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.

Pemafibrate

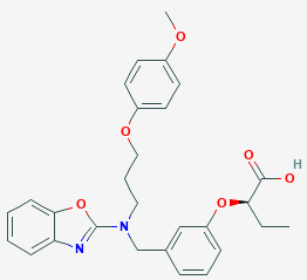
Evidence Summary

Pemafibrate shows a better therapeutic profile in reducing triglycerides relative to fibrates. It may reduce residual cardiovascular risk and protect the liver through FGF21.

Neuroprotective Benefit: Pemafibrate may enhance PPARα-mediated synaptic plasticity in males, but the contribution of PPARα to AD is controversial, and the ability of pemafibrate to act therapeutically in the CNS is currently unclear.

Aging and related health concerns: Pemafibrate lowers triglycerides and raises HDL-c in the context of dyslipidemia. It may have cardio- and hepato-protective activity by increasing production of FGF21.

Safety: Pemafibrate has a stronger benefit-risk profile than conventional fibrates. It lowers liver enzymes and can be used in those with hepatic or renal impairment, and is not associated with a significant risk for kidney dysfunction, but carries a risk for gallstones.

Availability: Rx in Japan	**Dose**: Oral tablets 0.1 mg BID	**Chemical formula:** $C_{28}H_{30}N_2O_6$ **MW**: 490.55 g/mol  Source: PubChem
Half-life: 1.5 to 2.5 hours	**Observational studies**: Pemafibrate shows a good therapeutic-safety profile in those with renal impairment or fatty liver disease.	
Clinical trials: There have been Phase 3 RCTs for dyslipidemia in Japan (range n=166 to 526). A global Phase 3 enrolling >10,000 participants is ongoing.		

What is it?

Pemafibrate (K-877) belongs to the therapeutic class of selective peroxisome proliferator-activated receptor alpha modulators (SPPARMα) [1]. Although some conventional fibrates activate PPARα, they also activate other PPAR isoforms to varying degrees, including those that have preferential selectivity for PPARα, such as fenofibrate. As such, conventional fibrates have a broader side effect profile. Pemafibrate is >2500 times more potent than fenofibrate and >5000 times more selective for PPARα relative to PPARγ or PPARδ in cell-based assays [2]. This **increased potency at PPARα** is conferred by its Y shape, which allows it to bind to the complete Y-shaped binding pocket of PPARα, to allow for complete activation, whereas the linear shape of conventional fibrates only allow for partial activation. As a result, pemafibrate has distinct pharmacokinetics and pharmacodynamics relative to conventional fibrates, which is why it is classified as part of a separate therapeutic class. Unlike conventional fibrates, combinatorial use with statins is not associated with increased risk for adverse events [3]. Pemafibrate lowers triglycerides by suppressing triglyceride synthesis in the liver and increasing the activity of lipoprotein lipase (LPL).

Pemafibrate (Parmodia®) was developed by Kowa Pharmaceuticals, and was approved for use in dyslipidemia in Japan in 2017. It has also been tested in dyslipidemic populations with concomitant type 2 diabetes, kidney disease, and fatty liver disease, and it shows a better benefit-risk profile in these populations relative to conventional fibrates. Phase 3 trials are ongoing in the United States and Europe. A large international Phase 3 trial (>10,000 participants) is ongoing to examine the impact of pemafibrate on residual cardiovascular risk.

Neuroprotective Benefit: Pemafibrate may enhance PPARα-mediated synaptic plasticity in males, but the contribution of PPARα to AD is controversial, and the ability of pemafibrate to act therapeutically in the CNS is currently unclear.

Types of evidence:

- 3 gene association studies for PPARα and AD
- 3 laboratory studies

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

The evidence has been mixed as to whether there is a genetic association between PPARα and Alzheimer's disease (AD). In a study including 104 AD patients and 123 healthy controls in Germany, the

PPARα L162V polymorphism was found to be more frequent in AD. The V-allele was associated with increased risk (Odds ratio [OR]: 2.244, 95% Confidence Interval [CI] 1.120 to 4.498) [4]. There was also a synergistic effect with polymorphisms in the insulin gene, such that the combination of the PPARα L162V variant with the INS-1 allele further increased risk (OR: 6.341, 95% CI 2.282 to 17.623). A larger study including 461 AD and 1395 controls of Caucasian origin in Sweden did not find any association between AD incidence or AD biomarkers with PPARα variants [5]. Meanwhile, a study from the Epistasis Project including 1,757 AD cases and 6,294 controls found a weak, but significant association between the PPARα 162LL genotype and increased AD risk in Northern Europeans (OR: 1.3, 95% CI 1.04 to 1.5) [6]. This association was driven by an interaction between PPARα 162LL and INS intron 0 TT in this population, and was primarily seen in women. The AD association for this PPARα variant was not present in a Northern Spanish population in which the PPARα-INS variant interaction was not present. Although the exact associations differ in different populations, the overall pattern suggests that alterations to PPARα and insulin signaling may confer risk for AD through disruption of glucose homeostasis and increasing the risk for metabolic disorders. It is unclear, however, whether directly targeting PPARα would have a meaningful impact on mitigating risk for AD.

Human research to suggest benefits to patients with dementia: None

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

Alzheimer's disease: POTENTIAL BENEFIT IN MALES (Preclinical in rodents)

Pemafibrate was found to have a neuroprotective effect in the 5XFAD transgenic mouse model, with respect to the improvement of hippocampal synaptic plasticity, however, this PPARα-mediated effect was only seen in male animals [7]. This is consistent with male-specific benefits seen in preclinical studies using conventional fibrates, such as fenofibrate. Overall, it appears that any therapeutics that depend on the activation of PPARα for therapeutic benefit will only have clinical utility in men. With respect to pemafibrate, the blood-brain-barrier (BBB) permeability has not been characterized, thus it is unclear whether it will be useful for conditions in the CNS.

Synaptic plasticity: PPARα activation increases expression of the glutamate AMPA receptor GluA1 subunit, and this process is important for mechanisms of synaptic plasticity, including long-term potentiation [7]. Knockdown of PPARα leads to a reduction in GluA1 levels and an impairment of long-term potentiation in male mice. Treatment of male 5XFAD mice with pemafibrate can improve synaptic plasticity, but pemafibrate has no effect on synaptic plasticity in female mice. The disparity stems from PPARα expression that is two times higher in the male brain, such that modulation of PPARα has a stronger impact on synaptic function in males.

***Neuroinflammation*:** Pemafibrate can mitigate pro-inflammatory cytokine production (IL-6, IL-1β, TNFα) in response to LPS stimulation in microglial cells. This anti-inflammatory effect is dependent on the activation of PPARα [8].

Excitotoxicity: Pemafibrate protected against the loss of retinal ganglion cells in response to an excitotoxic insult of NMDA in male rats [9].

APOE4 interactions: Not established

Aging and related health concerns: Pemafibrate lowers triglycerides and raises HDL-c in the context of dyslipidemia. It may have cardio- and hepato-protective activity by increasing production of FGF21.

Types of evidence:

- 3 meta-analyses of RCTs (3, 6, and 7) in dyslipidemia
- 1 clinical trial comparing pemafibrate monotherapy vs. combination with statins
- 1 single-arm Phase 3 clinical trial in dyslipidemia + renal impairment
- 1 single-arm pilot clinical trial in NAFLD
- 4 retrospective/observational studies (type 2 diabetes, NAFLD/NASH)
- 1 case series in IgA nephropathy
- Numerous laboratory studies

Dyslipidemia: BENEFIT

Pemafibrate is approved for use in dyslipidemia in Japan [1]. It is characterized as a selective peroxisome proliferator-activated receptor alpha modulator (SPPARMα), which has been recognized by the International Atherosclerosis Society as a new therapeutic class, which is distinct from conventional fibrates [2]. The Residual Risk Reduction Initiative (R3i) Foundation put out a consensus statement regarding the potential for SPPARMαs, including pemafibrate, to have clinical utility in reducing residual cardiovascular risk [2]. Clinical trials have demonstrated that it has a superior therapeutic profile relative to conventional fibrates, such as fenofibrate. Although the definitive trials to date have been completed in Japan, large Phase 3 trials currently ongoing in the United States and Europe are expected confirm the therapeutic superiority of pemafibrate.

Similar to conventional fibrates, pemafibrate's major therapeutic effect involves the reduction of circulating triglycerides, which are considered a causal risk factor for cardiovascular disease [2]. In Phase 2 and 3 RCTs, pemafibrate treatment consistently **lowered triglycerides and the pro-atherogenic lipoprotein apolipoprotein C-III (apoC-III) by approximately 50%,** and remnant cholesterol by approximately 80% [2]. A meta-analysis of seven RCTs (n=1,623 patients) found that pemafibrate use was associated with a significant reduction in circulating triglyceride concentration relative to placebo (Standardized mean difference [SMD]− 1.38; 95% CI − 1.63 to − 1.12; P < 0.001) [10]. Pemafibrate significantly increased HDL-c (SMD 0.77; 95% CI 0.66–0.89; P < 0.001) and reduced non-HDL-c (SMD − 0.39; 95% CI − 0.51 to − 0.28; P < 0.001).

Head-to-head studies indicate that pemafibrate is more efficacious than fenofibrate in lowering certain lipid species. A meta-analysis of three RCTs (n=744 patients) found that compared to fenofibrate,

pemafibrate was more effective at reducing triglycerides (MD -8.66; 95%CI -10.91 to -6.41), VLDL-c, (MD -12.19; 95%CI -15.37 to - 9.01), remnant lipoprotein cholesterol (MD -13.16; 95%CI -17.62 to -8.69), the chylomicron-associated lipoprotein apoB-48 (MD -12.74; 95%CI -17.71 to -7.76) and apoC-III (MD, -6.25; 95%CI, -11.85 to -0.64), as well as elevating the levels of HDL-c (MD 3.59; 95%CI 1.65 to 5.53) and the HDL-associated lipoprotein apoAI (MD 1.60; 95%CI 0.38 to 2.82) [11]. Pemafibrate and fenofibrate had similar efficacy in altering levels of total cholesterol, non-HDL-c, apoB, and apoA-II. The higher efficacy may be related to pemafibrate's superior selectivity and potency toward PPARα. Pemafibrate is >2500 fold more potent than fenofibrate in activating PPARα, and induces key PPARα target genes, VLDLR and ABCA1 at a ten-fold lower concentration [2].

Clinical studies failed to find a significant benefit for the addition of conventional fibrates to statin therapy for reducing residual cardiovascular risk, despite lowering triglycerides. Although some defined subpopulations may preferentially benefit, the general lack of benefit may stem from any protective effects being offset by the increased incidence of adverse events, especially with respect to liver function. In contrast, clinical trials have found that pemafibrate **can lower triglycerides in statin-treated patients without significantly increasing the risk for adverse events**, suggesting that it may be clinically useful for reducing residual risk [2]. A pooled analysis of Phase 2 and 3 RCTs (six studies, n=1253 patients) found that pemafibrate (0.2 and 0.4 mg/day) reduced triglycerides by approximately 50% in all participants, irrespective of whether they were treated with statins [3]. Pemafibrate-mediated decreases in apoB and very small LDL-c were also unaffected by the presence of statins.

Meta-analyses have revealed that pemafibrate marginally increases levels of LDL-c relative to placebo (SMD 0.19; 95% CI 0.06 to 0.33; P = 0.006), and relative to fenofibrate [10]. While increases in LDL-c are generally considered atherogenic, the increase in LDL-c with pemafibrate is consistent with its mechanism of action since both HDL-c and LDL-c are generated during the catabolism of triglyceride-rich lipoproteins. In an observational study (n=52), participants were separated according to the degree that pemafibrate (0.2 mg/day) increased their LDL-c levels (> 5.3% vs. < 5.3%) [12]. The effect on LDL-c was dependent on baseline LDL-c and triglyceride levels. Those with higher baseline triglycerides and lower total LDL-c, but a high percentage of small dense LDL-c within the LDL-c fraction, were the most likely to show increases in LDL-c. In this case, the small increase in LDL-c coupled with the large decrease in triglycerides is indicative of improved lipoprotein metabolism. Additionally, pemafibrate shifts the LDL-c population from the pathogenic small dense type toward the large buoyant type, which is expected to be a cardioprotective shift.

The benefit to cardiovascular outcomes has not yet been determined, but evidence from clinical and preclinical studies conducted thus far suggest that it may play a role in reducing residual cardiovascular

risk. Notably, pemafibrate has been shown to reduce fibrinogen levels to a greater degree than fenofibrate [13]. Fibrinogen is made in the liver and elevated levels are associated with increased risk for cardiovascular disease. Additionally, pemafibrate **raises serum levels of FGF21**, which is known to a have a variety of vasculoprotective effects [13]. The clinical benefit on cardiovascular outcomes will be assessed as part of the ongoing PROMINENT trial (NCT03071692).

Type 2 diabetes: BENEFIT FOR CONCOMITANT DYSLIPIDEMIA

Pemafibrate significantly reduces levels of triglycerides in type 2 diabetics with hyperlipidemia, and shows a good therapeutic profile in terms of both efficacy and safety in this population [1]. In the Phase 3 PROVIDE RCT (JapicCTI-142412) (n=166), pemafibrate (0.2 mg/day or 0.4 mg/day) significantly reduced fasting serum triglyceride levels by approximately 45% over 24 weeks, relative to placebo [14]. Pemafibrate significantly decreased non-HDL-c, remnant lipoprotein cholesterol, apoB-100, apoB-48, and apoC-III levels, while significantly increasing HDL -c and apoA-I levels. During the 24-week open-label phase, placebo patients were switched to pemafibrate (0.2 mg/day). At the end of the 52-week study, triglyceride levels were reduced by approximately 45% in all groups [15]. All pemafibrate groups showed decreases in remnant lipoprotein cholesterol, apoB-48, apoC-II, apoC-III, apoC-III/apoC-II and apoE, as well as increases in apoA-II, irrespective of concomitant statin treatment.

The activation of PPARα is associated with glucose homeostasis and insulin sensitivity, thus SPPARMαs are projected to improve glucose metabolism in the context of type 2 diabetes. In this study, the homeostasis model assessment of insulin resistance (HOMA-IR) score was significantly decreased in the 0.2 mg/day pemafibrate group after 24 weeks, and in the placebo group that switched to 0.2 mg/day pemafibrate during the open label period [15]. Fasting insulin levels also decreased. However, the overall effect on glucose homeostasis was unclear, since other glycemic parameters remained unchanged, including fasting plasma glucose, glycoalbumin, and HbA1c levels [14].

In a small combination trial (UMIN000038160) (n=27) comparing pemafibrate monotherapy with pemafibrate/statin combination therapy, the combination significantly decreased triglyceride levels (223 ± 155 to 126 ± 68 mg/dL), total cholesterol (193 ± 42 to 181 ± 34 mg/dL), non-HDL-c (141 ± 33 to 121 ± 23 mg/dL), and the Atherosclerosis index (2.88 ± 1.01 to 2.25 ± 1.03), while significantly increasing HDL-c (52 ± 15 to 60 ± 20 mg/dL) [16]. Glycemic parameters, including blood glucose and insulin levels, were not significantly changed.

These studies suggest that pemafibrate may be protective against diabetic cardiomyopathy. A large Phase 3 RCT (PROMINENT, NCT03071692) (n=10,391) is currently ongoing, and is designed to determine whether pemafibrate improves cardiovascular outcomes for type 2 diabetics with dyslipidemia.

Diabetic retinopathy: POTENTIAL BENEFIT (Preclinical in rodents)

Pemafibrate shows retinal protective effects in preclinical studies. In a streptozotocin-induced mouse model of diabetic retinopathy, pemafibrate treatment improved retinal function based on electroretinography measures, and protected against neuronal loss [17]. Retinal expression of the synaptic marker synaptophysin were also increased. Some of the retinal protective effects may be mediated by the increase in serum levels of fibroblast growth factor 21 (FGF21). Pemafibrate may reduce pathological retinal neovascularization by inhibiting ischemia-induced HIF1α through the activation of PPARα and FGF21 [18]. The restoration of mitochondrial function via the reduction of oxidative stress is also expected to contribute to the protective effect. In rats, pemafibrate was found to protect against NMDA-mediated excitotoxicity in the retinal ganglion cells [9]. The clinical efficacy of pemafibrate for metabolic-related retinopathies was to be determined in the PROMINENT-Eye Ancillary Study (NCT03345901), however this study was terminated due to a recruitment failure.

Kidney disease: BENEFIT FOR CONCOMITANT DYSLIPIDEMIA

Although preclinical studies suggest that conventional fibrates possess renoprotective properties through the activation of PPARα, they are contraindicated in patients with severe kidney disease because conventional fibrates are excreted via the kidneys, and impaired kidney function leads to elevated systemic exposure [19]. Unlike conventional fibrates, pemafibrate is metabolized by the liver and primarily excreted in the feces, such that kidney function does not significantly impact systemic exposure levels.

A case series including three patients with IgA nephropathy with hypertriglyceridemia treated with pemafibrate (0.1 mg/day) for 12 months showed that pemafibrate can safely lower triglyceride levels in this population, and may have a renoprotective effect [20]. In addition to lower triglycerides (57%, 56%, and 65%, respectively), pemafibrate reduced urinary protein excretion (by 43%, 54%, and 58%), and urinary liver-type fatty acid-binding protein (L-FABP) levels (30%, 37%, and 55%). These effects were not accompanied by changes to the estimated glomerular filtration rate (eGFR) or blood pressure in these individuals. In a Phase 3 open-label study (n=189), individuals with dyslipidemia and renal impairment were treated with pemafibrate (0.2-0.4 mg/day) for 52 weeks [21]. Triglyceride levels decreased to the same degree as demonstrated in populations without renal impairment (45.9%), including hemodialysis

patients, and the efficacy was not correlated with baseline eGFR. The subgroups with the lowest baseline eGFR showed the greatest reductions in chylomicron, vLDL, small LDL-c l levels, and increases in HDL-c, apoAI, and apoA-II. Larger, controlled trials are needed to confirm these results.

Based on preclinical studies, pemafibrate may exert its renoprotective effects by reducing the deposition of lipids in the kidney and reducing levels of associated oxidative stress [22].

Nonalcoholic steatohepatitis: POTENTIAL BENEFIT (small pilot clinical studies)

Unlike conventional fibrates which elevate liver enzymes, pemafibrate has been shown to **decrease liver enzymes** in dyslipidemic populations [1]. The results from small clinical studies suggest that it also improves hepatic function in the context of liver disease, particularly non-alcoholic fatty liver disease/ nonalcoholic steatohepatitis (NAFLD/NASH).

The effects of pemafibrate in the context of fatty liver disease have thus far been based on small retrospective and single-arm studies in which patients with liver disease were treated with pemafibrate for their concomitant dyslipidemia. Similar to dyslipidemic patients without liver disease, pemafibrate significantly lowered triglycerides and increased HDL-c levels in this population.

In an observational study (n=38), pemafibrate reduced liver enzymes alanine aminotransferase (ALT) (from 63.9 ±3.6 to 41.6 ±3.6 U/L), alkaline phosphatase (from 301 ±23 to 204 ±18 U/L) and γ-glutamyl transpeptidase (GGT) (from 76.8 ±11.8 to 37.5 ±6.3 U/L) in patients with NAFLD [23]. There were also improvements on markers of hepatic function, including the albumin-bilirubin score (from –2.90 ±0.04 to –3.07 ±0.03), and on the NAFLD fibrosis score (from –2.27 ±0.18 to–2.38 ±0.18). In a small (n=10) retrospective study, pemafibrate treatment for six months led to a reduction in liver enzymes ALT (from 51.5 to 23.0 U/L, P=0.005) and aspartate transaminase (AST) (from 43.5 to 28.0 U/L, P=0.008) in NASH patients, as well as a reduction in liver fibrosis markers FIB-4 and M2BPGi [24]. Similar reductions in the liver enzymes ALT (–47.4%) and GGT (–48.7%), as well as the AST to platelet ratio (APRI) fibrosis marker were seen in a separate small (n=17) retrospective study in NAFLD [25]. In a single-arm pilot study (n=20), serum ALT levels decreased from 75.1 IU/L to 43.6 IU/L (P = 0.001) after 12 weeks of pemafibrate treatment [26]. The change in ALT was correlated with the serum level of remnant-like protein cholesterol (r = −0.53), saturated fatty acids (r = −0.57), and the polyunsaturated / saturated fatty acid ratio (r = 0.46) at baseline.

Larger studies are currently ongoing to more comprehensively assess the effects of pemafibrate on liver function and disease progression in the context of NAFLD/NASH.

PPARα plays a key role in nutrient flux in the liver, and pemafibrate exerts its metabolic effects through the activation of hepatic PPARα. Through PPARα activation, pemafibrate can activate genes associated with a favorable clinical response, including ABCA1, VLDLR, and FGF21 [27]. Preclinical studies suggest that it mediates its beneficial effects by enhancing mitochondrial beta oxidation, reducing hepatic production of VLDL, reducing inflammation, and enhancing circulating levels of FGF21. In the STAM mouse model of NASH, pemafibrate reduces the expression of cell adhesion molecules involved in immune cell infiltration into the liver, as well as the expression of fibrosis-related genes in male mice [28]. In the AMLN mouse model, pemafibrate increased the ATP content of the liver and enhanced energy expenditure through the induction of UCP3 in the liver in male mice [29]. Pemafibrate also stimulated lipid turnover and reduced steatosis. There was also an improvement in insulin sensitivity in this model, which may be related to the increased expression and serum levels of FGF21 following pemafibrate treatment, as FGF21 exerts favorable effects on glucose and lipid metabolism.

Safety: Pemafibrate has a stronger benefit-risk profile than conventional fibrates. It lowers liver enzymes and can be used in those with hepatic or renal impairment, and is not associated with a significant risk for kidney dysfunction, but carries a risk for gallstones.

Types of evidence:

- 2 meta-analyses of 7 RCTs and 3 RCTs for pemafibrate in dyslipidemia
- 1 clinical trial comparing pemafibrate monotherapy vs. combination with statins
- 1 single-arm Phase 3 clinical trial in dyslipidemia + renal impairment
- 1 single-arm pilot clinical trial in NAFLD
- 1 case series in IgA nephropathy
- Numerous laboratory studies

A meta-analysis of seven RCTs for pemafibrate in dyslipidemia found that there was no significant difference in total adverse events between pemafibrate and placebo [10]. Total adverse events were lower for pemafibrate relative to fenofibrate (OR: 0.60, 95% CI 0.49 to 0.73; $P < 0.001$). A separate meta-analysis of three RCTs also found that pemafibrate treatment was associated with a lower incidence of total adverse events (OR: 0.68, 95%CI 0.53 to 0.86) and adverse drug reactions (OR: 0.36, 95%CI 0.24 to 0.54) relative to fenofibrate [11]. Unlike conventional fibrates, the use of pemafibrate in combination with statins did not increase the risk for adverse events, and rhabdomyolysis was not observed [3; 21]. The adverse event profile was similar in the context of dyslipidemia, type 2 diabetes, and NAFLD.

Similar to conventional fibrates, cholelithiasis, which is gallstone formation, was an adverse event associated with pemafibrate use in clinical trials [1].

Effects on kidney: Pemafibrate did not increase the risk for kidney dysfunction, and while serum creatine levels were higher than placebo, they were lower than fenofibrate [10]. Pemafibrate treatment is not associated with significant changes in creatine kinase activity. Adverse events were similar for those with and without renal dysfunction, suggesting that unlike conventional fibrates, pemafibrate can be safely used in individuals with renal impairment. Analyses also found that combining pemafibrate with statins does not increase the risk for adverse outcomes in the context of renal impairment [21].

Effects on liver: Pemafibrate reduced liver enzyme activity relative to both placebo (OR: 0.33; 95% CI 0.21 to 0.52; $P < 0.001$) and fenofibrate (OR: 0.14; 95% CI 0.10 to 0.20; $P < 0.001$), which is associated with an elevation of liver enzymes [16]. However, since pemafibrate is metabolized by the liver, systemic exposure is increased in the context of severe hepatic dysfunction, and thus is contraindicated in this population [19].

Sex-effect: A significant sex-effect has not been reported in terms of efficacy or safety for pemafibrate in clinical trials thus far. But, due to the known differences in PPARα expression between males and females [7], a sex-effect for some, yet to be tested, indications cannot be ruled out.

Drug interactions: Pemafibrate is metabolized through CYP2C8, CYP2C9, and CYP3A4 enzymes [19]. It shows minor inhibition of CYP2C9 and UGT1A1, and thus may show interactions with drugs that are metabolized with these enzymes. Use with cyclosporine increases the AUC of pemafibrate 14-fold, while use with rifampicin decreases the AUC to 0.2-fold, so pemafibrate should not be used with cyclosporine or rifampicin. Pemafibrate does not significantly interact with statins, digoxin, or warfarin.

Sources and dosing:

Pemafibrate (Parmodia®, K-877) is distributed by Kowa (Tokyo, Japan) and is approved for use in dyslipidemia in Japan. It is not yet approved in the US and Europe, but Phase 3 trials are ongoing. It is orally administered with a recommended dose of 0.1 mg BID, up to 0.2 mg BID.

Research underway:

Pemafibrate in an extended release tablet formulation is currently being tested in Phase 3 confirmatory trials (NCT04714151 and NCT04716595) in patients with dyslipidemia and high triglycerides. These trials are expected to be completed in late 2021 and 2022, respectively. It is also being tested in a controlled-

release formulation for dyslipidemia in a Phase 2 trial (NCT04079530) that was projected to complete in 2020. Pemafibrate is being tested in a Phase 2 trial for NAFLD (NCT03350165), which also had an estimated completion date in 2020. In order to assess the effect of pemafibrate on cardiovascular outcomes, it is being tested in a large multi-national Phase 3 trial 'Pemafibrate to Reduce Cardiovascular OutcoMes by Reducing Triglycerides IN patiENts With diabeTes' (PROMINENT) which includes over 10,000 participants (NCT03071692). This trial is expected to be completed in 2022.

There are additional observational and interventional trials registered in Japan for pemafibrate with respect to cardiac diastolic function in type 2 diabetes, endothelial function in hypertriglyceridemia, in the prevention of atherosclerotic disease in stroke, hemorheology in hypertriglyceridemia, urinary protein suppression in chronic kidney disease, sympathetic nerve activity in hypertriglyceridemia, primary biliary cholangitis, bile acid metabolism in fatty liver disease, metabolic parameters in type 2 diabetes, and NAFLD.

Search terms:

Pubmed, Google: Pemafibrate

- Alzheimer's disease, neurodegeneration, cardiovascular, diabetes, kidney disase, liver disease, clinical trials, safety, meta-anlalysis

Websites visited for Pemafibrate:

- Clinicaltrials.gov
- clinicaltrialsregister.eu
- UMIN
- PubChem
- DrugBank.ca

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