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

Seladelpar (PPARδ Agonists)

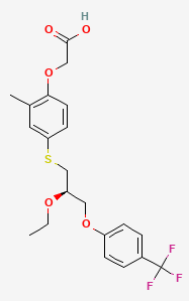
Evidence Summary

PPARδ is a metabolic modulator and elevated activity is associated with protection from metabolic disease. Clinically tested agonists have generally shown 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 benefits of tested agonists have been modest. Seladelpar's clinical benefits have been limited to date to a rare liver condition.

Safety: Most PPARδ agonists, including seladelpar, show a favorable safety profile, though long-term safety needs to be established. Adverse events are primarily gastrointestinal related. GW501516 may have a risk for tumor growth potentiation.

Availability: Rx	**Dose**: The recommended dose for primary biliary cholangitis is 10 mg/day, orally.	**Chemical formula:** $C_{21}H_{23}F_3O_5S$ **MW**: 444.5 g/mol  Source: PubChem
Half-life: 6 hours (in healthy adults) 3.8 to 6.7 hours (in adults with primary biliary cholangitis)	**BBB**: Not available	
Clinical trials: Tested in Phase 1, 2, and 3 (n=193; n=265) 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.	

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 crosstalk 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.

FDA approved PPARδ agonists

Seladelpar (MBX-8025) is a selective orally bioavailable PPARδ agonist, marketed under the brand name Livdelzi ® by Gilead Sciences. Seladelpar was granted accelerated approval by the FDA in August 2024 for

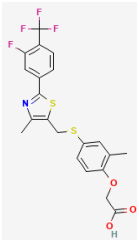
its use as a second-line treatment for the autoimmune liver disease, primary biliary cholangitis, in patients with an inadequate response to ursodeoxycholic acid (UDCA) alone (Press release). Seladelpar has also been granted conditional marketing authorization for this indication by the European Medicines Agency (EMA) in February 2025. Seladelpar was developed by CymaBay Therapeutics, formerly called Metabolex. CymaBay was acquired by Gilead Sciences in 2024 (Press release). It has an EC_{50} for PPARδ of 2nM, as well as 750- and 2500-fold selectivity over PPARα and PPARγ, respectively. Seladelpar has also been tested in patients with nonalcoholic steatohepatitis (NASH), but clinical development for that indication was terminated due to lack of efficacy.

Discontinued PPARδ agonists

Mavodelpar *(*REN001, formerly called HPP593), is a selective PPARδ agonist that was in clinical development for genetic mitochondrial myopathies by Reneo Pharmaceuticals, who licensed it from vTv Therapeutics. It has an EC_{50} for PPARδ of 31 nM, while the EC_{50}s for PPARα and PPARγ are over 10 µM. Clinical development was discontinued in late 2023 after mavodelpar failed to meet its primary or secondary endpoints in a Phase 2b trial in adult patients with primary mitochondrial myopathies (Press release). Reneo Pharmaceuticals subsequently merged with OnKure Therapeutics, which is focused on developing therapeutics for cancer (Press release).

Bocidelpar, also known as ASP0367 and MA-0211, is an orally bioavailable PPARδ modulator that was being developed for primary mitochondrial myopathies and Duchenne muscular dystrophy by Astellas Pharma, following their acquisition of Mitobridge. Its clinical development was discontinued in 2024 following its failure to meet the pre-specified criteria for efficacy in a Phase 2 trial in patients with primary mitochondrial myopathy (NCT04641962).

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, also called super cardarine, 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 by some self-experimenters in an unregulated manner as a performance enhancer for athletics.

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

Types of evidence:

- 3 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]. One study assessing genetic variants that modified the association between Aβ load and cognition in 2,953 participants from the A4 study identified rs71567499 (minor allele frequency 2.3%) [4]. PPARD is the closest gene to this variant, however, it is difficult to identify the causative gene for this variant due to the presence of several variants in strong linkage disequilibrium located in different genes. A study in postmortem brain tissue (n=45) found that the expression of PPARδ was reduced three-fold in the AD brain [5]. 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 as such 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:
Cognitive function: A study in PPARD knockout mice provides support for a role of PPARδ in cognition, and that alterations in PPARδ may play a role in high-fat diet-induced cognitive impairment [6]. Loss of PPARD disrupts insulin signaling in the hippocampus. The PPARD knockout mice show cognitive deficits on the novel object recognition task, which may stem from decreased dendritic spine density and increased glial reactivity in the hippocampus of these animals. This suggests that declines in PPARδ signaling may contribute to cognitive deficits.

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 [7]. 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 [8]. 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 [9]. GW0742 also improved synaptic plasticity and spatial memory in a mouse model (db/db) of diabetes-related cognitive impairment [10].

5a: A novel PPARδ agonist, 5a (EC_{50} = 0.7 nM) with >14,000-fold selectivity over hPPARα and hPPARγ and high oral bioavailability in rodents (F = 90.7 %) demonstrated anti-inflammatory and neuroprotective properties in rodent models of cognitive impairment [11]. 5a (30 mg/kg orally) prevented increases in pro-inflammatory cytokines and impairments on motor performance in LPS-treated mice. It also mitigated deficits on the Y-maze in 12-month-old APP/PS1 AD mice and attenuated deficit on the Y-maze, passive avoidance test, and Morris water maze in scopolamine-treated mice in a

dose-dependent manner. These effects on cognition were accompanied by a reduction in glial reactivity (GFAP), BACE-1 activity, and Aβ plaque loads in the brains of the APP/PS1 mice.

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 [12]. 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 PPARδ (L165, 041) and PPARγ (F-L-Leu) agonists reduced Aβ-induced neurotoxicity, improved mitochondrial function, and reduced neuroinflammation, but led to an increase in lipid peroxidation (HNE) [13]. Meanwhile, the PPARδ agonist GW0742 protected against corticosterone-induced oxidative stress in primary mouse astrocytes through the enhancement of pexophagy, the regulated degradation of damaged peroxisomes [14]. 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 [15]. GW50156 also protected against OHDA-induced toxicity in SH-SY5Y neuroblastoma cells through the modulation of intracellular iron levels, and preventing ferroptosis, which is iron overload-induced cell death [16].

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 [17]. 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 [18]. These behavioral effects were coupled with a reduction in neuronal differentiation, neurogenesis, and mature BDNF levels in the hippocampus [18]. 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 [18]. Treatment with the antidepressant, fluoxetine, also increased hippocampal levels of PPARδ [19]. 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 [20]. Treatment with the PPARδ agonist, GW0742 increased expression levels of both PPARδ and the serotonin transporter, and reversed depressive behavioral phenotypes [20]. 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 [21].

APOE4 interactions: Gene interactions between PPARD and ApoE variants may influence circulating lipid levels [22], 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 benefits of tested agonists have been modest. Seladelpar's clinical benefits have been limited to date to a rare liver condition.

Types of evidence:

- 5 clinical trials for seladelpar in primary biliary cholangitis (3), dyslipidemia, and NASH
- 3 clinical trials for GW501516 dyslipidemia
- 3 clinical trials for mavoldelpar in mitochondrial diseases
- 2 clinical trials for bocidelpar in mitochondrial diseases and muscular dystrophy
- 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) [23]. 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) [24]. 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 [25]. 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) [26]. However, a meta-analysis of six studies including a total of 7,464 cases and 10,084 controls did not find a significant association, which may indicate that ethnicity plays a role in this genetic association [26].

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) [27]. 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) [28]. 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) [29]. 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 [30]. 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 [31]. 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 [32]. 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 [33]. 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) [34]. 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=1,248), SNPs in PPARD were associated with essential hypertension [35]. 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) [36].

Preclinical studies support an anti-hypertensive role for PPARδ [37]. 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 [38].

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 [39]. 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) [40]. 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) [25]. 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 [41].

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 [41]. 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 [42]. 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) [43]. 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 [44]. 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 MODEST 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 [45]. 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 [46]. 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 [25].

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 [47]. 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 non-esterified fatty acids (NEFA) (−40%) [48]. 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 [49]. 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 [50]. 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. In the Phase 3 ENHANCE RCT in patients with primary biliary cholangitis, treatment with seladelpar for three months led to reductions in decreased mean total cholesterol, LDL-c, and triglycerides by 3.7%, 5.6%, and 5.9%, respectively, in the 5-mg group and by 4.4%, 8.2%, and 13.1%, respectively, in the 10-mg group, in comparison with reductions of 1.8%, 0.6%, and 0.6%, respectively, in the placebo group [51]. Levels of HDL-c were also increased by 6.7% in patients treated with seladelpar at the 10 mg dose, compared with a decrease of HDL-c by 3% in the placebo group.

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 [40; 52]. One study found an association between the rs7770619 polymorphism in a

Korean cohort (n=1,798), such that those with the CT genotype had reduced odds of type 2 diabetes, relative to the CC genotype (OR 0.168) [53]. 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 [54]. 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: NO CLEAR CLINICAL 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) [55]. 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 ALT (up to 41%) and GGT (up to 35%). There were also dose-dependent decreases in liver fibrosis. Based on these results, clinical development for this indication was discontinued.

Preclinical studies suggest that PPARδ dual agonists may be more effective for NAFLD/NASH [56; 57] [58] though to date none of the PPARδ mono or dual agonists have shown clinical efficacy for this indication.

Primary biliary cholangitis: 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 plays a role in the regulation of bile acids by inducing the release of FGF21 and inhibiting CYP7A1, which is a rate-limiting enzyme involved in the synthesis of bile acids [59]. PPARδ agonists (both selective, and dual PPAR agonists) have been investigated as second-line therapeutics for PBC, in individuals resistant to first-line therapy, ursodeoxycholic acid (UDCA). Around one-third of PBC patients are resistant or intolerant to UDCA [60]. Itch is a common symptom of PBC, and the most common second-line treatment, obeticholic acid, is known to exacerbate itch. Thus, the capacity to alleviate itch is considered an important feature of prospective therapies for PBC. Both the PPARδ agonist, seladelpar,

and the dual PPARδ/PPARγ agonist, elafibranor (see Elafibranor report) were approved as a second-line therapies for PBC in 2024 following successful Phase 3 RCTs.

Seladelpar: A meta-analysis of three RCTs including a total of 496 patients with PBC found that relative to placebo, seladelpar treatment was associated with the normalization of alkaline phosphatase (ALP) levels (Risk Ratio [RR] 13.94, 95% CI 4.05 to 47.97), and a greater biochemical response (RR 4.18, 95% CI 2.74 to 6.37), including the reduction of ALT levels, while total serum bilirubin levels were not significantly impacted [61]. This analysis included data from two Phase 3 RCTs and one Phase 2 RCT.
The strongest data comes from the 12-month randomized, double-blind, placebo-controlled Phase 3 RESPONSE trial (NCT04620733) in which 193 patients were randomized (2:1) to 10 mg seladelpar or placebo, and 176 completed the study [59]. Relative to placebo, a greater percentage of participants treated with seladelpar achieved the primary endpoint of a biochemical response at month 12, which was defined as an ALP level less than 1.67 times the upper limit of normal (ULN), with a decrease of 15% or more from baseline, and a normal total bilirubin level (61.7% vs. 20.0%; P<0.001). Responses were observed both in patients with and without evidence of liver cirrhosis. Normalization of ALP was achieved in 25% of patients treated with seladelpar, relative to none in the placebo group.
Normalization of ALT was also achieved by a greater percentage of patients treated with seladelpar (56.3% vs. 25.0%), while bilirubin levels were stable in both treatment groups. Seladelapar did not have any significant effects on measures of liver stiffness or fibrosis in this population.
Similar effects were observed in the Phase 3 ENHANCE RCT (NCT03602560), however, this 12-month study was terminated early while the liver safety findings from the NASH trial were being adjudicated [51]. As a result, an assessment of blinded data was performed at three months including 237 of the 265 randomized participants. This placebo-controlled trial included two oral doses of seladelpar, 5 mg and 10 mg. The biochemical response primary endpoint was achieved by a greater percentage of patients treated with seladelpar, particularly at the 10 mg dose (5 mg: 57.1% vs 10 mg: 78.2% vs placebo 12.5%). [55]. Similarly, ALP normalization was achieved by 27.3% of patients in the 10 mg arm, 5.4% of patients in the 5 mg arm, but none in the placebo arm.
Interim analysis from the open-label Phase 3 ASSURE trial (NCT03301506) confirms the findings of the Phase 3 RCTs, with a similar degree of composite biochemical responses achieved in those with (60%) and without (62%) prior use of fibrates or obeticholic acid over an 18 month period (Press release).
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 [62]. 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 (pruritus) is one of the most common presenting symptoms of PBC. These studies suggest that seladelpar may mitigate symptoms of itch, or at least not further exacerbate itch in the context of PBC. In the 12-month Phase 3 trial, patients with moderate-to-severe pruritus at baseline (numeric rating scale [NRS]≥4) experienced a greater reduction in itch at six months, relative to placebo (-3.2 points vs. -1.7 points) [59]. Similarly, in the ENHANCE trial, participants with moderate-to-severe pruritus treated with 10 mg seladelpar experienced a greater reduction in itch on the NRS at three months (-3.14 points vs. -1.55 points) [51]. An analysis of the ENHANCE study assessed the relationship between IL-31, bile acids, and itch in the context of PBC [63]. Baseline levels of IL-31 were found to be correlated with degree of pruritus, as well as levels of conjugated bile acids. Seladelpar dose-dependently reduced IL-31 levels, with reductions achieved in 91% of patients at the 10 mg dose and in 79% of patients at the 5 mg dose. Reductions in IL-31 levels were correlated with reductions in bile acids, and participants who experienced clinically meaningful reductions in itch (NRS≥2) tended to achieve the greatest degree of reduction in IL-31 levels. In an uncontrolled Phase 2 study of 101 patients treated with 5mg-titrated-to-10 mg or 10 mg of seladelpar for one year, itching improved in 53% at the 5/10 mg dose and in 93% at the 10 mg dose, based on questionnaires [64]. Improvements in itch-related sleep disturbances were also reported in 81%, and 78% of participants, respectively. Serum bile acids were also reduced by up to 38% over the course of that study.
Overall, these studies indicate that seladelpar may be a good second-line option for patients with PBC, particularly those experiencing pruritus, but there isn't strong evidence to indicate its clinical utility for other liver/metabolic conditions. Additional confirmatory Phase 3 studies are being conducted for PBC as part of the accelerated approval process.

Exercise/performance: PPARδ ACTIVITY MAY BOOST ENDURANCE
PPARδ variants have been associated with elite athlete performance. In a cohort of 1,364 Polish subjects including 660 athletes, A/C/C haplotype (rs2267668/rs2016520/rs1053049) was found to be less prevalent in athletes, especially strength-endurance athletes [65]. 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 [66]. 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 [67]. 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 [68]. 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 [69]. 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. In male mice, treatment with GW0742 (1mg/kg) protected against high-fructose corn syrup-induced metabolic dysregulation in skeletal muscle [70]. 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 [71]. 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 [72; 73].

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 [74]. 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. PPARδ can impact the development and function of T cells, and may dampen the cytolytic activity of anti-tumor T cells [75].
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 [76]. 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: NO CLEAR CLINICAL BENEFIT
PPARδ can promote mitochondrial biogenesis via the regulation of PGC-1α [68]. 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 were in development for primary mitochondrial myopathies, as well as other conditions involving defects in fatty acid oxidation and mitochondrial energy production. Due to failure to meet efficacy endpoints in Phase 2 trials, clinical development for this indication has been discontinued.

Mavodelpar (REN001): The STRIDE study was a randomized, double-blind, placebo-controlled Phase 2b trial in adult patients with primary mitochondrial myopathies due to mitochondrial DNA mutations (NCT04535609). Participants (n=213) were treated with oral mavodelpar at a dose of 100 mg/day or placebo for 24 weeks. Mavodelpar did not meet the primary efficacy endpoint of the change from baseline in the distance walked during the 12-minute walk test (12MWT) at week 24, nor the secondary efficacy endpoint of the change from baseline in the PROMIS Short Form Fatigue 13a score (Press release). Clinical development of mavodelpar was discontinued in response to the results of this trial, including the ending of the STRIDE-AHEAD study, an open-label two-year safety study including participants from STRIDE and a prior Phase 1b trial.
In the Phase 1b trial (NCT03862846) in patients with primary mitochondrial myopathies, treatment with mavodelpar (100 mg/day) for 12 weeks increased distance walked on the 12MWT, with associated improvements in gait mechanisms, particularly after six minutes, when fatty acid metabolism becomes more important, based on previously available corporate presentations (Press release). Patients also

reported improvements in the Fatigue Impact Scale and the SF36 Energy/Fatigue Score, relative to baseline.

Mavodelpar was also tested in an open label Phase 1b trial in 24 patients with long-chain fatty acid oxidation disorders (LC-FOAD) (NCT03833128). Improvements on the 12MWT and SF-36 Energy/Fatigue domain scores were observed in some patients, particularly those with the long-chain 3-hydroxy acyl-CoA dehydrogenase (LCHAD) subtype (Press release).

Mavodelpar was initially tested for its ability to improve muscle strength in a leg immobilization study in healthy volunteers (n=24) (NCT01524406). The participants were treated with mavodelpar or placebo for 28 days and wore a leg brace for the first 14 days. There was greater preservation in muscle strength with mavodelpar after removal of the leg brace, compared to placebo, while muscle biopsies indicated increased expression of PPARδ-regulated genes involved in fatty acid oxidation, lipid metabolism, and mitochondrial transport, based on previously available corporate presentations.

Bocidelpar (ASP0367): The randomized, double-blind, placebo-controlled Phase 2 MOUNTAINSIDE trial testing bocidelpar at low and high doses in patients with primary mitochondrial myopathy for 24 weeks was terminated due to failure to meet the pre-specified criteria for efficacy (NCT04641962). The primary efficacy endpoint was the change from baseline on the six-minute walk test. Clinical development of bocidelpar was subsequently discontinued.

Bocidelpar had previously been tested in a Phase 1b trial in pediatric male patients with Duchenne muscular dystrophy (NCT04184882). The study was terminated early due to recruitment challenges, as only eight patients were able to be enrolled (4:4 bocidelpar: placebo). Astellas indicated that bocidelpar was associated with clinically relevant improvement on key efficacy endpoints over 12 weeks, including a 36% mean improvement from baseline on the Assisted 6-Minute Cycling Test (A6MCT) maximal attained revolutions, compared with a slight decline (-0.8%) in the placebo group (Study summary).

Safety: Most agonists, including seladelpar, show a favorable safety profile, though long-term safety needs to be established. Adverse events are primarily gastrointestinal related. GW501516 may have a risk for tumor growth potentiation.

Types of evidence:

- 4 clinical trials for seladelpar
- 1 clinical trial for GW501516
- 4 clinical trials for Mavodelpar

- 3 clinical trials for Bocidelpar:
- User experiences from self-experimenters on online forums
- Numerous laboratory studies

Seladelpar: The incidence rates of adverse events and serious adverse events were generally balanced across clinical trials testing seladelpar [61]. According to the FDA prescribing label, the most common (≥5%) adverse events observed with seladelpar in clinical trials are headache, abdominal pain, nausea, abdominal distension, and dizziness. The label contains warnings for fracture risk, and liver test abnormalities, including serum transaminases.
A meta-analysis including three RCTs testing seladelpar in patients with primary biliary cholangitis (PBC) (n=486) indicated that the adverse events occurring with higher frequency in seladelpar-treated patients relative to placebo were abdominal pain (7.9% vs 2.6%) and headache (7.2% vs 1.7%) [5]. There was no cumulative increase in adverse events with longer term use, over two years, based on one study. However, more data regarding the long term safety of seladelpar is needed, and is currently being assessed in an open-label Phase 3 ASSURE trial (NCT03301506).The safety profile is consistent with prior studies based on interim analysis from the ASSURE trial, with no treatment-related serious adverse events, and a similar profile irrespective of prior use of fibrates or obeticholic acid (Press release).
In the 12-month Phase 3 RESPONSE trial in patients with PBC, adverse events rates were balanced between study arms, and were primarily of mild to moderate severity [59]. Adverse events that occurred at a higher rate with seladelpar included covid-19 (18.0% vs 15.4%), headache (7.8% vs 3.1%), abdominal pain (7.0% vs 1.5%), nausea (6.2% vs 4.6%), and abdominal distention (6.2% vs 3.1%). Pruritus was more common with placebo (4.7% vs 15.4%). Creatine kinase and serum creatinine levels were generally similar between groups, and the safety profile was similar in those with and without liver cirrhosis. The adverse event profile was also similar in the Phase 3 ENHANCE trial, which was terminated early [51]. Pruritus was more common with placebo, while abdominal pain and nausea were more common with seladelpar. There was a trend toward higher levels of serum creatinine and creatine kinase with seladelpar, though levels remained within the normal range.
Potential safety signals had previously been observed in Phase 2 studies. In a Phase 2 proof-of-concept trial in 35 patients with PBC, 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 [62]. 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 [55]. The most common treatment-emergent adverse events were nausea, uncontrolled diabetes, headache, and arthralgia.

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 the exception of a lowering of the liver enzyme GGT, other liver enzymes (ALT, AST), renal function, and hematology parameters were all unchanged [48]. 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 [77]. The clinical program was ultimately terminated due to a study in mice showing that GW501516 potentiated tumor growth in the Apc(min) model [76].
GW501516 is taken in an unregulated manner by some athletes and bodybuilders. Based on online forums, the primary complaints are headaches, insomnia, increased appetite, nausea, and dizziness.

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.

Mavodelpar (REN001): Mavodelpar was found to be well-tolerated in completed Phase 1 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, based on previously available corporate presentation data. Adverse events were generally mild or moderate. In an open-label Phase 1b trial in patients with LC-FAOD, the most common adverse events were mild to moderate rhabdomyolysis (n=4) and myalgia (n=4), and was generally well-tolerated (Press release). In the 24-week Phase 2 STRIDE trial in patients with primary mitochondrial myopathies, there were similar rates of adverse events and serious adverse events across groups (NCT04535609). There were higher rates of gastrointestinal events, rash, and increased blood creatine phosphokinase with mavodelpar.

Bocidelpar (ASP0367): In a Phase 1 trial (NCT03682484) in healthy volunteers (n=64 SAD; n=37 MAD), bocidelpar was tested at doses up to 120 mg in the SAD and up to 75 mg for the MAD cohorts [78]. 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. In a Phase 1b trial in male pediatric patients with Duchenne muscular dystrophy (n=8) (NCT04184882) treated with bocidelpar or placebo for 12 weeks, the frequency of treatment-emergent adverse events was similar between groups, with no significant safety signals (Study summary).

Drug interactions: According to Drugs.com, there are 150 drug interactions with seladelpar. There are major interactions for cholestyramine, colesevelam, colestipol, and rifampin. The FDA prescribing label indicates that concomitant use should be avoided with OAT3 inhibitors and strong CYP2C9 inhibitors. Monitoring for adverse events is advised for use with rifampin, dual moderate CYP2C9 and moderate to strong CYP3A4 inhibitors, CYP2C9 poor metabolizers using moderate to strong CYP3A4 inhibitors, and BCRP inhibitors. Seladelpar should be administered at least four hours before or after taking a bile acid sequestrant. There is also a warning that its use should be avoided in patients with complete biliary obstruction.

Sources and dosing:

Seladelpar is approved for use as a second-line treatment in patients with primary biliary cholangitis with an inadequate response or intolerance to UDCA. It is marketed under the brand name Livdelzi ® by Gilead Sciences. The recommended dose for PBC is 10 mg/day, orally, with or without food. 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.

NCT03301506 is a Phase 3 open-label trial (ASSURE) assessing the long-term safety of seladelpar in patients with primary biliary cholangitis. This approximately 10-year study has an estimated completion date in 2028.

NCT06060665 is a 52-week, randomized, double-blind, placebo-controlled, Phase 3 trial intended to determine the effects of seladelpar (10 mg/day) on normalization of alkaline phosphatase levels in

subjects with primary biliary cholangitis and an incomplete response or intolerance to ursodeoxycholic acid. The trial has an expected completion date in 2026.

NCT06051617 is a randomized, double-blind, placebo-controlled study to evaluate the effect of seladelpar (5 or 10 mg/day) on clinical outcomes in patients with primary biliary cholangitis and compensated cirrhosis (AFFIRM). This 36-month trial has an expected completion date in 2030.

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)
- DrugBank.ca (Seladelpar), (Cardarine)
- Drugs.com (Seladelpar)
- Cafepharma (Seladelpar)

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