and Phase 2 PIONEER positive signals); the only compound with the dual PPAR δ /g mechanism at the optimized 15-fold delta selectivity ratio that preclinical data suggest is more neuroprotective than either selective agonist; the only compound with a non-thiazolidinedione, non-GW501516 chemical scaffold that confers both PPAR γ safety advantages and absence of carcinogenicity signal; and the only compound with demonstrated brain penetration, dose-dependent effects on cerebral glucose metabolism in AD patients, and significant effects on AD biomarkers (amyloid-beta 42/40 ratio, neurogranin) in a randomized placebo-controlled trial.

The principal uncertainty is whether the Phase 2 biomarker and cognitive signals will replicate and strengthen in the planned Phase 2b/3 trial with 78 weeks of exposure. The pioglitazone TOMMORROW failure and the rosiglitazone REFLECT negative results are cautionary precedents, but the mechanistic differences between T3D-959 and the thiazolidinediones (brain penetration, PPARD selectivity, non-thiazolidinedione structure) provide a plausible basis for expecting a different clinical outcome. The planned Phase 2b/3 trial (NCT06964230) will be definitive.

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