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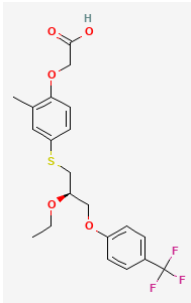
PPARδ Agonists

Evidence Summary

PPARδ is a metabolic modulator and elevated activity is associated with protection from metabolic disease. Agonists in clinical development tend to show modest effects, but reasonable safety.

Neuroprotective Benefit: PPARδ agonists may be neuroprotective in the context of a metabolic and inflammatory endophenotype.
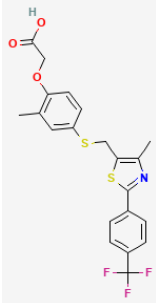
Aging and related health concerns: PPARδ agonists may promote a shift toward a more favorable metabolic profile, but the effects for current agonists appear to be modest.

Safety: Most agonists show a favorable safety profile. Mild side effects are primarily gastrointestinal related. Some agonists may have a risk for tumor growth potentiation.

Seladelpar (MBX-8025)

| **Availability**: In clinical trials/research use	**Dose**: Dosed at 5 or 10 mg/day orally in RCTs for primary biliary cholangitis	**Chemical formula:** $C_{21}H_{23}F_3O_5S$ **MW**: 444.5 g/mol
Half-life: N/A	**BBB**: N/A	
Clinical trials: Tested Phase 1, 2, and 3 clinical trials for primary biliary cholangitis, as well as Phase 2 RCTs for hepatic impairment and NASH	**Observational studies**: None for seladelpar. Genetic variants in PPARD are associated with a variety of cardiometabolic diseases.	Source: PubChem

GW501516 (Cardarine)

Availability: Research use/ clinical use has been terminated	**Dose**: N/A Used at 10 or 20 mg/day orally by self-experimenters	**Chemical formula:** $C_{21}H_{18}F_3NO_3S_2$ **MW**: 453.5g/mol
Half-life: ~24 hours	**BBB**: weak penetration	
Clinical trials: Tested in Phase 1 and 2 studies for metabolic diseases (lipid disorders and obesity).	**Observational studies**: It is used as an illegal performance enhancer by athletes.	Source: PubChem

What is it?

Peroxisome proliferator-activated receptor delta (PPARδ), also called PPARβ/δ, is a member of the family of ligand-inducible PPAR nuclear hormone receptors [1]. As transcription factors, PPARs are involved in the induction of genes involved in metabolic homeostasis. PPARδ plays a primary role in the regulation of fatty acid metabolism. It is highly expressed in skeletal muscle, and is involved in the metabolic adaptations to exercise. Its activation tends to promote mitochondrial biogenesis and the utilization of lipids as an energy source through increased beta oxidation. It is the least well studied of the three PPAR family members, and consequently, drug development for PPARδ modulators has lagged behind those for PPARα and PPARγ. Through its role in the regulation of lipid metabolism, PPARδ activity appears to influence risk for a variety of cardiometabolic diseases. It may also protect against cellular damage in other contexts where metabolism is altered, such as ischemic injury and cerebral hypometabolism. PPARδ agonists have primarily been in development for metabolic indications, such as dyslipidemia, insulin resistance, and mitochondrial myopathies. These agonists tend to have a more favorable safety profile relative to PPARγ agonists, but due to the extensive cross-talk between the PPARs and the modest effects seen in clinical trials thus far, dual agonists or combination therapies may be needed for robust clinical efficacy.

Seladelpar, also called MBX-8025, is a selective orally bioavailable PPARδ agonist being developed for the autoimmune liver disease, primary biliary cholangitis. It has an EC_{50} for PPARδ of 2nM, as well as 750- and 2500-fold selectivity over PPARα and PPARγ, respectively. It has Orphan Drug Designation for this condition in the U.S. and Europe. It is being developed by CymaBay Therapeutics, formerly called Metabolex.

REN001, formerly called HPP593, is a selective PPARδ agonist being developed for genetic mitochondrial myopathies. It has an EC_{50} for PPARδ of 31 nM, while the EC_{50}s for PPARα and PPARγ are over 10 μM. It has been granted Orphan Drug Designation by the FDA for primary mitochondrial myopathies. It is being developed by Reneo Pharmaceuticals, which has licensed it from vTv Therapeutics.
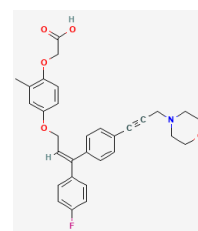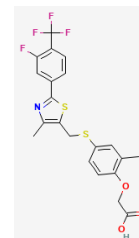

Source: PubChem

Bocidelpar, also known as ASP0367 and MA-0211, is an orally bioavailable PPARδ modulator being developed for primary mitochondrial myopathies and Duchenne muscular dystrophy by Astellas Pharma, following their acquisition of Mitobridge. It has received Fast Track Designation by the FDA.

GW501516, also called cardarine or endurobol, is a selective PPARδ agonist developed by GlaxoSmithKline for metabolic disorders, but clinical development was terminated due to a safety signal of possible cancer potentiation in a preclinical rodent study. It has an EC_{50} for PPARδ of 1 nM, and over 1000-fold selectivity relative to PPARα and PPARγ. It is a banned substance by world athletic agencies due to its illegal, unregulated use as a performance enhancer.

GW0742 is a selective PPARδ agonist developed by GlaxoSmithKline which is very similar to GW501516. It has an EC_{50} for PPARδ of 1 nM and over 1000-fold selectivity relative to PPARα and PPARγ. It has only been formally tested in preclinical studies, however, it is used in an unregulated manner as a performance enhancer for athletics.

Source: PubChem

Neuroprotective Benefit: PPARδ agonists may be neuroprotective in the context of a metabolic and inflammatory endophenotype.

Types of evidence:

- 2 gene association studies for PPARD
- Numerous laboratory studies

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

The contribution of changes in PPARδ activity as a risk factor for dementia is unclear. Genetic association studies find that while PPARD variants can influence metabolic risk factors, they do not show a clear direct association with Alzheimer's disease (AD) risk [2; 3]. A study in postmortem brain tissue (n=45) found that the expression of PPARδ was reduced three-fold [4]. This reduction occurred concomitantly with elevated markers of oxidative stress, such as lipid peroxidation, as well as reduced expression of mitochondrial complex genes. This suggests that a reduction in PPARδ may be part of a profile of altered brain energy metabolism, but it isn't clear how much PPARδ contributes, such that PPARδ agonists may need to be used in combination with other therapies to exert a clinically meaningful effect.

Human research to suggest benefits to patients with dementia:

PPARδ selective agonists have not yet been tested in humans for this indication. The dual PPARδ/PPARγ agonist T3D-959 is currently undergoing clinical testing in Alzheimer's disease patients (see T3D-959 report).

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

Alzheimer's disease: POTENTIAL BENEFIT AT EARLY STAGES (Preclinical)

PPARδ agonists show neuroprotection in preclinical AD models primarily by limiting inflammation, likely through the mitigation of metabolic stress, as immune cell activity is highly influenced by metabolic conditions. Therefore, this class of drugs may be best suited to patients with metabolic dysfunction and high inflammation.

GW0742: In the 5XFAD mouse model, treatment with the PPARδ agonist GW0742 (30 mg/kg in water for 2 weeks) starting at age 4.5 months, reduced parenchymal Aβ load, pro-inflammatory mediators (C3, C1qa, IL-6, CCL2, CXCR2 and IL-1β), and neuronal loss [5]. The protective effects in this model were attributed to its mitigation of neuroinflammation-induced neuronal loss, as it failed to show a direct neuroprotective effect against glutamate-induced excitotoxicity in neurons, but did prevent inflammatory cell death in microglia-neuron co-cultures. A separate study in this model with treatment starting at two months of age similarly found reductions in Aβ plaque burden and glial activation [6]. The reduction in Aβ was concomitant with an increase in levels of the amyloid degrading enzymes, neprilysin and insulin degrading enzyme. Notably, a sex-effect was apparent in this study with a greater effect seen in male mice. In the Aβ42-induced model, co-infusion of GW0742 to the hippocampus, prevented the Aβ-induced downregulation of PPARδ, neuroinflammation, neuronal loss, and spatial memory deficits in male mice [7]. GW0742 also improved synaptic plasticity and spatial memory in a mouse model (db/db) of diabetes-related cognitive impairment [8].

Due to the context-dependent effects of PPAR signaling, the choice of model and experimental design are likely to influence outcomes. In the mutant APP overexpressing Tg2576 model, high levels of oxidative stress, leading to elevated lipid peroxidation products, such as 4-HNE, led to increased activation of PPARδ, which altered the balance of brain derived neurotrophic factor (BDNF) signaling in a manner which reduced cell survival [9]. This process was most evident at later disease stages. Lipid peroxidation products, including 4-HNE have been shown to act as agonists for PPARδ, leading to the activation of this pathological signaling cascade. In a slice culture model, the combination of PPAR-δ (L165, 041) and PPAR-γ (F-L-Leu) agonists reduced Aβ-induced neurotoxicity, improved mitochondrial function, and reduced neuroinflammation, but led to an increase in lipid peroxidation (HNE) [10]. Consequently, the efficacy of PPARδ agonists may depend on the patient population, in terms of sex, disease stage, metabolic status, and inflammatory endophenotype.

Parkinson's disease: POTENTIAL BENEFIT (Preclinical)

GW501516: In the MPTP model, treatment with the PPARδ agonist, GW50156 (60, 120, or 240 μg/day i.c.v.) reduced pro-inflammatory mediators (IL-1β, IL-6, and TNF-α), NLRP3 inflammasome activation, and oxidative stress, which was coupled with an attenuation of dopaminergic neuronal loss and associated motor impairments in male mice [11].

Huntington's disease: POTENTIAL BENEFIT (Preclinical)

Mutant huntingtin protein (Htt) was shown to interact with PPARδ and repress its transactivation. Mice lacking PPARδ in striatal neurons had reduced brain size, motor abnormalities, and smaller mitochondria [12]. Overexpression of PPARδ or treatment with the PPARδ agonist *GW50156* improved mitochondrial function and reduced cell death in HD neurons. Similarly, treatment with the PPARδ agonist, *KD3010* (50 mg/kg i.p.) starting during the preclinical stage (six weeks old) mitigated motor and neurological impairments in HD (N171-82Q model) mice.

Depression: POTENTIAL BENEFIT (Preclinical)

The expression level of PPARδ in the hippocampus has been associated with depressive-phenotypes in rodent models. The knockdown or inhibition of PPARδ in the hippocampus leads to the induction of depressive-like phenotypes, such as increased immobility time on the forced swim and tail suspension tests in male mice [13]. These behavioral effects were coupled with a reduction in neuronal differentiation, neurogenesis, and mature BDNF levels in the hippocampus [13]. PPARδ overexpression or treatment with the PPARδ agonist *GW0742* enhanced neural stem cell proliferation and neuronal differentiation in the hippocampus, and reduced depressive phenotypes in chronic mild stress and learned helplessness models in male mice [13]. Treatment with the antidepressant, fluoxetine, also increased hippocampal levels of PPARδ [14]. Chronic mild stress led to a reduction in hippocampal expression of PPARδ in male rats, along with a decrease in expression of the serotonin transporter [15]. Treatment with the PPARδ agonist, GW0742 increased expression levels of both PPARδ and the serotonin transporter, and reversed depressive behavioral phenotypes [15]. The antihypertensive, telmisartan, showed an anti-depressant effect in male mice, which was associated with an elevation of hippocampal levels of PPARδ and the serotonin transporter [16].

APOE4 interactions: Gene interactions between PPARD and ApoE variants may influence circulating lipid levels [17], but it has not been established whether the efficacies of PPARδ agonists are influenced by ApoE genotype.

Aging and related health concerns: PPARδ agonists may promote a shift toward a more favorable metabolic profile, but the effect for current agonists appear to be modest.

Types of evidence:

- 3 clinical trials for seladelpar in primary biliary cholangitis (3), dyslipidemia, and NASH
- 3 clinical trials for GW501516 dyslipidemia
- 3 clinical trials for REN001 in mitochondrial diseases
- Numerous gene association studies for PPARD
- Numerous laboratory studies

Genetic variants in the PPARD gene have been associated with a variety of cardiometabolic diseases. The associations are driven by the regulation of lipid utilization and metabolism. Increased PPARδ function increases lipid utilization as an energy source, leading to lower circulating levels of oxidative stress-inducing free fatty acids, atherogenic lipid species, and pro-inflammatory mediators. This is generally accompanied by a leaner body composition. This profile then lowers a variety of risk factors for metabolic syndrome and cardiovascular disease. Consequently, genetic variants that increase PPARD expression or function are generally associated with decreased risk. However, since these metabolic features are polygenic and PPARD tends to show gene-gene interactions, general trends emerge with respect to the protective role of PPARD, but the associations of individual variants are highly susceptible to haplotype effect, which can lead to different effects of individual variants in different ethnic groups.

The most well-studied PPARD variant is rs2016520, which is located in the 5' untranslated region. The minor allele, usually indicated as C, may increase expression of PPARD, however, the functional consequence *in vivo* may depend on a haplotype of multiple variants, and has not been fully elucidated. In terms of nomenclature, different studies refer to this variant (rs2016520) as either +294T/C, -87A/G, or -87T/C, though the reason for this discrepancy is unclear. Therefore, associations for these variants will be described using the nomenclature used in individual studies.

Cardiovascular disease

Variants in the PPARD gene have been associated with coronary disease. In a cohort of 880 Chinese subjects, the G-alleles of rs3777744 and rs3798343 were associated with lower risk of coronary artery disease (Odds Ratio [OR] 0.714, 95% Confidence Interval [CI] 0.567 to 0.849) [18]. In a Russian case-control cohort (313 cases and 132 controls), the C allele of the (rs2016520) 294T/C SNP was associated with increased odds of coronary artery disease (OR 2.12) [19]. The C allele of the 294T/C SNP was also

found to be associated with coronary heart disease, and lower HDL-c, as well as higher LDL-c and total cholesterol in a German cohort [20]. A case-control study of 657 cases and 640 controls in a Chinese cohort found that the rs2016520-G allele was associated with reduced risk for coronary heart disease (OR 0.821, 95%CI 0.692 to 0.975) [21]. However, a meta-analysis of six studies including a total of 7464 cases and 10084 controls did not find a significant association, which may indicate that ethnicity plays a role in this genetic association [21].

Cerebral ischemia: POTENTIAL BENEFIT (Preclinical)

Activation of PPARδ may modify stroke risk and mitigate damage by limiting inflammatory damage in response to ischemic conditions.

In a gene association study involving 196 Tunisian patients with ischemic stroke and 192 controls, the C allele in the +294T/C polymorphism (rs2016520) in the PPARD gene was more frequent in stroke patients relative to controls, such that carrying a C allele was associated with higher odds of stroke (OR 1.76, 95 % CI 1.17 to 2.66) [22]. The interaction was primarily for those without diabetes. The biological mechanism for this effect is unclear, since this variant was not found to alter the plasma lipid profile in this population. The 294-C allele was also associated with increased risk of ischemic stroke in a population of Chinese Uyghurs (n=200) (OR 1.79, 95% CI 1.11 to 2.89) [23]. The allele-associated risk was stronger in males (OR 1.99, 95%CI 1.06 to 3.72) and the obese (OR 2.36, 95%CI1.19 to 4.67). The rs2016520 SNP was found to be associated with an increased risk for intracerebral hemorrhages in a population of Han Chinese (n=864) (OR 2.72) [24]. The effect was specific for males (OR 3.98). Carriers of the AA genotype had higher levels of LDL-c, which was positively correlated with intracerebral hemorrhage. The association was only seen in homozygotes (AA genotype), not in heterozygous carriers (AG genotype).

GW 501516: The metalloprotease MMP-9 was found to be a direct repressed target of PPARδ [25]. Elevations in MMP-9 increase cerebrovascular permeability, leading to BBB leakiness and infiltration of immune cells. Cerebral ischemia leads to a reduction in PPARδ, and subsequent induction of MMP-9 and associated cerebrovascular damage. Treatment with the PPARδ agonist GW501516 prevents the induction of MMP-9 under ischemic conditions.

GW0742: In the middle cerebral artery occlusion (MCAO) model of ischemic stroke, treatment with GW0742 ten minutes before reperfusion reduced infarct volume, edema, and BBB leakage in male mice [26]. The primary effect was on the reduction of pro-inflammatory mediators and metalloprotease (MMP-9) activity. The therapeutic efficacy was dependent on the timing of administration relative to

both artery occlusion and reperfusion, suggesting that it may have a critical therapeutic window. The timing effect may be related to the inflammatory profile, such that treatment is most effective during a specific phase where the inflammatory response turns from protective to deleterious. Pre-treatment with GW0742, 30 minutes prior to the induction of collagenase-induced intracerebral hemorrhage attenuated edema, BBB leakage, and neuronal loss [27]. Treatment prevented the intracerebral hemorrhage-induced acute reduction in PPARδ. The protective effects were related to a reduction in pro-inflammatory mediators and apoptotic factors.

SAR145: In the MCAO model, treatment with SAR145 (10 mg/kg), an orally bioavailable lipophilic PPARδ agonist, directly after filament removal, reduced lesion size (18 ± 10%) and mortality in mice, but did not show a consistent effect on functional neurological outcomes [28]. It is unclear whether the lack of neuroprotection is a function of the experimental design or this particular PPARδ agonist.

Hypertension: PPARδ MAY HAVE ANTI-HYPERTENSIVE PROPERTIES

SNPs in PPARD have been associated with hypertension. In a Korean cohort (n=1793), the rs7770619 C>T polymorphism was associated with a lower risk of hypertension (CT genotype adjusted OR 0.478, 95% CI 0.238 to 0.960) [29]. Normotensive individuals with the CC genotype had higher systolic blood pressure relative to the CT genotype (CC 116.7 ± 0.32 mmHg, CT 113.0 ± 1.36 mmHg; p = 0.007). Individuals with the CT genotype also had lower levels of the plasma oxidative stress marker malondialdehyde (MDA), lower serum glucose, and higher adiponectin levels. In a Chinese Han population (n=1248), SNPs in PPARD were associated with essential hypertension [30]. In the rs2016520 (294T/C) SNP, C allele carriers had a lower risk of essential hypertension relative to those with the TT genotype (adjusted OR 0.61, 95% CI 0.49 to 0.78). Carriers of the G allele in the rs9794 SNP also showed lower risk relative to the CC genotype (adjusted OR 0.65, 95% CI 0.53 to 0.83). There was also an interaction between the SNPs such that carriers of both alleles had the lowest risk (OR 0.32, 95% CI 0.23 to 0.62). Carriers of the G allele of rs9794 were also shown to have lower risk for high blood pressure (adjusted OR 0.63, 95% CI 0.46 to 0.87) in a separate Chinese cohort (n=820) [31].

Preclinical studies support an anti-hypertensive role for PPARδ [32]. The PPARδ agonist, ***GW0742*** decreased systolic blood pressure and reduced vascular remodeling in spontaneous hypertensive rats, and angiotensin II-infused mice. GW0742 has also been shown to protect against high-fat diet-induced hypertension in mice. Additionally, GW0742 protected endothelial cell function by reducing plasma glucose levels and protecting against free fatty acids. Mitigation of endothelial cell dysfunction and vascular inflammation may be key mechanisms of PPARδ-mediated cardiovascular protection. The antihypertensive drug telmisartan has also been shown to have PPARδ agonist activity [33].

Metabolic disease

In a cohort of 340 French Canadians, the -87T>C polymorphism in PPARD was found account for 2.2% of the variance in HDL-c levels, and to have an interaction with dietary fat intake [34]. Carriers of this SNP showed reduced risk for metabolic syndrome (OR 0.62, 95% CI 0.40 to 0.97), though the effect was modified by dietary fat intake, such that only those consuming less than 34.4% of energy from fat showed protection. This variant is associated with higher transcriptional activity of PPARD. A haplotype of PPARD variants [-13454 (G), -87 (T), 2022+12 (G), 2629 (T), 2806 (C)] was associated with body mass index (BMI) in a cohort of nondiabetic Korean participants (n=249) [35]. Those homozygous for this haplotype had the highest BMI, while those without it had the lowest BMI. Homozygotes also had lower fasting glucose levels. The C allele in the (rs2016520) 294T/C SNP was found to be associated with lower BMI in a middle-aged obese Caucasian population (n=462) [20]. However, in a study of 7,495 Caucasian subjects in Denmark did not find significant associations between 12 PPARD SNPs (rs34474204, rs7758272, rs6902123, rs9470001, rs6457816, rs9658119, rs9380506, rs9470015, rs2016520, rs4713854, rs2076169 and rs2076167) and metabolic parameters [36].

Genetic variants in PPARD have been shown to moderate the metabolic outcomes of lifestyle interventions. PPARδ is induced in response to exercise, which may underlie some of the metabolic adaptations to exercise, thus variants that reduce PPARδ function or induction capacity may impair this process. Consequently, PPARδ agonists may augment the benefits for lifestyle interventions. The minor (G) allele of the SNP rs2267668 in PPARD was associated with a lower degree of improvement in aerobic fitness following a nine-month lifestyle intervention (n=136) in German participants [36]. Carriers of the minor allele showed reduced mitochondrial function in cultured skeletal muscle cells, thus this variant may reduce beneficial mitochondrial adaptations to exercise. In a study of 156 participants in Germany at risk for type 2 diabetes, carriers of the minor alleles for the PPARD variants rs1053049 (C), rs6902123 (C), and rs2267668 (G) showed less fat loss, muscle gains, and hepatic lipid improvement following a lifestyle intervention, relative to non-carriers [37]. In contrast, carriers of the rs2267668 minor G allele showed greater weight loss, which was associated with improved glucose homeostasis (HbA1c), greater triglyceride reduction, and greater improvement in liver enzymes relative to A/A homozygotes following a lifestyle intervention in a Japanese cohort (n=109) [38]. The authors speculate that A/A homozygotes may have expended less energy during the intervention. In a study of 162 Polish Caucasian women, the results of a 12-week training program were impacted by PPARD genotype [39]. The rs2267668/rs2016520/rs1053049 G/C/T haplotype was associated with a lack of training-induced body mass changes, while the G/C/C haplotype with reductions in triglycerides, total cholesterol, and improvements in fat free mass.

Dyslipidemia: POTENTIAL BENEFIT

In a study of 820 Chinese participants, variants in PPARD were found to be associated with non-HDL-c levels. Carriers of the rs1800206-V allele and rs3856806-T allele were found to have higher levels of non-HDL-c [40]. The rs1800206-V allele, rs2016520-C allele, rs3856806-T allele and rs1805192-A allele were significantly associated with hypertriglyceridemia, with odds ratios of 3.88 (95% CI 2.69 to 5.60), 0.71 (95% CI 0.52 to 0.96), 1.40 (95% CI 1.03 to 1.90) and 2.56 (95% CI 1.88 to 3.49), respectively [41]. In a study of 967 Caucasian female participants with hyperlipidemia, the minor C allele in the 294T/C SNP was associated with lower levels of plasma HDL-c [20].

GW501516: In normolipidemic male volunteers (n=24), treatment with the PPARδ agonist, GW501516 at 2.5 or 10 mg/day for two weeks led to reductions in serum triglycerides from baseline (−15.4±6.5%, and 23.4±7.0%, respectively), though differences were not significant relative to placebo [42]. There were also increases in HDL-c level, and a 7.7% improvement in apoA1 levels in the 10 mg group, relative to placebo. In healthy overweight male participants (n=18), treatment with GW501516 (10 mg/day) for two weeks led to significant reductions in fasting plasma triglycerides (−30%), apolipoprotein B (−26%), LDL cholesterol (−23%), insulin (−11%), and fasting plasma nonesterified fatty acids (NEFA) (−40%) [43]. This was accompanied by a 20% reduction in liver fat content and 30% reduction in urinary isoprostanes, a marker of oxidative stress. These metabolic effects appear to be partially mediated by an increase in fatty acid oxidation in skeletal muscle, as evidenced by increased expression of carnitine palmitoyl-transferase 1b (CPT1). Cultured human skeletal muscle cells also show an upregulation of genes involved in fatty acid oxidation, including CPT1, with GW501516 treatment. In dyslipidemic men with central obesity (n=13) (NCT00841217), GW501516 (2.5 mg/day) for six weeks significantly decreased VLDL-, IDL-, and LDL-apoB concentrations relative to placebo in a cross-over trial [44]. This effect was mediated by an increase in the VLDL-apoB fractional catabolic rate. GW501516 also decreased the total plasma apoC-III concentration and their production rate. These changes decrease the cholesterol content in VLDL and lead to more buoyant LDL particles, which is consistent with a less atherogenic lipoprotein profile.

Seladelpar: In overweight patients with atherogenic dyslipidemia (n=166) (NCT00701883), treatment with the PPARδ agonist, seladelpar, (50 or 100 mg/day for eight weeks shifted the profile of LDL particles from less small dense particles to more large LDL particles in over 90% of patients [45]. This represents a shift toward a less atherogenic profile. Co-administration with statins (atorvastatin 20 mg/day) led to a complementary improvement on the lipoprotein profile.

Diabetes/insulin resistance: POTENTIAL BENEFIT (Preclinical)

Several studies have found modest associations between PPARD variants with insulin sensitivity and glucose levels, however, most studies failed to find a clear association between these variants and type 2 diabetes itself [35; 46]. One study found an association between the rs7770619 polymorphism in a Korean cohort (n=1798), such that those with the CT genotype had reduced odds of type 2 diabetes, relative to the CC genotype (OR 0.168) [47]. This was accompanied by lower levels of the oxidative stress marker MDA.

Preclinical models support a role for PPARδ agonists as anti-diabetic agents. Treatment of streptozotocin-induced diabetic male rats with the PPARδ agonist *GW0742* reduced insulin resistance, as measured by HOMA-IR [48]. Glucose homeostasis was improved, based on glucose infusion rate, insulin sensitivity, and level of hyperglycemia. These effects were accompanied by increased glucose uptake and utilization in skeletal muscle and reduced hepatic gluconeogenesis.

Nonalcoholic Steatohepatitis: POTENTIAL BENEFIT

Seladelpar: In a Phase 2 52-week study, seladelpar (10, 20 or 50 mg/day) was tested in patients with biopsy confirmed NASH with a NAFLD activity score (NAS) ≥4 (n=181) (NCT03551522) [49]. The study was terminated when 52-week liver biopsies revealed unexpected pathology (42/152), which was subsequently determined to be unrelated by an independent review panel. Liver fat content decreased relative to baseline, but not relative to placebo, thus it failed to meet its primary endpoint. Seladelpar treatment led to dose-dependent reductions in the liver enzymes alanine aminotransferase (ALT) (up to 41%) and gamma-glutamyltransferase (GGT) (up to 35%). There were also dose-dependent decreases in liver fibrosis.

Preclinical studies and the clinical study with elafibranor (see Elafibranor report) suggest that PPARδ dual agonists may be more effective for NAFLD/NASH.

ZLY06: The dual PPARδ/PPARγ partial agonist ZLY06 (20 mg/kg oral) was found to improve glycemic control in the high-fat diet/streptozotocin and ob/ob rodent models of diabetes without causing weight gain [50]. It also improved the blood lipid profile in ob/ob mice by reducing triglycerides, total cholesterol, and LDL-c. In the methionine choline-deficient (MCD)-diet induced NASH model in db/db male mice, ZLY06 (30 mg/kg) treatment during the induction period reduced liver enzymes ALT and AST, and reduced liver total cholesterol and triglyceride content to a greater degree than elafibranor [51]. The attenuation of liver inflammation, oxidative stress, fibrosis, and NASH score was comparable to elafibranor.

ZLY032: The dual free fatty acid receptor 1 (FFA1)/ PPARδ agonist ZLY032 (40 mg/kg) was found to improve lipid metabolism, and reduce liver enzymes and inflammation and in the MCD-diet induced and CCl₄-induced NASH models in male mice [52].

Primary biliary cholangitis: POTENTIAL BENEFIT

Primary biliary cholangitis (PBC) is a chronic disease involving the degeneration of the bile ducts in the liver. It involves liver inflammation, and may be a type of autoimmune condition. It primarily affects women. PPARδ agonists are being investigated as second-line therapeutics for PBC, in individuals resistant to first-line therapy, ursodeoxycholic acid (UDCA).

Seladelpar: In a placebo-controlled, Phase 2 study (NCT02609048) patients with PBC (n=35) were treated with 50 or 200 mg/day of the PPARδ agonist seladelpar plus UDCA for 12 weeks [53]. On the primary outcome of change in baseline alkaline phosphatase, the results were -2% ±16% in the placebo group, -53% ±14% in the seladelpar 50 mg group, and -63% ±8% in the seladelpar 200 mg group. Itch and fatigue are the most common presenting symptoms of PBC, and in an uncontrolled Phase 2 study of 101 patients treated with 5 mg-titrated-to-10 mg or 10 mg of seladelpar for one year, itching (pruritus) improved in 53% at the 5/10 mg dose and in 93% at the 10 mg dose, based on questionnaires [54]. Improvements in itch-related sleep disturbances were also reported in 81%, and 78% of participants, respectively. Serum bile acids were also reduced up to 38% over the course of the study. In the Phase 3 ENHANCE RCT (n=240) (NCT03602560), a response on the primary composite endpoint was achieved by 78.2% of patients in the 10 mg arm, 57.1% of patients in the 5 mg arm, and 12.5% of patients in the placebo arm [55]. Similarly, alkaline phosphatase normalization was achieved by 27.3% of patients in the 10mg arm, 5.4% of patients in the 5 mg arm, but none in the placebo arm.

Exercise/performance: PPARδ ACTIVITY MAY BOOST ENDURANCE

PPARδ variants have been associated with elite athlete performance. In a cohort of 1364 Polish subjects including 660 athletes, the A/C/C haplotype (rs2267668/rs2016520/rs1053049) was found to be less prevalent in athletes, especially strength-endurance athletes [56]. The combination of the PPARGC1A Gly482Ser (rs8192678) Gly/Gly and PPARδ 294T/C (rs2016520) C/C genotypes was found to be more prevalent in elite endurance athletes [57]. Since exercise capacity is influenced by a variety of genes, and PPARδ shows a variety of gene interactions, the associations of individual variants may not be consistent across cohorts, but the evidence across studies suggests that changes to PPARδ expression or function can influence exercise capacity, especially with respect to endurance.

PPARδ is highly expressed in type 1 slow-twitch muscle fibers, which primarily use oxidative phosphorylation, and are associated with endurance [58]. Expression of PPARδ increases in response to fasting and exercise, and this is thought to be one of adaptations that underlie the metabolic benefits of exercise. PPARδ is important for adaptive increases in mitochondrial enzymes in skeletal muscle in response to exercise [59]. Mice overexpressing PPARδ are referred to as 'marathon mice' due to their increased endurance capacity [1]. Muscle-specific overexpression of PPARδ results in increased muscle glycogen content, glucose transporter activity, and mitochondrial oxidative capacity. In contrast, muscle specific knockout of PPARδ results in decreased fatty acid oxidation and increased adiposity.

Due to its ability to change the body's fuel preference from glucose to lipids, the PPARδ agonist, **GW501516**, is used as a performance enhancing drug by athletes to increase fat-burning capacity and muscle production. It is currently a WADA banned substance ([USADA](#)). In mice, three weeks of treatment was shown to increase running endurance (31.2% increase in exhaustive running distance) and increase the level of slow-twitch, mitochondrially-rich muscle fibers with high oxidative capacity [60]. GW501516 treatment led to an increase in serum unsaturated fatty acid levels and increased utilization of fatty acid oxidation metabolic pathways. Biomarkers of fatty acid oxidation were also increased in the skeletal muscle. GW0501516 worked synergistically with exercise to trigger mobilization of triglycerides and fatty acid oxidation. Due to cancer concerns with GW501516, some athletes are instead using the related compound, **GW0742.** In male mice, treatment with GW0742 (1mg/kg) protected against high-fructose corn syrup-induced metabolic dysregulation in skeletal muscle [61]. The treated mice were protected against the diet-induced increases in serum triglycerides and LDL, reduction in HDL, impairment in insulin sensitivity, and increase in the inflammatory marker IL-6. GW0742 treatment increased muscle glucose uptake, fatty acid oxidation, and induction of the myokine, FGF-21. A study in mice found that in addition to its effects on skeletal muscle, GW0742 exerted effects on cardiac muscle, resulting in cardiomyocyte enlargement [62]. This effect may also improve endurance, and was not associated with pathological cardiac hypertrophy. Indeed, several preclinical rodent studies have found GW0742 to be cardioprotective in the context of pathological cardiac hypertrophy [63; 64].

Cancer: PPARδ MAY POTENTIATE TUMOR GROWTH (Preclinical)

The relationship between PPARδ and cancer is complex and context-dependent. PPARδ expression/activity has been correlated with patient outcomes in a variety of cancers [65]. In the majority of cases, PPARδ is elevated in tumor tissue, and higher activity is associated with worse prognosis. Discrepancies in preclinical studies may stem from different experimental conditions, which suggests that the effects of PPARδ activity may depend on the tumor environment. The primary

mechanisms by which PPARδ promotes cancer cell growth are through regulation of metabolism, angiogenesis, cell survival, and migration. PPARδ activity promotes cellular metabolic remodeling, which may drive cancer cell proliferation and survival. The activation of PPARδ has been implicated in the pro-metastatic effects of dietary fats in colorectal cancer. PPARδ has a pro-angiogenic role by regulating the expression of VEGFA, which can promote tumor microvessel formation. PPARδ also promotes tumor cell survival by inhibiting oxidative stress-induced apoptosis. While these features may be beneficial in the context of wound healing, they can also potentiate cancer cell growth.

The clinical development of the PPARδ agonist **GW501516** was terminated by GlaxoSmithKline following a study showing that it potentiated tumor growth in the Apc(min) mouse model of intestinal cancer [66]. Due to the different clinical profiles of PPARδ agonists, this may not necessarily be a class effect, and the tumorigenic potential of different PPARδ agonists would need to be independently determined. Overall, these studies suggest that some agonists may potentiate tumor growth under some conditions, but at this point there isn't evidence to indicate that PPARδ agonists are themselves tumorigenic.

Primary mitochondrial myopathies: POTENTIAL BENEFIT

PPARδ can promote mitochondrial biogenesis via the regulation of PGC-1α [59]. The increased production of mitochondria is part of the metabolic program induced by PPARδ, which shifts to increased lipid utilization, involving beta oxidation of fatty acids, and thus an increase in oxidative phosphorylation. Consequently, PPARδ agonists are being developed for primary mitochondrial myopathies, as well as other conditions involving defects in fatty acid oxidation and mitochondrial energy production.

REN001: The PPARδ agonist, REN001 was tested for its ability to improve muscle strength in a leg immobilization study in healthy volunteers (n=24) (NCT01524406). The participants were treated with REN001 or placebo for 28 days and wore a leg brace for the first 14 days. There was greater preservation in muscle strength with REN001 at one hour (-5.9 vs -36.2) and one week (32.8 vs 2.7) after removal of the leg brace, compared to placebo (Corporate presentation). Muscle biopsies indicated increased expression of PPARδ-regulated genes, including PDK4, ANGPTL4, and SLC25A34, which are involved in fatty acid oxidation, lipid metabolism, and mitochondrial transport, respectively.

In a Phase 1b trial in patients with primary mitochondrial myopathies, treatment with REN001 (100 mg QD) for 12 weeks increased distance walked on the 12-minute walk test (12MWT) by an average of 104 meters, with a baseline of 600 meters (Corporate presentation). 76% (13/17) of participants showed an increase of at least 60 meters. This was associated with improvements in gait mechanisms, particularly

after six minutes, when fatty acid metabolism becomes more important. Patients also reported improvements in the Fatigue Impact Scale (-11 pts) and the SF36 Energy/Fatigue Score (+11), relative to baseline.

Interim results from six patients in an open-label Phase1b trial in patients with long-chain fatty acid oxidation disorders (LC-FOAD) treated with REN001 at 50 mg (n=3) and 100 mg (n=21) QD for 12 weeks showed that 5 out of 6 showed improvement on the 12MWT and the SF-36 Physical Functioning domain (Corporate presentation).

Safety: Most agonists show a favorable safety profile. Mild side effects are primarily gastrointestinal related. Some agonists may have a risk for tumor growth potentiation.

Types of evidence:

- 3 clinical trials for seladelpar
- 1 clinical trial for GW501516
- 4 clinical trials for REN001
- 1 clinical trial for Bocidelpar:
- User experiences from self-experimenters on online forums
- Numerous laboratory studies

Seladelpar: In patients with primary biliary cholangitis, three patients (one at 50 mg dose, two at 200 mg dose) discontinued due to grade 3 increases in the liver enzyme ALT, which also led to the termination of the study [53]. These elevations were rapid, asymptomatic, and reversible within 2-4 weeks of drug cessation. Biological or clinical characteristics could not be determined which differentiate these patients from the rest of the study participants. The most frequently reported adverse events were pruritus, nausea, diarrhea, dyspepsia, muscle spasms, and dizziness. A 52-week Phase 2 trial in NASH patients was terminated due to unexpected pathology in liver biopsy results at week 52 (42/152 subjects). An independent review subsequently concluded that the pathology was present at baseline and was not drug-related. Otherwise, adverse events were balanced across arms, and none of the nine serious adverse events were related to seladelpar [49]. The most common treatment-emergent adverse events were nausea, uncontrolled diabetes, headache, and arthralgia. A 52-week study with treatment at 5 or 10 mg in primary biliary cholangitis was also terminated early

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while the independent review was being conducted [55]. The most common adverse events were pruritis and abdominal pain.

GW501516: In overweight, but otherwise healthy males, treatment with 10 mg/day of GW501516 for two weeks was not associated with any symptomatic side effects, and with the exception of a lowering of the liver enzyme GGT, other liver enzymes (ALT, AST), renal function, and hematology parameters were all unchanged [43]. There was also a trend toward a body weight reduction (−1.7 ± 0.7 kg).

In rodents, high doses (300 mg/kg) were associated with toxicity resulting in a reduction in food intake and body weight [67]. The clinical program was ultimately terminated due to a study in mice showing that GW501516 potentiated tumor growth in the Apc(min) model [66].

GW0742: This compound has not been clinically tested, and while it has been used in a variety of preclinical studies, safety/toxicology data is limited.

REN001: REN001 was found to be well-tolerated in all four completed clinical trials, which included healthy subjects receiving single doses up to 250 mg or at 200 mg for 28 days, obese subjects with dyslipidemia dosed up to 200 mg for 14 days, and patients with primary mitochondrial myopathies dosed at 100 mg for 12 weeks (Corporate presentation). Adverse events were generally mild or moderate.

Bocidelpar: In a Phase 1 trial (NCT03682484) in healthy volunteers, bocidelpar was tested at doses up to 120 mg in the single ascending dose (SAD) (n=64) and up to 75 mg for the multiple ascending dose (MAD) (n=37) cohorts [68]. It showed dose-proportional exposure, with negligible accumulation with repeated dosing. There were no discontinuations, and all treatment-emergent adverse events were mild, and none were considered drug-related. Adverse events included headache, dry skin, nausea, and rhinorrhea. An elevation of amylase or lipase above the upper limit of normal levels was seen (n=11 for bocidelpar, n=4 for placebo), but all cases subsequently returned to normal and resolved without treatment.

Drug interactions: Interactions have not been established for PPARδ agonists, but they may interact with other metabolic regulators, particularly thiazolidinediones, which are PPARγ agonists.

Sources and dosing:

Seladelpar is being developed for clinical use by CymaBay Therapeutics, it is dosed at 10 mg/day orally in clinical trials for primary biliary cholangitis. MBX-8025 is available for research use from commercial

suppliers. REN001 is being developed by Reneo Pharmaceuticals, and Bocidelpar is being developed by Astellas Pharma. Safe and effective doses have not been established for either of these drugs for any indication. GW501516 and GW0742 are available from commercial suppliers for research use

Research underway:

Seladelpar: There are currently three active clinical trials for seladelpar on Clinicaltrials.gov for Primary Biliary Cholangitis.

REN001: There are currently four active clinical trials for REN001 on Clinicaltrials.gov for Fatty acid oxidation disorders, Primary mitochondrial myopathies, and McArdle disease.

Bocidelpar: There are currently five active clinical trials for bocidelpar on Clinicaltrials.gov for Primary mitochondrial myopathies, reduced oxygenation, Duchenne muscular dystrophy, kidney impairment, and hepatic impairment.

Search terms:

Pubmed, Google: PPARδ Agonist, PPARD, Seladelpar, MBX-8025, REN001, HPP593, Bocidelpar, ASP0367, GW501516, GW0742

- Alzheimer's disease, neurodegeneration, depression, aging, cardiovascular, diabetes, NASH, cancer, exercise, clinical trial, safety

Websites visited for PPARδ Agonists:

- Clinicaltrials.gov (Seladelpar, REN001, Bocidelpar, GW501516)
- PubChem (Seladelpar), (GW501516), (GW0742), (REN001)
- DrugBank.ca (Seladelpar), (Cardarine)
- Cafepharma (Seladelpar)

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