*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 has a better therapeutic profile in reducing triglycerides relative to fibrates, particularly with respect to safety, and can reduce elevated liver enzymes, though efficacy may be impacted by sex.

**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. Clinical studies suggest it can reduce hepatic inflammation and fibrosis, but does not appear to reduce residual cardiovascular risk.

**Safety:** It 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.

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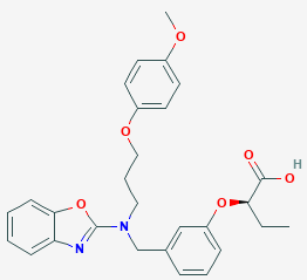
| **Availability**: Rx in Japan | **Dose**: Oral tablets<br>0.1 mg BID | **Chemical formula:** $C_{28}H_{30}N_2O_6$<br>**MW**: 490.55 g/mol |
| **Half-life**: 1.5 to 2.5 hours | **Observational studies**: Pemafibrate shows a good therapeutic-safety profile in those with renal impairment or fatty liver disease. Numerous retrospective studies indicate it can reduce liver enzymes and may mitigate liver fibrosis. |  <br>Source: PubChem |
| **Clinical trials**: There have been Phase 3 RCTs for dyslipidemia in Japan (range n=166 to 526), and a global Phase 3 RCT for dyslipidemia and type 2 diabetes (n=10,495). A variety of additional small trials have also been conducted in populations with hypertriglyceridemia plus type 2 diabetes, and/or liver disease (primarily NAFLD). | | |

**What is it?**

Pemafibrate (K-877) belongs to the therapeutic class of selective peroxisome proliferator-activated receptor alpha modulators (SPPARMα) [1]. Although conventional fibrates also activate PPARα, they also activate other PPAR isoforms to varying degrees, including those that have preferential selectivity for PPARα, such as fenofibrate. As such, they 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 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. It was tested for residual cardiovascular risk in a large multinational Phase 3 trials including (>10,000 participants). In 2023, pemafibrate received orphan drug designations for primary biliary cholangitis by the FDA and EMA.

**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 PPAR 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 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. Clinical studies suggest it can reduce hepatic inflammation and fibrosis, but does not appear to reduce residual cardiovascular risk.

*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
- 1 Phase 3 RCT (PROMINENT) in type 2 diabetes + hypertriglyceridemia
- 4 clinical trials in patients with type 2 diabetes + hypertriglyceridemia
- 2 clinical trials in dyslipidemia in combination with statins
- 1 Phase 2 clinical trial in NAFLD
- 1 clinical trial in patients with NAFLD in combination with low carbohydrate diet
- 1 clinical trial for primary biliary cholangitis with dyslipidemia
- 1 post-hoc analysis of Phase 2 and 3 RCTs for pemafibrate in dyslipidemia
- 8 observational studies of pemafibrate in patients with NAFLD
- 5 observational studies of pemafibrate in patients with hypertriglyceridemia
- 2 observational studies in patients with hypertriglyceridemia + chronic kidney disease
- 1 observational study of pemafibrate in patients with type 2 diabetes + hypertriglyceridemia
- 1 observational study of pemafibrate in patients with type 2 diabetes + NAFLD
- 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.

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 [2]. A pooled analysis of Phase 2 and 3 RCTs (six studies, n=1,253 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]. In this analysis, 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.

Triglycerides have been implicated as a contributor to residual risk of atherosclerotic cardiovascular disease (ASCVD) [13]. Residual risk refers to the observation that a subset of patients with adequately controlled LDL-c, usually in response to statin treatment, still go on to develop ASCVD. Triglyceride-rich remnant lipoproteins can contain 5-20 times more cholesterol per particle relative to LDL, and induce low grade inflammation in the vascular wall [14]. Therefore, drugs that can reduce levels of triglycerides and remnant cholesterol were thought to be good candidates for the reduction of residual cardiovascular risk.

Pemafibrate may help mitigate postprandial hyperlipidemia, which has been associated with ASCVD risk [15]. ApoB-48 is a component of non-fasting triglycerides, and thus can be a useful marker related to postprandial hyperlipidemia and insulin resistance. A level of 4.34 µg/ml has been proposed as the optimal cut-off value for discriminating coronary artery disease [16]. The open-label randomized PROUD48 study assessed the percentage change in fasting apoB-48 in statin-treated patients with dyslipidemia taking pemafibrate (0.4 mg/day) or omega-3 fatty acid ethyl (4 g/day) for 16 weeks [16]. Pemafibrate was associated with greater reductions in apoB-48 of −3.10 µg/ml (interquartile range [IQR] −5.63 to −1.87), or by −50.8% (IQR −62.9 to −30.3%) than those taking omega-3 ethyl, which only showed reductions of −17.5% (IQR −38.3 to 15.3%).

The impact of pemafibrate on cardiovascular outcomes was tested in the large Phase 3 PROMINENT trial (NCT03071692). This trial included 10,497 patients with type 2 diabetes and mild to moderate hypertriglyceridemia, defined as having triglyceride levels between 200 and 499 mg/dL and HDL-c levels of ≤40 mg/dL [17]. Participants had to have LDL-c levels ≤100 mg/dL, with or without statins. In this study, the median baseline fasting triglyceride level was 271 mg/dL per deciliter, the HDL-c level was 33 mg/dL, and the LDL-c level was 78 mg/dL. The very well controlled LDL-c levels in this population is noteworthy, and is thought to have contributed to the study outcomes. Pemafibrate was tested at a dose of 0.4 mg/day (0.2 mg twice per day), with a median follow-up of 3.4 years. The primary endpoint of the study was the occurrence of a major adverse cardiovascular events, measured by a composite of nonfatal myocardial infarction, ischemic stroke, coronary revascularization, or death from cardiovascular causes. Major adverse cardiovascular events occurred in 572 patients in the pemafibrate group and in

560 patients in the placebo group (Hazard Ratio [HR]: 1.03, 95% CI 0.91 to 1.15). No significant differences in adverse cardiovascular events were observed despite significant reductions, based on the median change from baseline at four months, on triglycerides (-26.2%, 95% CI −28.4 to −24.10), VLDL-c (-25.8%, 95% CI −27.8 to −23.9), remnant cholesterol (-25.6%, 95% CI −27.3 to −24.0), and apoC-III (-27.6%, 95% CI −29.1 to −26.1) in patients treated with pemafibrate relative to placebo. The lack of benefit may be related to the manner in which pemafibrate reduces levels of large triglyceride-rich lipoproteins, such that they are transferred to LDL particles, rather than being sent to the liver for removal. Consequently, pemafibrate treatment led to small increases in the levels of LDL-c (12.3%, 95% CI 10.7 to 14.0) and apoB (4.8%, 95% CI 3.8 to 5.8) in this trial. The researchers involved in this trial have speculated that the increase in LDL-c may have negated any potential benefits of triglyceride lowering in this population.

The increases in LDL-c seen with pemafibrate in prior studies, typically in the absence of a corresponding increase in apoB, have generally been thought to be cardioprotective in representing a shift towards more cholesterol per LDL particle rather than an increase in the number of LDL particles. This is associated with a shift toward less of the highly atherogenic small dense LDL-c (sdLDL-c). For example, a Phase 2 RCT including 408 statin-treated patients with dyslipidemia from 68 European sites found that 12 weeks of pemafibrate raised LDL-c by 9.2 to 20.5%, depending on the dose, but had no significant effects on levels of apoB [18]. The increase in LDL-c was associated with dose-dependent increases in particle size, ranging from 1.47 to 3.39 Angstroms, leading to a reduction in levels of sdLDL-c. Of note, only 20% of participants were on statin regimens aimed at keeping LDL-c levels <70 mg/dL, and the majority of participants were on statin regimens with target levels <100 to <130 mg/dL. Subsequent studies have found that the baseline LDL-c level may impact the manner in which pemafibrate impacts sdLDL-c. A trial including 1,508 patients with type 2 diabetes and dyslipidemia, along with 670 non-diabetic controls found that the association between sdLDL-c and conventional lipid parameters is weaker in diabetes patients [19]. Participants were stratified by LDL-c levels of ≤69 mg/dL, 70–99 mg/dL, 100–139 mg/dL, and ≥140 mg/dL. The slope of the regression curve between sdLDL-c and triglycerides was found to flatten as LDL-c decreased, with slopes of 0.04, 0.10, 0.13, and 0.18, respectively for controls, and 0.07, 0.09, 0.13, and 0.18, respectively for diabetes patients. As such, the sdLCL-c/triglyceride ratio is lower at lower LDL-c ranges, indicating that the involvement of triglycerides in sdLDL-c levels is reduced as LDL-c levels decrease. Consequently, the lack of cardiovascular benefit in the PROMINENT trial may have been at least partially related to the inability of pemafibrate to significantly lower sdLDL-c in trial participants with low (≤80 mg/dL) LDL-c.

While pemafibrate does not appear to reduce residual cardiovascular risk in individuals with low levels of LDL-c well controlled by statins, subsequent studies have been conducted to determine if there are particular subpopulations who might benefit from pemafibrate.

A retrospective observational study including 98 patients with hypertriglyceridemia in which around one third were taking statins and half were diabetic found that treatment with pemafibrate for three months was associated with a reduction in the levels of sdLDL-c from 48.9mg/dL (IQR 35.7 to 57.9) to 38.8 mg/dL (IQR 30.0 to 45.1) [20]. The median level of LDL-c at baseline in this cohort was 111 mg/dL (IQR 75 to 136), and generally did not increase over the three-month treatment period (104 mg/dL, IQR 81 to 136). A lower baseline level of LDL-c was associated with a smaller decrease in sdLDL-c ($r = -0.651$), while greater decreases in both triglycerides and LDL-c were associated with greater reductions in sdLDL-c. The rate of adverse cardiovascular events, including heart failure, coronary artery disease, and stroke, decreased from 0.133 events/year at one year pre-treatment to 0.021 events/year after one year with treatment (incidence rate ratio: 0.16, 95% CI 0.14 to 0.17, $p < 0.001$).

In the open-label PRESTIGE study 97 participants with type 2 diabetes and hypertriglyceridemia treated with statins (atorvastatin, pitavastatin, or rosuvastatin) were randomized to receive either pemafibrate (0.2 mg/day) or a doubling of their statin dose for 12 weeks [21]. Despite being on statins, sdLDL-c levels were higher (median 51 mg/dL) than in the general population (33 mg/dL). The reduction of sdLDL-c was greater in the pemafibrate group than the statin doubling group in terms of both absolute levels (pemafibrate: −16 mg/dL, 95% CI −30 to −6 vs. statin doubling group, −3 mg/dL, 95% CI−14 to 4) and as a percentage (−32.8 vs −8.1%). ApoB levels decreased to a similar amount (7-9%) in both treatment groups. The LDL-c levels at the end of the study were 108 ± 25 mg/dL in the pemafibrate group, which were not significantly changed from baseline, and 90 ± 23 mg/dL in the statin doubling group, which were −8 ± 20% lower than baseline. These LDL-c levels are higher than in the PROMINENT trial and are within the range where triglyceride levels have been shown to meaningfully influence sdLDL-c levels. These studies suggest that pemafibrate may help reduce cardiovascular risk in individuals who have elevated levels of sdLDL-c and are unable to achieve low levels (<70 mg/dL) of LDL-c through statins alone stemming from either resistance or intolerance to high doses. At this point, the optimal cutoff for sdLDL-c in terms of determining at risk populations has not yet been established, nor has the degree of lowering needed for potential cardiovascular benefit.

Evidence from preclinical studies suggests that pemafibrate may have additional cardioprotective properties, and may play a role in reducing residual cardiovascular risk. Notably, pemafibrate has been shown to reduce fibrinogen levels to a greater degree than fenofibrate [22]. 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 [22].

**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 [23]. 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 [24]. 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 [24]. 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 [23].
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 2.25 ± 1.03), while significantly increasing HDL-c (52 ± 15 to 60 ± 20 mg/dL) [25]. Glycemic parameters, including blood glucose and insulin levels, were not significantly changed.

Numerous additional trials have been conducted testing pemafibrate in patients with type 2 diabetes and dyslipidemia, and generally showed that reductions in triglycerides and remnant lipoprotein cholesterol were similar to those observed in non-diabetic populations.
A post-hoc analysis of six phase 2 and phase 3 RCTs testing pemafibrate at a dose of 0.1, 0.2 or 0.4 mg/day in Japanese participants with dyslipidemia (n=1,253) found that relative to placebo, pemafibrate

was associated with reductions in fasting glucose, fasting insulin, and HOMA-IR [26]. The strongest effects were seen with the highest dose (0.4 mg/day), with least square mean changes from baseline by − 0.25 mmol/L (95% CI − 0.36 to −0.14) for fasting plasma glucose, by 3.31 µU/mL (95% CI − 4.37 to −2.26) for fasting serum insulin, and by − 1.28 (95% CI − 1.71 to −0.84) for HOMA-IR. The direction of changes on these glucose markers was similar for participants with and without type 2 diabetes. No significant effect was seen for HbA1c.

The PARM-2D study was a prospective observational study assessing the lipid profile in patients with type 2 diabetes and hypertriglyceridemia in real-world clinical practice (n=504) taking pemafibrate or conventional fibrates for 52 weeks [27]. Glycemic control, as measured by HbA1c and fasting plasma glucose, was not significantly altered over the course of the study in either group. A sub-analysis of 279 participants who did not change their treatment for diabetes or receive insulin/ insulin secretagogues during the study period similarly showed there was no significant difference in HbA1c [28]. The pemafibrate-treated group showed improvements on HOMA2-R, a measure of insulin resistance (−0.15 vs. 0.08; estimated treatment difference −0.23, 95% CI −0.44 to −0.02), as well as maintenance of β-cell function based on the disposition index (0.015 vs. −0.023; estimated treatment difference 0.037, 95% CI 0.005 to 0.069). These effects on insulin-related parameters were associated with improvements on lipids profiles and liver enzymes. The HOMA2-R largely reflects insulin resistance in the liver, thus the benefits with pemafibrate likely stem from improvements to metabolic function in the liver.

A retrospective longitudinal study including 246 patients with dyslipidemia found that diabetic patients treated with SGLT2 inhibitors did not show the increase in LDL-c levels observed in response to pemafibrate treatment observed in participants who were not taking SGLT2 inhibitors [29]. This suggests that the class of anti-diabetic agent used may impact the cardiovascular benefit profile of pemafibrate.

The impact of pemafibrate (0.2 mg/day) on hemorheology, or the flow properties of blood, was assessed in a non-randomized, controlled study in 96 patients with type 2 diabetes or metabolic syndrome and hypertriglyceridemia [30]. There were no significant differences on measures of blood transit time, or adherent leukocyte counts after 16 weeks, suggesting that pemafibrate did not alleviate endothelial dysfunction.

A small study in 17 patients with type 2 diabetes and hypertriglyceridemia examined the impact of pemafibrate (0.2 mg/day for 8-16 weeks) on cardiac diastolic function, a feature of diabetic cardiomyopathy [31]. This pilot study found that pemafibrate was associated with an increase in the peak early diastolic annular velocity (e') (7.24 ± 0.58 vs 7.94 ± 0.67), and a reduction in the early diastolic filling velocity (E)/e' ratio (9.01 ± 0.94 vs 8.20 ± 0.91), suggestive of improved diastolic function. Larger trials are needed to validate this finding.

**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 [32]. 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 FGF21. Pemafibrate may reduce pathological retinal neovascularization by inhibiting ischemia-induced HIF1a through the activation of PPARα and FGF21 [33]. 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 [34]. 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. 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 [35].

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 [36]. 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 [37]. 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.

Several studies demonstrated that pemafibrate has a good safety profile in patients with chronic kidney disease, particularly in relation to conventional fibrates. Though, to date, the evidence primarily indicates that pemafibrate does not worsen kidney function, not that it improves it. A retrospective study in 39 patients with chronic kidney disease (eGFR 20-60 mL/min/1.73 $m^2$) found that treatment with pemafibrate did not significantly alter serum creatinine levels or eGFR, except in participants that were switching from conventional fibrates, in which case there were improvements (decreases) in creatinine and (increased from 45.2 ± 9.9 to 50.1 ± 8.6 mL/min/1.73 $m^2$) eGFR [38]. A separate retrospective study in 47 patients with hypertriglyceridemia and chronic kidney disease similarly found that switching from conventional fibrates (fenofibrate or bezafibrate) to pemafibrate was associated with a mean improvement in eGFR of 10.2 mL/min/1.73 $m^2$ [39]. No change in markers of renal function was observed when switching to pemafibrate from a treatment not associated with renal toxicity.

**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 clinical studies suggest that it may also improve hepatic function in the context of liver disease, particularly non-alcoholic fatty liver disease/ nonalcoholic steatohepatitis (NAFLD/NASH).
Similar to dyslipidemia patients without liver disease, pemafibrate significantly lowers triglycerides in patients with concomitant fatty liver disease. 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 (ALP) (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 [35]. 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 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 [40]. 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 [41]. 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 [42]. 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.
The beneficial effect of pemafibrate on liver enzymes has been observed in numerous observational studies, and confirmed in subsequent clinical trials. Following the failure of pemafibrate to meaningfully

impact residual cardiovascular risk in the PROMINENT trial, clinical development of pemafibrate has largely pivoted towards NAFLD/NASH, which as of 2023 has been renamed metabolic dysfunction-associated steatotic liver disease (MASLD), and metabolic dysfunction-associated steatohepatitis (MASH), respectively [43]. Since the trials were conducted prior to the name change, the original nomenclature (NAFLD/NASH) will be used in the discussion of these studies.

In the PROMINENT trial it was observed that there was a lower incidence of hepatic adverse events in the pemafibrate group than in the placebo group (219 patients vs. 265 patients; HR: 0.83, 95% CI 0.69 to 0.99), as well as a lower number of patients in the pemafibrate group with investigator reported NAFLD (155 patients vs. 200 patients; HR: 0.78, 95% CI, 0.63 to 0.96), suggesting that pemafibrate may be having a hepatoprotective effect in this population [17]. A post-hoc analysis of six trials for pemafibrate conducted in Japan including 1,253 patients with dyslipidemia found that, relative to placebo, pemafibrate was associated with significant reductions in liver enzymes including ALT (by − 7.6 U/L, 95% CI − 9.3 to −6.0), GGT (by − 37.3 U/L, 95% CI − 41.6 to −32.9), ALP (by − 84.7 U/L, 95% CI − 88.9 to −80.5), and total bilirubin (by − 2.27 µmol/L, 95% CI − 2.69 to −1.85) [26]. Pemafibrate was also associated with increased levels of FGF21, a metabolism regulating hormone produced by the liver, particularly at the highest tested dose (0.4 mg/day), which showed an increase in FGF21 of 369.5 pg/mL, relative to placebo.

Compared with conventional fibrates, this hepatoprotective effect appears to be relatively specific to pemafibrate. Relative to bezafibrate, treatment with pemafibrate is associated with a higher percentage of patients achieving ALT normalization. In one study (n=34), ALT normalization rates after one year were 60% (12/20) for pemafibrate and 14.3% (2/14) for bezafibrate [44]. Another study (n=60) also found that by 24 weeks pemafibrate reduced ALT levels (−21.9±36.5) to a greater degree than bezafibrate (−10.6±41.3) [45]. In participants with chronic liver disease (n=58), switching from bezafibrate to pemafibrate led to ALT normalization in 58% of patients with abnormally elevated ALT at baseline [46]. Complete responses of liver dysfunction were achieved in 23% (9/39) of patients with incomplete responses at baseline. Patients with cholestatic liver disease appeared to show preferential benefit on liver responses relative to those with NAFLD. In a study in patients with primary biliary cholangitis and dyslipidemia (n=75) treated with ursodeoxycholic acid (UDCA), the addition of pemafibrate or transition from bezafibrate to pemafibrate led to reductions in the liver enzymes ALP (from 445.8 ± 236.5 U/L to 269.0 ± 121.4 U/L), and GGT (from 99.5 ± 113.3 U/L to 55.8 ± 72.7 U/L) [47]. Decreases in liver enzymes were also observed in the PARM-T2D study, which assessed the effects of pemafibrate, relative to conventional fibrates, on patients with type 2 diabetes and dyslipidemia in real-

world clinical practice [27]. A sub-analysis of participants with NAFLD (n=293) found that pemafibrate use was associated with a reduction in ALT levels from 29 to 22 U/L in this population [48].

Liver biopsy is currently the gold standard in the diagnosis of NAFLD/NASH, however, there have been a lot of efforts to develop and validate non-invasive markers, many of which are imaging related [49]. The MRI-proton density fat fraction (MRI-PDFF) is a non-invasive assessment of liver fat levels. A Phase 2 trial (NCT03350165) in 188 patients with high-risk NAFLD, based on MRI-PDFF-determined liver fat content ≥10%, assessed the impact of pemafibrate (0.2 mg/twice per day) for 72 weeks on the percent change in MRI-PDFF [50]. There was no significant difference on this measure at the end of 24 weeks (pemafibrate −5.3% vs placebo −4.2%), but there was a decrease in liver stiffness based on magnetic resonance elastography (MRE) of −5.0% (95% CI −8.5 to −1.6) at 24 weeks, and −7.3% (95% CI −11.1 to −3.5) at 72 weeks. A retrospective study including 179 patients with NAFLD similarly found that 48 weeks of pemafibrate had no effect on liver fat assessed by MRI-PDFF, but reduced MRE-based liver stiffness (from 2.93 to 2.55) [49]. This was coupled with a reduction in measures of liver fibrosis, including the MEFIB index, which is a combination of MRE (≥3.3 kPa) and the FIB-4 index (≥1.6), and the MAST score, which is based on a combination of MRE, MRI-PDFF, and AST levels ( -12.17 + 7.07 log MRE + 0.037 PDFF + 3.55 log AST). These measures can be used to identify individuals at highest risk for clinical progression of NAFLD/NASH.

In the PARM-T2D sub-study, liver fibrosis, based on the FIB-4 index worsened in those taking conventional fibrates, but remained stable in those taking pemafibrate [48]. FIB-4 scores slightly improved (mean change −0.05, 95% CI − 0.22 to − 0.02) in patients with severe liver dysfunction, as defined by ALT levels greater than two times the upper limit of normal (UNL). A post-hoc analysis of a retrospective longitudinal study including 134 patients with hypertriglyceridemia taking pemafibrate for at least one year found a significant decrease in the FIB-4 index in patients with a baseline FIB-4 index ≥ 1.45 (from 2.55 ± 2.66 to 2.03 ± 0.83), as well as reductions in the AST to platelet ratio index (APRI) (from 0.43 ± 0.73 to 0.30 ± 0.22), and hepatic steatosis index (HSI) (from 40.1 ± 9.7 to 38.3 ± 6.8) [51].

Improvements in liver function markers can be confounded by weight loss. The improvements seen with pemafibrate were not associated with weight loss, and in the majority of studies, treatment with pemafibrate was not associated with changes in body mass. The combination of pemafibrate with dietary interventions that promote weight loss may enhance hepatoprotection. A small clinical study in 38 patients with NAFLD and hypertriglyceridemia looked at the combination of pemafibrate with a low carbohydrate diet consisting of 20% (80 g) protein, 42% (75 g) fat, and 38% (140 g) sugar, and a total of

1,600 kcal/day. Similar to other studies with pemafibrate, reductions were seen in liver enzymes and liver stiffness, but unlike studies testing pemafibrate alone, a reduction in hepatic fat, based on the MRI-PDFF was also observed (from 16.6% to 12.3%). In participants classified as overweight at baseline (BMI >25), the reductions in hepatic steatosis were associated with weight loss, while it was unrelated to weight loss in the non-overweight/obese participants.

The reduction in measures of liver fibrosis independent from reductions in levels of liver fat are thought to be related to a decrease in inflammation-related fibrosis [49]. A retrospective study including 71 non-diabetic patients with NAFLD found that treatment with pemafibrate for at least six months was associated with a reduction in levels of Mac-2 binding protein glycosylation isomer (M2BPGi) (from 0.67 ±0.04 to 0.56 ±0.03), a blood-based biomarker of liver fibrosis that is strongly impacted by the degree of liver inflammation [52]. A similar reduction in M2BPGi (from 0.73 to 0.62) with pemafibrate treatment was observed in a small cohort (n=7) of patients with NAFLD and type 2 diabetes for whom SGLT2 inhibitors failed to normalize ALT levels [53].

The mechanism driving this reduction in liver inflammation, but not fat content may be related to changes in the immune response to hepatic lipid accumulation due to alterations in the profile of lipid droplets [54]. A preclinical study in the STAM mouse model found that pemafibrate treatment was associated with a change in the distribution of lipid droplets toward smaller sizes without impacting the overall lipid content [54]. Large droplet steatosis is associated with hepatic inflammation and fibrosis. Pemafibrate may then reduce hepatic inflammation by preventing the formation of large lipid droplets. In the STAM model, the decrease in lipid droplet size was associated with a reduction in the adhesion and migration of pro-inflammatory macrophages into the liver.

PPARα has been shown to be sexually dimorphic in the livers of both mice and humans. Gene expression analysis from human liver tissue indicated a greater number of genes correlating with PPARα expression in males relative to females [55]. Studies in mice indicate that males are more susceptible to diet induced NAFLD and hepatic steatosis stemming from PPARα deficiency [55]. Gene expression analysis indicated that the livers from female mice were more responsive to pemafibrate. It has not yet been established whether pemafibrate's hepatoprotective effect is sexually dimorphic in human patients, but there is some observational data to suggest that it may be. A study aimed at identifying predictors toward pemafibrate efficacy in NAFLD patients in clinical practice, as defined by decrease in serum ALT of >30%, found that females were more likely to be responders [56].

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 [57]. 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 [58]. 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 [59]. 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:** It 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 for dyslipidemia + renal impairment
- 1 single-arm pilot clinical trial for NAFLD
- 1 case series in IgA nephropathy
- 1 Phase 3 multi-national PROMINENT RCT for hypertriglyceridemia + type 2 diabetes
- 1 Phase 2 RCT for hypertriglyceridemia in combination with statins (European cohort)
- 1 Phase 2 RCT for high-risk NAFLD
- 1 clinical trial for primary biliary cholangitis with dyslipidemia
- 1 open-label trial for dyslipidemia + type 2 diabetes in combination with statins
- 1 post-hoc analysis of Phase 2 and 3 RCTs for pemafibrate in dyslipidemia
- 2 observational studies of pemafibrate treatment for dyslipidemia
- 2 observational studies in patients with hypertriglyceridemia +chronic kidney disease switching from conventional fibrates to pemafibrate
- 2 observational studies of pemafibrate treatment in patients with NAFLD

- 1 observational study of pemafibrate for hypertriglyceridemia + type 2 diabetes
- 1 observational study in patients with chronic liver disease switching from bezafibrate
- 1 study of real-world adverse events from a pharmacist database
- 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; 37]. The adverse event profile has been found to be similar in the context of dyslipidemia, type 2 diabetes, and NAFLD.

A post-hoc analysis of six RCTs in Japanese participants (n=1,253) found that adverse event rates with pemafibrate were similar to placebo [26]. An assessment of event data from the community pharmacists belonging to the Japan Pharmaceutical Association found that in a cohort of 1,294 patients prescribed pemafibrate, the incidence rate of any adverse event was 11.8% (95% CI 10.2% to 13.7%) [60]. The most commonly reported events for pemafibrate were increased blood pressure (1.3%), myalgia (0.6%), and pain in the extremities (0.5%). Over half of the cases related to blood pressure were deemed by the pharmacists as unrelated to pemafibrate. Subsequent studies have been conducted in other ethnic populations. The Phase 2 RCT including 408 statin-treated adults with hypertriglyceridemia from Europe also found that rates of treatment-emergent adverse events and serious adverse events with pemafibrate were similar to placebo [18]. Creatinine increases above the upper limit of normal (1.3 mg/dL women, 1.5 mg/dL for men) were observed in 1.5% (6) patients taking pemafibrate. Significant increases in homocysteine were also observed in patients treated with pemafibrate, however, the rate (<20%) was lower than has been reported for fenofibrate (30–66%). No other clinical safety concerns were identified in this population.

The PROMINENT trial included 10,497 patients with type 2 diabetes and mild-to-moderate hypertriglyceridemia with well-controlled LDL-c (with or without statins) [17]. This study included participants from 24 countries and the most ethnic diversity in its clinical cohort relative to other trials testing pemafibrate. Similar to other studies, the rate of serious adverse events was similar between the study arms, though the nature of the adverse events differed. More investigator-reported adverse renal events occurred in the pemafibrate group (1463 patients vs. 1347 patients; HR: 1.12, 95% CI 1.04 to

1.20), but there were no sustained impacts on renal function measures, such as eGFR, once the drug was discontinued, suggesting that it does not negatively affect the kidney itself. The incidence of investigator-reported venous thromboembolism was higher also in the pemafibrate group (71 patients vs. 35 patients; HR: 2.05, 95% CI 1.35 to 3.17), while hepatic related adverse events were lower with pemafibrate (219 patients vs. 265 patients; HR: 0.83, 95% CI 0.69 to 0.99).

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

*Effects on kidney*: Clinical studies indicate that Pemafibrate does not increase the risk for kidney dysfunction. Most studies show that pemafibrate does not significantly impact levels of serum creatinine or eGFR, but in cases where they are impacted, the effect is marginal in comparison to conventional fibrates [10]. Additionally, some studies have found that switching from conventional fibrates to pemafibrate can improve these measures of renal function [38; 39]. 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 [37].

*Effects on liver*: Pemafibrate has been associated with a reduction in 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; $P < 0.001$) [25]. Observational studies in patients with cholestatic liver disease and NAFLD have shown similar reductions in liver enzymes [46]. A clinical study in patients with primary biliary cholangitis found that pemafibrate had a better safety profile on liver and kidney function relative to conventional fibrates, and could be safely combined with UDCA, the primary treatment used for this condition [47]. 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 [34].

*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; 55], 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 [34]. 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 orally administered with a recommended dose of 0.1 mg BID, up to 0.2 mg BID.

**Research underway:**

According to Clinicaltrials.gov, there are currently two active clinical trials testing pemafibrate. a Phase 3 confirmatory study in patients with hypercholesterolemia and statin intolerance (NCT05923281), and a Phase 2 study to evaluate the efficacy and safety of Pemafibrate in participants with primary biliary cholangitis with inadequate response to ursodeoxycholic acid (UDCA) and/or obeticholic acid treatment (NCT06247735). Several clinical studies are also registered in Japan (UMIN).

**Search terms:**
Pubmed, Google: Pemafibrate

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

Websites visited for Pemafibrate:

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