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REVIEW

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PPAR agonists for the treatment of cholestatic liver diseases: Over a decade of clinical progress

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Abstract

Primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC) are characterized by the destruction of the small bile ducts and the formation of multifocal biliary strictures, respectively, impairing bile flow. This leads to the hepatic accumulation of bile acids, causing liver injury and the risk of progression to cirrhosis and liver failure. First-line therapy for PBC is ursodeoxycholic acid, although up to 40% of treated individuals are incomplete responders, and there is no effective therapy for PSC, highlighting the need for better therapeutic options in these diseases. In addition, pruritus is a common symptom of cholestasis that has severe consequences for quality of life and is often undertreated or untreated. Nuclear receptors are pharmacological targets to treat cholestasis due to their multifactorial regulation of hepatic enzymatic pathways, particularly in bile acid metabolism. The peroxisome proliferator-activated receptor (PPAR) is of significant clinical interest due to its role in regulating bile acid synthesis and detoxification pathways. PPAR agonism by fibrates has traditionally been explored due to PPARα's expression in the liver; however, recent interest has expanded to focus on newer PPAR agonists that activate other PPAR isoforms, for example, δ, γ, alone or in combination. Several PPAR agonists have been investigated as second-line therapy for people living with PBC, including the recent accelerated United States Food and Drug Administration approval of elafibranor and seladelpar. This review evaluates available data on the efficacy and safety of the five PPAR agonists investigated for the treatment of cholestasis and associated pruritus in PBC and PSC, namely fenofibrate, bezafibrate, saroglitazar, elafibranor, and seladelpar.

Keywords: bile acids, fibrates, primary biliary cholangitis, primary sclerosing cholangitis, pruritus

Abbreviations: C4, 7α -hydroxy-4-cholesten-3-one; FDA, United States Food and Drug Administration; LS, least squares; NRS, numerical rating scale; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; PSC, primary sclerosing cholangitis; QOL, quality of life; UDCA, ursodeoxycholic acid; VAS, visual analog scale.

David N. Assis and Nisanne S. Ghonem contributed equally to this work.

INTRODUCTION

Bile formation and secretion are critical physiological processes of the liver. Bile acids are major components of bile and are essential for the digestion and absorption of lipids from the intestinal lumen, as well as for the excretion of endogenous molecules and xenobiotics.[1] However, bile acids are hydrophobic molecules that become cytotoxic at elevated concentrations. Cholestasis is defined as an impairment of bile flow that may result from physical obstruction, secretory defects,[2] genetic abnormalities,[3–6] or immune-mediated[7,8] destruction of the bile ducts. In primary human hepatocytes, pathophysiological levels of bile acids stimulate the release of proinflammatory signaling molecules that cause mitochondrial injury,[9] leading to necrotic cell death when elevated to biliary concentrations.[10]

Cholestatic liver diseases, for example, primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC), are characterized by the accumulation of bile acids in the liver, which leads to hepatocyte damage and progressive liver fibrosis.[11] The first-line treatment for adults living with PBC is ursodeoxycholic acid (UDCA, 13–15 mg/kg/d), which can improve transplant-free survival independent of the disease stage.[12] However, up to 40% of people living with PBC incompletely respond to UDCA therapy, and a complete biochemical response is seldom achieved for advanced cirrhosis.[13] Furthermore, treatment with UDCA does not improve the long-term survival of people living with PSC, which has no effective therapy.[14] Until recently, the only United States Food and Drug Administration (FDA)-approved second-line therapy for people living with PBC was obeticholic acid (OCA); however, this drug can exacerbate pruritus[15] and includes a boxed warning regarding use in advanced cirrhosis. Furthermore, required postmarketing studies under the accelerated approval regulatory process intended to confirm efficacy in clinical outcomes were hampered by poor enrollment and lack of demonstrated improved outcomes.[16] Interestingly, in November 2024, the FDA declined to grant full approval of OCA for the treatment of PBC, due to the drug's less-than-favorable benefit-risk profile.

In addition to the above, quality of life (QOL) is frequently impaired for people living with PBC and/or PSC, often in the form of cholestatic pruritus. While this symptom can be adequately controlled in most cases with currently available treatments, it can be significantly challenging to treat in a minority of individuals with refractory pruritus. When this occurs, pruritus has devastating negative consequences, including interruption of sleep, work, and socialization, thereby negatively affecting overall QOL. Therefore, improved treatment options are needed to prevent disease progression and to improve QOL for people living with PBC and/or PSC.

THE ROLE OF PEROXISOME PROLIFERATOR-ACTIVATED RECEPTOR AGONISM IN CHOLESTASIS

Peroxisome proliferator-activated receptor (PPAR) agonists are a major new therapeutic drug category for cholestatic liver diseases. PPAR is a ligand-activated transcription factor of the nuclear receptor superfamily, with 3 distinct PPAR isoforms (α, δ, or γ) encoded by different genes.[17–19] After ligand binding, PPAR translocates to the nucleus, where it forms a heterodimer with the retinoid x receptor and binds to PPAR response elements in target genes, consisting of direct repeats of the consensus sequence AGGTCA spaced by one nucleotide.[20]

PPARα is highly expressed in tissues involved with fatty acid catabolism, such as the liver, kidney, intestines,[21] and brown adipose tissue.[22] PPARα regulates cellular transport[23,24] and β-oxidation[25,26] of fatty acids and attenuates inflammatory responses,[27,28] resulting in the longstanding FDA approval of fenofibrate, a PPARα agonist, to treat hyperlipidemia. PPARα ligands include both synthetic activators, e.g., fibrates and Wy-14,643, and endogenous molecules, such as fatty acids and their derivatives.[29] In contrast, PPARδ (also known as PPARβ) is more ubiquitously expressed within the skeletal muscle, adipose tissue, liver, kidney, intestines,[21] and heart,[30] where it participates in the control of energy homeostasis by promoting fatty acid β-oxidation[31,32] and mediates anti-inflammation.[30] Natural ligands of PPARδ include fatty acids and their metabolites,[33] similar to PPARα. PPARγ is also ubiquitously expressed with some localization in adipose tissue, intestines,[21] and macrophages[34] and is critical for adipocyte differentiation,[35,36] insulin sensitization,[37,38] fatty acid transport,[23,24] and anti-inflammatory signaling.[39,40] PPARγ is activated by the anti-diabetic thiazolidinedione derivatives, as well as natural ligands such as polyunsaturated fatty acids[33] and arachidonic acid metabolites.[41] Therefore, each PPAR isoform is differentially distributed and possesses unique functions that can be therapeutically advantageous.

The efficacy of PPAR agonists in treating cholestasis is largely attributed to PPAR activation,[42] though each agent differs in its affinity for PPAR subtypes (α, δ, and γ). A comparative list of PPAR agonists and their potency is provided in Table 1. Fenofibrate, a selective PPARα agonist, has been investigated both in the laboratory and human pilot studies as second-line therapy in combination with UDCA and was found to significantly reduce serum markers of liver injury and the toxicity of the total bile acid pool for people living with PBC[46] and also for those with PSC who experience an insufficient response to UDCA therapy.[46,47] Bezafibrate, a pan-PPAR agonist (activates α, δ, and γ) with longstanding use in Japan for PBC and approved by the European Medicines Agency for the

TABLE 1 Comparative potency of human PPAR agonists, based on cell-based transactivation assays

PPAR agonist	PPAR isoform	Human PPAR receptor EC50 (μM)		
		α	β/δ	γ
Fenofibrate[a]	α	9.5[43]–30[42]	100[42]–500[43]	61[43]–300[42]
Bezafibrate	α, δ, γ	30[43]–50[42]	20[42]–87[43]	60[42]–178[43]
Saroglitazar	α, γ	6.5×10^{-7}[44]–0.19[45]	> 10[45]	0.003[44]–0.31[45]
Elafibranor[45]	α, δ	0.39	3.13	2.12
Seladelpar[45]	δ	1.64	0.02	3.53

[a]Data reported for fenofibric acid.
Honda et al.[43]
Willson et al.[42]
Jain et al.[44]
Kamata et al.[45]

treatment of hyperlipidemia, reduces serum markers of cholestasis and the bile acid precursor 7α-hydroxy-4-cholesten-3-one (C4), as well as serum concentrations of the bile acids chenodeoxycholic acid and deoxycholic acid in PBC.[48] Notably, the current PBC Practice Guidance from the American Association for the Study of Liver Disease states that "fibrates can be considered off-label alternatives for people living with PBC and an inadequate response to UDCA, although fibrates are discouraged for those with decompensated liver disease."[49]

While the effect of these fibrates in cholestatic liver diseases has been well-described[50,51] newer PPAR agonists have been investigated to treat cholestasis in PBC, each with varying selectivity for the PPAR isoforms (α, δ, and γ), including elafibranor (α and δ), seladelpar (δ), and saroglitazar (α and γ). This review covers the results reported in clinical studies of fibrates (fenofibrate and bezafibrate), and clinical studies of newer PPAR agonists (elafibranor, seladelpar, and saroglitazar), illustrated in Figure 1.

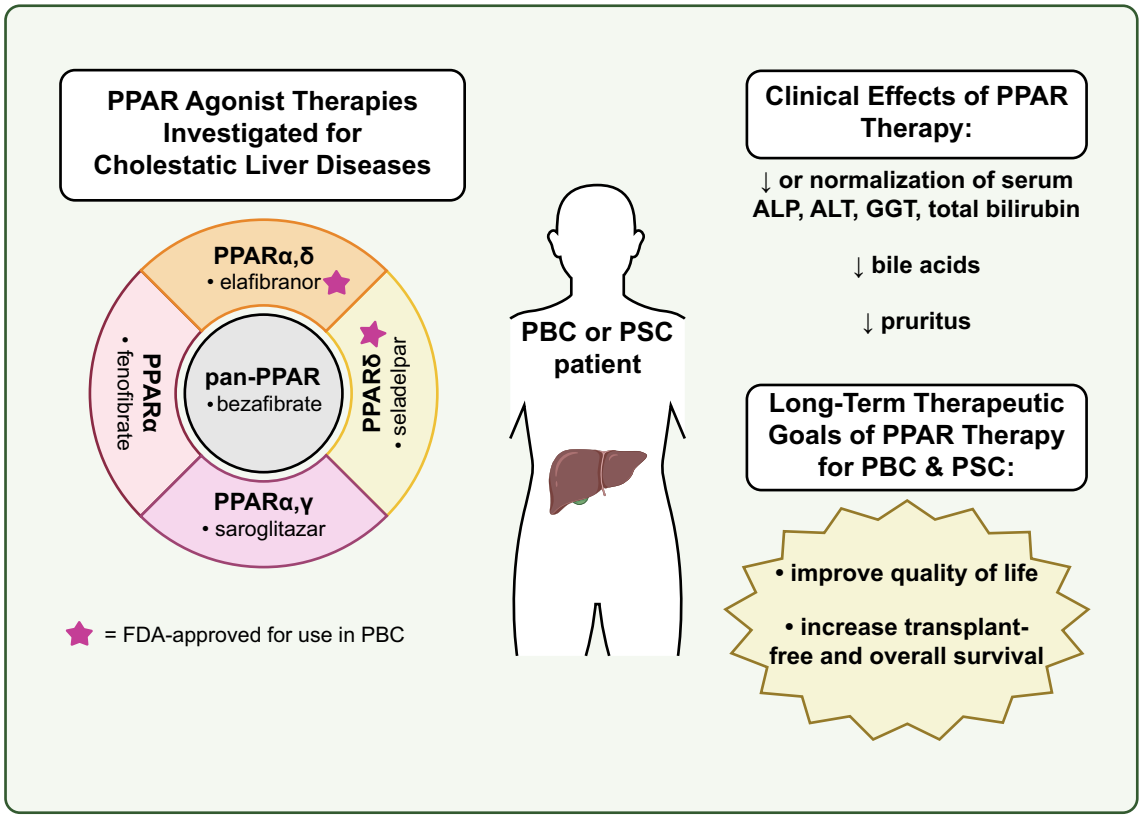

FIGURE 1 Overview of PPAR agonists that have received accelerated FDA approval as second-line therapy for PBC (elafibranor and seladelpar) and PPAR agonists under clinical investigation to treat PBC and PSC (fenofibrate, bezafibrate, and saroglitazar). Created in BioRender.com. Abbreviations: FDA, Food and Drug Administration; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; PSC, primary sclerosing cholangitis.

An overview of the clinical outcomes and safety profile of each of these PPAR agonists is provided in Table 2.

CLINICAL STUDIES OF PPAR AGONISTS FOR PBC AND PSC

Fenofibrate

Fenofibrate is a PPARα agonist currently FDA approved to treat hyperlipidemia

In PBC, the first phase 2 pilot study for individuals (n = 20) receiving fenofibrate (160 mg/d) showed significant reductions in serum ALP, AST, and IgM levels.[56] An open-label clinical trial in treatment-naive people living with PBC (n = 117) found that the addition of fenofibrate (200 mg/d) with UDCA resulted in significantly higher biochemical response rates compared to study subjects started on only UDCA, such that 62% of subjects treated with fenofibrate+UDCA had normal ALP levels by month 12, compared to 40% in the UDCA-only group.[52]

In PBC, 5 additional studies in China are recruiting to test fenofibrate: (1) an open-label long-term study (NCT06365424); (2) a phase 2/3 clinical trial (NCT06174402); (3) and (4) two phase 3 clinical trials (NCT05751967; NCT02823366); (5) a phase 2/3 clinical trial focused on compensated cirrhosis (NCT05749822).

In PSC, a prospective, open-label pilot study showed that fenofibrate (160 mg/d) significantly decreased serum ALP and ALT with 6 months of treatment (n = 8).[60] In a small, randomized, double-blind, placebo-controlled trial performed in Iran, fenofibrate (200 mg/d) significantly reduced serum ALP and ALT levels within 24 weeks (n = 15), with no adverse effects reported.[59] No clinical trials of fenofibrate are currently enrolling people living with PSC.

Bezafibrate

Bezafibrate is a pan-PPAR agonist currently approved outside of the United States to treat hyperlipidemia

In PBC, the BEZURSO study, a 2-year, double-blind, placebo-controlled phase 3 clinical trial was completed to assess the safety and efficacy of bezafibrate (400 mg/d) with UDCA in adults (n = 100) with insufficient response to UDCA monotherapy.[51] Significant reductions in serum biomarkers, including ALP, GGT, ALT, and total bilirubin were observed in the bezafibrate-treated group. Furthermore, nearly two-thirds of study subjects receiving bezafibrate had normalized ALP levels after 24 months with improved pruritus and liver stiffness measurements by transient elastography. No significant changes between treatment groups regarding total and endogenous bile acid levels were observed, despite the decrease in the proportion of endogenous bile acids within the bile acid pool with bezafibrate treatment.[51] A 10-year retrospective study in Japan demonstrated a significant reduction in all-cause mortality or liver transplant in persons treated with bezafibrate and UDCA versus UDCA alone.[62] Despite not being a clinical trial, this is one of the only long-term studies to measure this endpoint in the context of fibrate therapy in PBC.

In PBC, there are 2 clinical trials recruiting to test the efficacy of bezafibrate: (1) an observational study focused on macrophage activation markers and bile acid composition in Denmark (NCT04514965); (2) a phase 3 clinical trial in Mexico (NCT04751188). In addition, 2 phase 2 studies of bezafibrate in combination with OCA are active: (1) across the United States (NCT05239468); (2) throughout Australia, Europe, and Asia (NCT04594694).

In PSC, a phase 3 clinical trial in France is underway to test the safety and efficacy of bezafibrate in adults (NCT04309773).

Saroglitazar

Saroglitazar is a dual PPARα and PPARγ agonist currently approved in India to treat diabetic dyslipidemia

In PBC, a proof-of-concept single-arm study (n = 7) was conducted testing saroglitazar (4 mg/d) for 16 weeks as an adjunct treatment with UDCA.[74] Rapid reductions in serum ALP were noted as early as week 4, in addition to decreases in serum GGT levels. Despite early study termination (due to low enrollment), the rapid reductions in serum ALP levels suggested a clinical benefit of saroglitazar in PBC. In a double-blind, phase 2 proof-of-concept trial of people living with PBC (n = 37) with inadequate responses to UDCA, study subjects were randomized to 3 groups (placebo, saroglitazar 2 or 4 mg/d) for 16 weeks.[73] Significant reductions in mean serum ALP levels were observed in both treatment groups at week 16, and up to half of the subjects on saroglitazar had complete normalization of ALP levels within 16 weeks of treatment.

In PBC, there are 2 studies testing saroglitazar in the United States and abroad: (1) a recruiting open-label extension (NCT06427395); (2) an active phase 2/3 clinical trial (NCT05133336).

In PSC, there are no clinical trials of saroglitazar currently enrolling.

TABLE 2 Clinical outcomes and safety profile of PPAR agonists studied in PBC and/or PSC

PPAR agonist; condition (year)	Study design (NCT), treatment regimen (no. of patients treated)	Primary and secondary endpoints (study results)[a]	Adverse event profile[b]
Fenofibrate (treatment-naive); PBC (2023)[52]	Open-Label Clinical Trial (NCT02823353), UDCA: 13–15 mg/kg (n = 60) vs. UDCA: 13–15 mg/kg+Feno: 200 mg (n = 57)	Primary endpoint:Barcelona criteria (81.4%, $p = 0.048$) Additional endpoints: ALP normalization (62%, $p = 0.042$) ALP < 200 U/L (84.4%, $p = 0.038$)	↑ ALT, grade 1 (n = 8, 14%), grade 2 (n = 3, 6%) ↑ AST, grade 1 (n = 11, 19%), grade 2 (n = 1, 2%) ↑ Total bilirubin, grade 1 (n = 1, 2%) ↑ SCr, grade 1 (n = 6, 11%), grade 2 (n = 3, 6%) *Feno d/c*: pruritus (n = 1, 2%)
Fenofibrate; PBC (2016)[53]	Retrospective Clinical Study, UDCA: 13–15 mg/kg+Feno: 200 mg (median, n = 23)	Primary endpoint: UK-PBC Risk score (no change) Additional endpoints: ↓ median ALP ($p < 0.0001$ at year 1; $p = 0.03$ at year 3) POISE criteria (> 75% at year 1) ALP normalization (80% at year 5)	Deterioration of SCr and estimated globular filtration rate (n = 1, 4%), attributed to chronic kidney disease, patient continued Feno *Feno d/c*: ALT 4–5x ULN (n = 2, 9%); intolerance (n = 4, 17%)
Fenofibrate; PBC (2016)[54]	Retrospective clinical study, UDCA: 13–15 mg/kg (n = 74) vs. UDCA: 13–15 mg/kg+Feno: 145 mg (n = 46)	Primary endpoint: Improved decompensation-free and transplant-free survival vs. UDCA alone (Kaplan-Meier analysis with log-rank = 0.05; "ever- vs. never-treated" Cox model, $p = 0.0002$) Additional endpoints: ALP < 1.67xULN (41%, $p = 0.0001$) Final mean ALP (274 ± 172 IU/L UDCA vs. 184 ± 98 IU/L UDCA+Feno, $p = 0.002$)	*Feno d/c*: pedal edema (n = 1, 2%); transaminases ~5x ULN at 5.4 y (n = 1, 2%); doubling of bilirubin (n = 2, 4%); doubling of SCr and hepatitis with cirrhosis at BL (n = 1, 2%)
Fenofibrate; PBC (2012)[55]	Prospective Clinical Study, UDCA: 13–15 mg/kg+Feno: 200 mg (n = 22)	Biochemical response (pre-Feno vs. post-Feno, respectively): ALP normalization (68% by month 3) ALP (237.1 ± 113.0 U/L vs. 124.3 ± 44.9 U/L, $p = 0.000$) GGT (328.7 ± 201.7 U/L vs. 181 ± 118.7 U/L, $p = 0.000$) AST (71.2 ± 28.8 U/L vs. 57.4 ± 33.4 U/L, $p = 0.012$) ALT (91.6 ± 55.3 U/L vs. 57.4 ± 38.9 U/L, $p = 0.000$) Additional endpoints:triglycerides (2.1 ± 0.9 μmol/L vs. 1.5 ± 0.7 μmol/L, $p = 0.000$) Cholesterol (7 ± 0.4 μmol/L vs. 6.1 ± 1.7 μmol/L, $p = 0.007$)	Pruritus (n = 1, 5%) leading to Feno d/c, then Feno was readministered without adverse effects
Fenofibrate; PBC (2011)[56]	Phase 2 pilot study (NCT00575042), UDCA: 13–15 mg/kg+Feno: 160 mg (n = 20)	Primary endpoint (median at BL vs. week 48, respectively): ALP (351 vs. 175 U/L, $p < 0.0001$) Additional endpoints: AST (52 vs. 42 U/L, $p = 0.0032$) IgM (279 vs. 266 mg/dL, $p = 0.0076$)	Transient ↑ ALT/ AST > 2–5x ULN (n = 2, 10%) Renal insufficiency (n = 1, 5%), attributed to other causes and persisted after study concluded *Patient withdrawal*: severe ulcerative esophagitis that resolved after therapy (n = 1, 5%); severe heartburn (n = 1, 5%)
Fenofibrate; PBC (2010)[57]	Pilot study, UDCA: 600 mg (n = 4) vs. UDCA: 600 mg+Feno: 200 mg (n = 6)	Biochemical response (*P-value* reported vs. BL): ALP (−32.6%, $p = 0.012$) GGT (−44%, $p = 0.031$) ALT (−16.9%, $p = 0.029$) Total cholesterol (−9.5%, $p < 0.049$) Triglycerides (−25.6%, $p < 0.049$)	None
Fenofibrate; PBC and PSC (2021)[58]	Retrospective clinical study, UDCA: 13–15 mg/kg (PBC: n = 16; PSC: n = 11) vs.	Biochemical response: ALP (−76%, $p < 0.01$) ALP normalization (82%)	Not reported

TABLE 2. (*continued*)

PPAR agonist; condition (year)	Study design (NCT), treatment regimen (no. of patients treated)	Primary and secondary endpoints (study results)[a]	Adverse event profile[b]
	UDCA: 13–15 mg/kg+Feno: 145–160 mg (PBC: n = 16; PSC: n = 12)	ALT (−55%, $p < 0.01$) AST (−46%, $p < 0.05$) Triglycerides (−34%, $p = 0.06$) Bile acid response (vs. UDCA monotherapy): Total serum bile acids (−54%, ns), bile acid glucuronides (+2.1-fold; $p < 0.01$)	
Fenofibrate; PBC and PSC (2020)[46]	Retrospective Clinical Study, UDCA: 13–15 mg/kg (PBC: n = 18; PSC: n = 11) vs. UDCA: 13–15 mg/kg+Feno: 160 mg (PBC: n = 12; PSC: n = 8)	Biochemical response: ALP (PBC: −78%, $p < 0.05$; PSC: −86%, $p < 0.001$) ALP normalization (84%) ALT normalization (~80%) AST normalization (~70%) Bile acid response (vs. UDCA monotherapy): C4 (PBC: −49%; PSC: −24%,); PBC and PSC: −38% Total serum bile acids (PBC and PSC: −60%, ns) Serum primary bile acids (PBC and PSC: −78%, $p < 0.01$) Serum conjugated bile acids (PBC and PSC: −76%, $p < 0.01$)	None
Fenofibrate; PSC (2022)[59]	Placebo-controlled trial, UDCA: 13–15 mg/kg (n = 15) vs. UDCA: 13–15 mg/kg+Feno: 200 mg (n = 15)	Primary endpoint: ALP < 50% BL or normalization (66.7%, $p = 0.009$) ALP (−64.8%, $p = 0.004$) Additional endpoint: ALT (−52.8%, $p = 0.006$)	None
Fenofibrate; PSC (2019)[60]	Open-label pilot study (NCT01142323), UDCA: 0–1500 mg+Feno: 160 mg (n = 8)	Primary endpoint: ALP (290 vs. 165.5 IU/L, $p = 0.02$) Additional endpoint: ALT (108 vs. 75 IU/L, $p = 0.04$)	SCr (0.89 vs. 1.0, $p = 0.01$) Total bilirubin worsened leading to endoscopic retrograde cholangiopancreatography (n = 1, 12.5%), total bilirubin improved, and the patient continued Feno
Fenofibrate +bezafibrate; PBC (2021)[61]	Observational study, UDCA: 97.8% on unreported dose +Feno: 145–900 mg (n = 47) or Beza: 200–900 mg (n = 203) or	*Biochemical Response:* ALP (−41%, $p < 0.001$) ALP normalization (44.8%, $p < 0.001$) POISE criteria (61.2%, $p < 0.001$)	*Feno d/c*: renal impairment (n = 1, 2%); dyspepsia or GERD (n = 1, 2%); asthenia (n = 1, 2%); myalgia or bone pain (n = 1, 2%); hypertransaminasemia (n = 1, 2%); neutropenia (n = 1, 2%) Beza d/c: dyspepsia or GERD (n = 3, 1.5%); dizziness (n = 1, 0.5%); myalgia or bone pain (n = 1, 0.5%); depression (n = 1, 0.5%); pulmonary thromboembolism (n = 1, 0.5%)
Fenofibrate +bezafibrate; PSC (2018)[47]	Retrospective clinical study, UDCA: 15–20 mg/kg+Feno: 200 mg or Beza: 400 mg (n = 20)	Biochemical response (at month 3 vs. BL): ALP (−41%, $p = 0.0002$) GGT (−26%, $p = 0.001$) ALT (−38%, $p = 0.010$) AST (−18%, $p = 0.055$) ↓ pruritus ($p = 0.021$)	*Fibrate d/c*: aggravation of cholestasis, likely related to PSC progression (n = 3, 15%); gallbladder carcinoma (n = 1, 5%); cramps (n = 1, 5%); cardiologist decision (n = 2, 10%); inflammatory bowel disease flare (n = 1, 5%); gastric ulcer (n = 1, 5%); biliary stones (n = 2, 10%); acute cholangitis (n = 2; 10%)
Bezafibrate; PBC (2021)[62]	Retrospective clinical study, UDCA: (n = 3162) vs. UDCA+Beza: (n = 746)(Doses not reported)	Primary endpoint: All-cause mortality or need for liver transplantation (−67%, $p < 0.0001$ vs. UDCA) ↓ Liver-related mortality or liver transplantation ($p \leq 0.0016$ vs. UDCA)	~ 6% rate of permanent d/c of Beza (causes not specified)

TABLE 2. (*continued*)

PPAR agonist; condition (year)	Study design (NCT), treatment regimen (no. of patients treated)	Primary and secondary endpoints (study results)[a]	Adverse event profile[b]
Bezafibrate; PBC (2021)[63]	Prospective clinical study, UDCA: 13–15 mg/kg+OCA: 5–10 mg+Beza: 400 mg (n = 11)	Biochemical response (BL triple therapy vs. 1-y triple therapy): ALP (201 ± 56 vs. 112 ± 42 U/L, $p = 0.0005$) ALP normalization (70%) Bilirubin (11.6 ± 8.6 μmol/L vs. 8.7 ± 7.7 μmol/L, $p = 0.0026$) Bilirubin ≤ 0.6xULN (80%)	↑ ALT, grade 1 (n = 1, 9%) *Beza d/c*: myalgia (n = 1, 9%)
Bezafibrate; PBC (2018)[51]	Phase 3 (NCT01654731), UDCA: 15 mg/kg (median, n = 50) vs. UDCA: 15 mg/kg (median) +Beza: 400 mg (n = 50)	Primary endpoint: Normal serum levels of ALP, AST, ALT, total bilirubin, albumin, and a normal prothrombin index (31%, $p < 0.001$) Additional endpoint: ALP normalization (67%)	SCr levels (5% above BL) Stage 2 or 3 chronic kidney disease at year 2 (n = 4, 8% or n = 1, 2%, with a history of diabetes and hypertension) *Beza d/c*: aminotransferase > 5x ULN (n = 3, 6%); rhabdomyolysis with concomitant statin therapy (n = 1, 2%)
Bezafibrate; PBC (2018)[64]	Prospective clinical study, UDCA: 13–16 mg/kg+Beza: 400 mg (n = 48)	Biochemical response: Median ALP (2.4x to 1x ULN, $p < 0.001$) ALP normalization at year 1 (74%) Median pruritus visual analog scale (3.7 to 0, $p < 0.001$)	Liver transplant (n = 3, 6%) Death due to advanced liver disease (n = 1, 2%)
Bezafibrate; PBC (2015)[65]	Prospective clinical study, UDCA: 12–15 mg/kg (n = 14) vs. UDCA: 12–15 mg/kg+Beza: 400 mg (n = 13)	Primary endpoint: Mean ALP at year 8 (461 IU/L UDCA vs. 290 IU/L UDCA+ Beza, $p < 0.05$) Additional endpoint: Mean Mayo risk score at year 8 (1.42 UDCA vs. 0.91 UDCA+ Beza, $p < 0.05$)	Mean SCr at year 8 (0.56 vs. 0.94 mg/dL, $p < 0.05$) *Beza d/c:* ↑ SCr and worsening renal function that remained abnormal (n = 1, 8%); ↑ SCr and CK with muscle pain (n = 1, 8%)
Bezafibrate; PBC (2014)[66]	Prospective clinical study, UDCA: 13–16 mg/kg+Beza: 400 mg (n = 30)	Biochemical response: ALP (895 ± 95 U/L vs. 359 ± 38, $p < 0.001$) ALP normalization (54%) ALT (80 ± 7 vs. 51 ± 5 U/L, $p < 0.001$) GGT (384 ± 59 vs. 194 ± 29 U/L, $p < 0.001$) Cholesterol (315 ± 30 mg/dL vs. 274 ± 19 mg/dL, $p < 0.02$) Triglycerides (125 ± 13 mg/dL vs. 107 ± 13 mg/dL, $p < 0.01$)	*Beza d/c*: heartburn (n = 2, 7%); nausea and heartburn (n = 2, 7%)
Bezafibrate; PBC (2013)[48]	Prospective clinical study, UDCA: 10–13 mg/kg (n = 31) vs. UDCA: 10–13 mg/kg+Beza: 400 mg (n = 19)	Biochemical response: ↓ ALP ($p < 0.001$), ↓ GGT ($p < 0.001$), ↓ ALT ($p < 0.001$), ↓ IgM ($p < 0.001$), ↓ total cholesterol ($p < 0.005$), ↓ LDL ($p < 0.05$), ↓ triglycerides ($p < 0.001$) Additional endpoints: ↓ C4 ($p < 0.01$), ↓ FGF19 ($p < 0.05$), ↓ chenodeoxycholic acid ($p < 0.05$), ↓ deoxycholic acid ($p < 0.05$)	Not reported
Bezafibrate; PBC (2010)[67]	Prospective clinical study, UDCA: 900–1500 mg+Beza: 400 mg (n = 8)	Biochemical Response (pre-Beza vs. post-Beza, no *p*-values reported in this study): Mean ALP (201.2 U/L vs.98.4 U/L) ALP normalization (75%) Mean GGT (130 U/L vs.71.8 U/L)	None
Bezafibrate; PBC (2003)[68]	Prospective clinical study, UDCA: 600 mg (n = 11) vs. UDCA: 600 mg+Beza: 400 mg (n = 11)	*Biochemical Response:* ALP normalization (45%) ↓ ALP ($p < 0.01$) ↓ GGT ($p < 0.05$)	None
Bezafibrate; PBC and PSC (2021)[69]	Phase 3 (NCT02701166), Placebo (n = 36; 78% on unreported dose of UDCA) vs. Beza: 400 mg (n = 38; 82% on unreported dose of UDCA)	Primary endpoint: ≥ 50% reduction of itch intensity as measured on the visual analog scale after 21 d (45%, $p = 0.003$ vs. placebo) Additional endpoints:	↑ SCr (3% from BL, $p < 0.001$) *Beza d/c*: acute bacterial cholangitis and emergency endoscopic retrograde

TABLE 2. (*continued*)

PPAR agonist; condition (year)	Study design (NCT), treatment regimen (no. of patients treated)	Primary and secondary endpoints (study results)[a]	Adverse event profile[b]
		↓ total score of the 5D itch questionnaire ($p = 0.002$ vs. placebo) ALP (−35%, $p = 0.03$) GGT (−24%, $p < 0.001$) ALT (−21%, $p = 0.001$)	cholangiopancreatography (n = 1, 3%)
Bezafibrate; PBC and PSC (2006)[70]	Prospective clinical study, UDCA: 77% on unreported dose (PBC), 0–600 mg (PSC) +Beza: 400 mg (PBC: n = 22; PSC: n = 6)	Primary endpoint (reported as reduction index: postadministration/preadministration serum levels; PSC data did not reach statistical significance); ALP (PBC: 0.46 ± 0.05, $p < 0.0001$; PSC: 0.37 ± 0.08, ns) GGT (PBC: 0.62 ± 0.07, $p < 0.0001$; PSC: 0.66 ± 0.19, ns) IgM (PBC: 0.82 ± 0.04, $p < 0.0001$)	None
Bezafibrate; PSC (2015)[71]	Prospective Clinical Study, UDCA: 67% on unreported dose+Beza: 400 mg (n = 12)	Primary endpoint: ↓ ALP ($p < 0.01$) ↓ ALT ($p < 0.05$)	*Beza d/c:* allergy-like reaction (n = 1, 8%)
Bezafibrate; PSC (2010)[72]	Retrospective clinical study, UDCA: 0–900 mg+Beza: 400 mg (n = 7)	Primary endpoints (reported as mean reduction indexes): postadministration/ preadministration serum levels, no *p*-values reported in this study): ALP (0.69), GGT (0.83), AST (1.35), ALT (0.95) Reduction index < 1.0 for all hepatobiliary enzymes (n = 3, 43%) Normalization of all hepatobiliary enzymes (n = 2, 29%)	*Beza d/c:* ↑ hepatobiliary enzymes (n = 1, 14%)
Saroglitazar; PBC (2022)[73]	Phase 2 (NCT03112681), UDCA: 13.4 mg/kg (mean, n = 10) vs. UDCA: 13.4 mg/kg (mean) +Saro: 2 mg (n = 14) or 4 mg (n = 13)	Primary endpoint: ALP (2 mg: −50.1%, $p < 0.001$; 4 mg: -49%, $p < 0.001$) Additional endpoints: ALP normalization (2 mg, 50%, $p = 0.019$; 4 mg: 38.5%, $p = 0.046$) GGT (2 mg: −124.5 U/L LS mean, $p = 0.042$) Triglycerides (2 mg: −34.1 mg/dL LS mean, $p = 0.024$)VLDL (2 mg: −6.7 mg/dL LS mean, $p = 0.026$)	*Saro d/c:* ALT and AST > 5x BL (n = 2, 16% of 4 mg group); ALT > 3x BL and AST > 5x BL (n = 1, 8% of 4 mg group); ALT > 2x BL with stable AST (n = 1, 7% of 2 mg group)
Saroglitazar; PBC (2021)[74]	Proof of Concept, UDCA: 417 mg (mean)+Saro: 4 mg (n = 7)	Primary endpoint: ALP (−48%; $p = 0.003$) Additional endpoints: ALP normalization (71%) GGT (−60.8%; $p = 0.001$)	ALT = 2.6x BL at week 16 that worsened to 5-10x ULN after study ended (n = 1, 14%), resolved spontaneously at 1-year follow-up
Elafibranor; PBC (2024)[75]	Phase 3 (NCT04526665), Placebo (n = 53; 96% on unreported UDCA dose) vs. Ela: 80 mg (n = 108; 94% on unreported UDCA dose)	Primary endpoint: POISE criteria (51%, $p < 0.001$) Additional endpoint: ALP normalization (15%; $p = 0.002$)	SCr rise 25% above BL (n = 11, 10%) *Ela d/c:* CK > 5x ULN with or without symptoms or > 3x ULN with symptoms (n = 4, 4%); ↑ aminotransferases (> 3x BL if BL was elevated or > 3–5x ULN if BL was normal) or bilirubin > 2x ULN or both (n = 1, 0.9%)
Elafibranor; PBC (2021)[76]	Phase 2 (NCT03124108), UDCA: 14.19 mg/kg (mean, n = 15) vs. UDCA: 14.19 mg/kg (mean) +Ela: 80 mg (n = 15) or 120 mg (n = 15)	Primary endpoint: ALP (80 mg: −48.3%, $p < 0.001$; 120 mg: −40.6%, $p < 0.001$) Additional endpoints: GGT (80 mg: −37.1%, $p < 0.001$; 120 mg: −40%, $p < 0.01$) C4 (80 mg: −7.8 nmol/L, $p = 0.009$; 120 mg: −9.65 nmol/L, $p = 0.096$; median change from BL)	SCr (8 μmol/L LS mean, 120 mg group, $p = 0.005$) Mild and reversible ↑ SCr (n = 1, 7% of 120 mg group) Aminotransferases > 3x BL at end of treatment visit (n = 1, 7% of 80 mg group) ↑ aminotransferases at last on-treatment visit (n = 1, 7% of

TABLE 2. (*continued*)

PPAR agonist; condition (year)	Study design (NCT), treatment regimen (no. of patients treated)	Primary and secondary endpoints (study results)[a]	Adverse event profile[b]
		Cholesterol (80 mg: −0.4 mmol/L LS mean, $p = 0.040$) LDL (80 mg: −0.3 mmol/L LS mean, $p = 0.044$) Triglycerides (120 mg: −0.3 mmol/L LS mean, $p = 0.032$) hsCRP (80 mg: −0.49 mg/L, $p < 0.001$; 120 mg: −0.68 mg/L, $p = 0.049$; geometric mean ratio) IgM (80 mg: −0.5 g/L, $p = 0.024$; 120 mg: −0.6 g/L, $p = 0.012$; LS mean)	120 mg group), likely due to suspected flare of autoimmune hepatitis *Ela d/c:* ischemic stroke 24 hours after first intake (n = 1, 7% of 120 mg group)
Seladelpar; PBC (2024)[77]	Phase 3 (NCT04620733), UDCA: 14.9 mg/kg (mean, n = 65) vs. UDCA: 15 mg/kg (mean)+Sel: 10 mg (n = 128)	Primary endpoint: POISE criteria (61.7%, $p < 0.001$) Additional endpoints: ALP normalization (25%, $p < 0.001$) Peak Pruritus Numerical Rating Scale (−1.5 points LS mean, $p = 0.005$; in patients with moderate to severe pruritus at BL)	ALT or AST > 3x ULN (n = 9, 7%) CK > 3x ULN (n = 2, 2%) Liver enzymes > 5x ULN with amoxicillin use (n = 1, 0.8%), leading to Sel d/c, then Sel was readministered without adverse effects
Seladelpar; PBC (2023)[78]	Trial Extension (NCT03301506), UDCA: 15 mg/kg (mean)+Sel: 2 mg (n = 10), 5 mg (n = 46), or 10 mg (n = 50) at BL with dose escalation based on biochemical response	Primary endpoint: Safety and tolerability Additional endpoints: (no *p*-values in this study, change from BL to year 2) POISE criteria (79%) ALP (−49.8%) ALP normalization (42%) GGT (−45.6%) ALT (−39.3%) AST (−19.2%) Total bilirubin normalization (43%)	Doses were not reported for the following events: *Sel d/c:* total bilirubin > 1.5x BL (n = 1, 0.9%); systemic scleroderma due to pre-existing condition (n = 1, 0.9%); malignant neoplasm (n = 1, 0.9%); ↑ total bilirubin, grade 2, and AST, grade 2, with rheumatoid arthritis flares and nonsteroidal anti-inflammatory drug use (n = 1, 0.9%)
Seladelpar; PBC (2023)[79]	Phase 3 Early termination (NCT03602560), UDCA: 15.3 mg/kg (mean, n = 87) vs. UDCA: 15.3 mg/kg (mean)+Sel: 5 mg (n = 89) or 10 mg (n = 89)	Primary endpoint: POISE criteria (5 mg: 57.1%, $p < 0.0001$; 10 mg: 78.2%, $p < 0.0001$) Additional endpoints: ALP (5 mg: −35.7%, 5 mg, $p < 0.0001$; 10 mg: −44.2% $p < 0.0001$) ALP normalization (10 mg: 27.3%, $p < 0.0001$) Peak Pruritus Numerical Rating Scale (10 mg: −3.14 mean decrease from BL, $p = 0.02$) ALT normalization (5 mg: 52%, 10 mg: 50%)	*Sel d/c:* pruritus (n = 1, 1% of 5 mg group); adenoid cystic carcinoma (n = 1, 1% of 5 mg group); pruritus, insomnia and rheumatoid arthritis (n = 2, 2% of 10 mg group)
Seladelpar; PBC (2022)[80]	Phase 2 (NCT02955602), UDCA: 15 mg/kg (mean)+Sel: 2 mg (n = 11) or 5 mg (n = 53) or 10 mg (n = 55)	Primary endpoint: ALP (2 mg: −33%, $p = 0.01$; 5 mg: −40%, $p < 0.0001$; 10 mg: −44%, $p < 0.0001$) Additional endpoints: ALP normalization (10 mg: 33%, $p < 0.05$) Total bilirubin (10 mg: −7%, $p = 0.02$) ALT (5 mg: −30.9%, $p < 0.0001$; 10 mg: −31.3%, $p < 0.0001$) AST (5 mg: −12.8%, $p = 0.01$; 10 mg: −14%, $p < 0.0001$) GGT (2 mg: 32.3%, $p = 0.01$; 5 mg: −34.2%, $p < 0.0001$; 10 mg: −32.5%, $p < 0.0001$) 5′-nucleotidase (2 mg: −23.9%, $p = 0.04$; 5 mg: −30.3%, $p < 0.0001$; 10 mg: −22.8%, $p < 0.0001$) C4 (5 mg: −4.5 ng/mL, $p < 0.04$; 10 mg: −7.2 ng/mL, $p < 0.04$) Mean pruritus visual analog scale (5 mg: −10 mm, $p \leq 0.009$; 10 mg: −17 mm; $p \leq 0.009$)	Doses were not reported for the following events: CK > 2.5x ULN (n = 4, 3%), all with clinical explanations and/or returned to normal while on Sel Transient increases in bilirubin (n = 2, 2%) ↑ ALT with worsening of rheumatoid arthritis and ibuprofen use (n = 1, 0.8%) ↑ ALT and AST concomitant with rifampicin use for pruritus, (n = 2 total, 2%; n = 1 led to Sel d/c, n = 1 resolved without intervention) *Sel d/c:* gastroesophageal reflux, grade 1 (n = 1, 0.8%); pruritus, grade 1 (n = 1, 0.8%); pneumonia, grade 3 (n = 1, 0.8%); ↑ ALT, grade 2 and AST, grade 3, concomitant with rifampicin use (n = 1, 0.8%)

TABLE 2. (*continued*)

PPAR agonist; condition (year)	Study design (NCT), treatment regimen (no. of patients treated)	Primary and secondary endpoints (study results)[a]	Adverse event profile[b]
Seladelpar; PBC (2017)[81]	Phase 2 Early termination (NCT02609048), UDCA: 16 mg/kg (mean, n = 13) vs. UDCA: 14–15 mg/kg (mean) +Sel: 50 mg (n = 13) or 200 mg (n = 12)	Primary endpoint: ALP (50 mg: −53%, $p < 0.0001$; 200 mg: −63%, $p < 0.0001$) Additional endpoints: C4 (50 mg: −54.8%, $p = 0.0060$; 200 mg: −77%, $p = 0.0022$) FGF-19 (50 mg: −49%, $p = 0.047$; 200 mg: −78.1%, $p = 0.006$)	↑ ALT, grade 2, (n = 2, 17% of 200 mg group) *Sel d/c:* ↑ ALT, grade 3, (n = 1, 8% of 50 mg group; n = 2, 17% of 200 mg group);↑ SCr and muscle pain, (n = 1, 8% of 200 mg group)

[a]Endpoints reported for data with significance ($p \leq 0.05$), not including normalization data or POISE criteria.
[b]Safety data reported for events related to liver and kidney function, and all events that led to drug discontinuation or withdrawal.
Abbreviations: Beza, bezafibrate; BL, baseline; C4, 7α -hydroxy-4-cholesten-3-one; CK, creatine phosphokinase; Ela, elafibranor; Feno, fenofibrate; hsCRP, high sensitivity C-reactive protein; LS, least squares; ns, not significant; OCA, obeticholic acid; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; PSC, primary sclerosing cholangitis; Saro, saroglitazar; SCr, serum creatinine; Sel, seladelpar; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.
Liu et al.[52]
Hegade et al.[53]
Cheung et al.[54]
Han et al.[55]
Levy et al.[56]
Liberopoulos et al.[57]
Gallucci et al.[58]
Ghonem et al.[46]
Hatami et al.[59]
Abdalla et al.[60]
Reig et al.[61]
Lemoinne et al.[47]
Tanaka et al.[62]
Smets et al.[63]
Corpechot et al.[51]
Reig et al.[64]
Hosonuma et al.[65]
Lens et al.[66]
Honda et al.[48]
Hazzan et al.[67]
Kanda et al.[68]
de Vries et al.[69]
Kita et al.[70]
Mizuno et al.[71]
Mizuno et al.[72]
Vuppalanchi et al.[73]
Vuppalanchi et al.[74]
Kowdley et al.[75]
Schattenberg et al.[76]
Hirschfield et al.[77]
Mayo et al.[78]
Hirschfield et al.[79]
Bowlus et al.[80]
Jones et al.[81]

Elafibranor

Elafibranor is a dual PPARα and PPARδ agonist that recently received accelerated approval by the FDA as a second-line treatment for PBC[82]

In PBC, a phase 2 randomized, double-blind, placebo-controlled study evaluated elafibranor (80 mg/d, n = 15; and 120 mg/d, n = 15) in subjects with an incomplete response to UDCA and found significant reductions in serum ALP levels versus placebo.[76] In addition, serum markers of inflammation and immune reactivity, for example, high sensitivity C reactive protein and IgM, were significantly reduced in the elafibranor-treated group, along with circulating levels of the bile acid precursor C4.[76] The ELATIVE trial, a 52-week phase 3 clinical trial of elafibranor (80 mg/d) in PBC (n = 108) demonstrated that the primary endpoint (ALP < 1.67 x upper limit of normal with an ALP reduction of ≥ 15% from baseline and normal total bilirubin, termed the POISE criteria) was achieved in 51% of elafibranor-treated study subjects versus 4% for placebo.[75] The response to elafibranor treatment appeared as early as 4 weeks after initiation of treatment, and ALP normalization was achieved in 15% of subjects.

In June 2024, elafibranor (IQIRVO) received accelerated approval by the FDA for PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as monotherapy for those unable to tolerate UDCA.[82] It is important to understand that the current regulatory framework for accelerated FDA approval of elafibranor as second-line therapy for people living with PBC, which is based on serum surrogate endpoints, requires the verification of long-term clinical benefit through confirmatory trials. The required post-accelerated approval clinical trial to study the long-term effects of elafibranor (80 mg/d) for people living with PBC is recruiting throughout the United States and abroad (NCT06016842; ELFIDENCE). This clinical trial will assess the event-free survival of subjects treated with elafibranor versus placebo to determine the clinically relevant endpoints of time to transplantation/death.

In PBC, 2 additional studies of elafibranor are recruiting: (1) a phase 3 study evaluating serum ALP normalization in the United States and abroad (NCT06383403); (2) a phase 4 study to evaluate its everyday efficacy and safety in the United States (NCT06447168).

In PSC, an active phase 2 study (NCT05627362) is testing the efficacy of elafibranor in centers throughout the United States, Canada, and Europe.

Seladelpar

Seladelpar is a PPARδ agonist that recently received accelerated approval by the FDA as a second-line treatment for PBC[83]

In PBC, a phase 2 trial conducted with seladelpar (50 or 200 mg/d) was terminated early due to 3 cases of reversible, asymptomatic increases in serum ALT of 5–20 x upper limit of normal.[81] However, clinically relevant reductions in ALP in other studies led to a dose-finding phase 2 study (n = 119) using lower doses (2, 5, and 10 mg/d). Normalization of serum ALP levels was observed in 31% of study subjects (10 mg/d cohort) as early as week 12, while dose-dependent reductions in serum C4 levels were observed in the 5 and 10 mg/d cohorts.[80]

The ENHANCE study, a placebo-controlled phase 3 study of adjunct seladelpar (5 or 10 mg/d) in PBC (n = 178), reported improvements in serum liver biochemistries after 3 months (5 and 10 mg/d with significantly greater reductions in serum ALP and pruritus in the 10 mg/d cohort,[79] although the study was terminated early due to hepatotoxicity concerns in an unrelated concurrent trial for metabolic-associated steatohepatitis. Reductions in serum C4 and IgM were also found in the seladelpar-treated group versus placebo. Furthermore, significant decreases in total serum bile acids and the major glycine-conjugated primary bile acids, for example, glycochenodeoxycholic acid and glycocholic acid, as well as significant reductions in serum IL-31, a pruritogenic cytokine, were reported in the seladelpar group (10 mg/day).[84] A 2-year study was subsequently conducted to test the long-term safety and efficacy of seladelpar (5 and 10 mg) in people living with PBC.[78] Seladelpar achieved serum ALP normalization in 23%–26% of subjects by year 1 and in 42% of subjects by year 2, in addition to reductions in serum ALT and GGT.[78]

The RESPONSE study, a phase 3 clinical trial of seladelpar (10 mg/d), was completed in PBC (n = 128).[77] Just over 60% of seladelpar-treated subjects met the primary endpoint (POISE criteria) at 12 months versus 20% in the placebo group, and normalization of ALP levels was observed in 25% of the seladelpar-treated group versus 0% for placebo. Furthermore, the seladelpar group had greater improvement in pruritus as determined by the numerical rating scale (NRS) score and serum IL-31 levels.[77]

In August 2024, seladelpar (LIVDELZI) received accelerated approval by the FDA for PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as monotherapy for adults unable to tolerate UDCA.[83] Similar to the requirements for elafibranor, the accelerated approval pathway from the FDA currently requires confirmatory trials for seladelpar to demonstrate improvement in outcomes such as transplant-free survival and death. As such, the phase 3/4 AFFIRM study (NCT06051617) is recruiting people living with PBC in the United States and abroad to determine the clinically relevant endpoints of time to transplantation/death in subjects treated with seladelpar versus placebo.

In PBC, 2 additional clinical trials investigating seladelpar are recruiting: (1) a phase 1 study focused on hepatic impairment throughout the United States and abroad (NCT04950764); (2) a phase 3 study investigating serum ALP normalization in the United States (NCT06060665).

In PSC, a phase 2 study (NCT04024813) was completed in centers across the United States, Canada, and Poland; however, the results are not currently available.

EFFECTS OF PPAR AGONISTS ON PRURITUS

Pruritus is commonly reported in people living with chronic cholestatic liver diseases, and it can negatively impact their overall QOL due to fatigue, disturbances in sleep, and the inability to work. In a study of PSC (n = 137), pruritus and fatigue were reported in 38% and 71% of study subjects, with symptoms reported to be

worse after 7 PM,[85] indicating the potential interference with sleep. In PBC, an observational study found that 81% of individuals (n = 211) reported pruritus, with 37% of those classified as having clinically significant itch (PBC-40 score ≥ 7).[86] The PBC-40 scores for individuals with clinically significant itch were consistent with scores from the 5-D itch scale, and these individuals reported the highest level of fatigue (PROMIS fatigue instrument) and scored worse on all QOL assessments. Of note, only 50% of people with clinically significant itch were receiving treatment.[86] Such data suggests a clear need for greater attention to this important symptom. This can first be addressed through more intentional inquiries during routine clinical visits and early institution of currently available antipruritic therapies. For those with inadequate responses to existing approaches, the introduction of newer therapies must be considered.

Importantly, PPAR agonists have recently gained attention for their demonstrated reductions in pruritus. Although earlier studies of fenofibrate[52,56] and bezafibrate[51] were not designed to investigate the impact on pruritus, more recent clinical trials for PPAR agonists have included pruritus as a secondary endpoint. Notably, the fibrates for the itch trial (termed FITCH) held pruritus reduction as the primary study endpoint. Among study subjects with moderate to severe pruritus (≥ 5 on visual analog scale, VAS), 55% and 41% of subjects with PBC or PSC, respectively, reported ≥ 50% reduction on VAS after 21 days of bezafibrate treatment (400 mg/d) versus 11% in the placebo arm.[69] Furthermore, the median VAS decreased from 7.3 at baseline to 4.0 at day 21 of treatment and returned to 7.0 after discontinuation of bezafibrate, demonstrating its efficacy in reducing cholestatic itch.

In a phase 2 trial of saroglitazar, no worsening of pruritus was reported based on the PBC-40 questionnaire, along with nonsignificant changes in QOL scores.[73] No assessment could be made in the smaller study of saroglitazar because only 1 out of 7 subjects reported pruritus at baseline.[74] More information is needed to understand the role of saroglitazar in pruritus.

Elafibranor did not significantly change the least-squares mean change on the NRS in study subjects with moderate to severe pruritus (≥ 4 on NRS) at baseline through week 24 or 52 in the ELATIVE trial.[75] However, changes from baseline in the itch domain of PBC-40 and total score on the 5-D itch scale appeared to favor elafibranor over placebo.[75] Similarly, elafibranor treatment trended toward favorable improvements in VAS and the PBC-40 (itch domain) scores in subjects who reported pruritus at baseline in the phase 2 trial.[76]

In the RESPONSE trial of seladelpar, subjects with moderate to severe pruritus at baseline (≥ 4 on NRS) treated with seladelpar showed significant reductions from baseline versus placebo-treated subjects (−3.2 vs. −1.7 points) at month 6 ($p = 0.005$).[77] Reduction in itch also appeared to be greater in seladelpar-treated subjects versus placebo using the 5-D itch total score (excluding direction) at month 12 in subjects with moderate to severe pruritus at baseline.[77] Similar results were found in the ENHANCE trial where significant decreases in NRS scores, but not PBC-40, were found in the seladelpar (10 mg/d) group versus placebo at month 3 in subjects with moderate to severe pruritus at baseline (≥ 4 on NRS).[79] This downward trend was maintained through month 6; however, the effect was no longer statistically significant likely due to the decreased number of subjects.[79] Significant and sustained decreases in pruritus from baseline were also found in a phase 2 trial of seladelpar (5 or 10 mg/d),[80] using the VAS over 1 year. Importantly, changes in VAS score significantly correlated with total 5-D itch (r = 0.6635) and PBC-40 itch domain (r = 0.6015) scores.[87] Subjects also reported improved sleep after 1 year of seladelpar treatment according to 5-D itch and PBC-40 responses, suggesting that seladelpar was effective in reducing markers of cholestasis and improving QOL.

Overall, the effects of PPAR agonists on pruritus are encouraging, although their long-term effects on pruritus have not been determined and it is unclear whether improvements in cholestatic itch will be sustained ≥ 1 year. Nevertheless, as described above, significant reductions in pruritus have been found following bezafibrate and seladelpar treatment, whereas saroglitazar and elafibranor do not appear to worsen itch. More data is needed to elucidate the effect of fenofibrate on pruritus. However, the use of different methods to evaluate pruritus, for example, VAS, PBC-40, or NRS, and different values to define clinically significant itch, make it difficult to directly compare the efficacy among PPAR agonists in reducing cholestatic itch.

While it is critical to understand self-reported pruritus intensity through the above tools, it may also be advantageous to further study the role of candidate pruritogenic cytokines, such as serum IL-31 levels, in cholestatic itch. Recently, a post hoc analysis of phase 3 data reported dose-dependent reductions in serum IL-31 in subjects treated with seladelpar (5 and 10 mg/d), which correlated with pruritus NRS (r = 0.44 and r = 0.54).[84] However, the discrepancy between the major reduction in serum IL-31 and the modest reduction in pruritus in the group that responded to seladelpar raises questions as to the direct role of IL-31 in the pathophysiology of seladelpar-induced itch reduction.[88] Head-to-head comparisons of antipruritic efficacy between newer PPAR agonists and older fibrates, such as the pan-PPAR agonist bezafibrate, which was successfully studied in the FITCH trial designed to evaluate pruritus efficacy, are currently lacking.

FUTURE COMBINATION THERAPY: UDCA, OCA, AND A PPAR AGONIST?

Since its accelerated FDA approval in May 2016, OCA has been a second-line therapeutic option for people living with PBC that has shown improvements in surrogate endpoints in clinical trials of PBC[15,89,90] despite the common adverse effects of pruritus and fatigue.[91] In PBC, a retrospective study found that treatment with dual therapies (UDCA+OCA, n = 86 or UDCA+fibrate, n = 250) showed similar biochemical improvements; however, dual therapy with a fibrate led to significantly greater ALP reductions, while OCA dual therapy more effectively decreased transaminase values. Interestingly, pruritus, the most common side effect reported in the OCA dual therapy group, was not reported in the fibrate dual therapy group.[61] Similarly, a multicenter evaluation of second-line therapies found that people living with PBC achieved similar biochemical responses at month 12 when treated with UDCA+OCA (n = 349) or UDCA+fibrate (n = 108), although the magnitude of ALP reduction was greater with fibrate dual therapy and ALT normalization was more often achieved with OCA dual therapy.[92] Second-line therapy discontinuation due to itch occurred only in individuals treated with adjunct OCA, and the odds of itch improvement were ~3-fold greater with fibrate dual therapy compared to OCA. Notably, neither treatment was found to be superior; rather, baseline values of ALP and ALT and history of pruritus influenced the probability that an individual would respond to either OCA or fibrates,[92] presenting a possible evidence-based approach to second-line treatment selection.

For the sizeable subset of people who do not adequately respond to second-line therapy with PPAR agonists, triple therapy, for example, UDCA+OCA+fibrate could be an alternative option. Triple therapy significantly reduced serum ALP and bilirubin levels with higher likelihoods of achieving ALP, GGT, and ALT normalization compared to dual therapy in a retrospective study (n = 58) of high-risk individuals with PBC who did not previously respond to UDCA with OCA or with fibrates.[93] Importantly, adding a fibrate to dual UDCA+OCA regimens resulted in significant improvements in pruritus, and no individuals reported myalgia after fibrate introduction. Lastly, adding bezafibrate to existing dual therapy of UDCA+OCA in persons living with PBC (n = 13) significantly reduced ALP and bilirubin compared to dual therapy alone; however, 3 individuals developed myalgia after bezafibrate introduction.[63] Although more studies are needed to elucidate the safety of triple therapy, these data support the potential utility of triple therapy for persons living with PBC who do not experience a therapeutic response to UDCA as a candidate third-line regimen and suggest that combining drugs from different therapeutic classes may have additive benefits to treat PBC via multiple mechanistic pathways.

SAFETY PROFILE OF PPAR AGONISTS IN PBC AND PSC

Overall, PPAR agonists have an excellent safety profile in human studies. Side effects reported in phase 3 trials for elafibranor and seladelpar that were significantly greater than the placebo groups include gastrointestinal symptoms (abdominal pain, nausea, and abdominal distension), elevations in aminotransferases, myalgias with and without elevations in creatine phosphokinase levels, mild increases in serum creatinine and rare episodes of rhabdomyolysis usually in association with statins. Increases in pruritus have also been reported. Dose reductions reversed most of these abnormalities. There is no data to guide clinicians in the monitoring for potential myositis and serum creatinine changes, though monitoring with serum creatine phosphokinase and serum creatinine during the first 6–12 months may be considered in newly treated individuals. Further details of the safety events are reported (Table 2).

Competition for the cytochrome P450 3A4 enzyme may increase sensitivity to statin toxicity, particularly with hydrophobic drugs such as lovastatin. However, with close monitoring, it is possible to safely administer statins and PPAR agonists.[94] The label for elafibranor recommends monitoring people receiving concurrent statins for signs or symptoms of muscle injury.[82] Furthermore, all people receiving elafibranor should be assessed for myopathy, with consideration of creatine phosphokinase assessment periodically or if there is any new or worsening myalgia.

The use of PPAR agonists in refractory cholestasis has been almost exclusively studied in precirrhotic individuals or in those with compensated cirrhosis. Clinical studies of seladelpar have shown similar safety profiles in individuals with PBC and compensated cirrhosis[78,80] and cirrhosis according to specific trial criteria[77] versus non-cirrhotic individuals. Due to the potential for altered metabolism and transporter function, further studies are needed before use in decompensated cirrhosis (Child-Pugh Class B and C) can be considered. As such, their long-term safety and tolerability in decompensated cirrhosis, as well as their impact in preventing disease progression to decompensated cirrhosis and liver transplantation, have yet to be evaluated.

SPECIAL POPULATIONS

Based on currently available information, individuals with decompensated cirrhosis should not receive fibrates or newer PPAR agonists, given the lack of safety data and the risk of hepatotoxicity. Further studies will be necessary to determine the potential use, the optimal dosing, and the timing, of these medications in such situations. Regarding pregnancy and breastfeeding, the label for elafibranor states that the drug may cause harm in pregnancy based

on preclinical studies, though there is insufficient data from human pregnancies for a full assessment of risk.[82] Furthermore, elafibranor is a weak inducer of CYP3A and therefore the drug may reduce systemic levels of hormonal contraceptives, thus increasing the risk of contraceptive failure. There is little data to guide clinicians on the safety of lactation while on PPAR agonists, but the label for elafibranor advises women not to breastfeed within 3 weeks of the last dose of the drug.

THE ROAD AHEAD

The accelerated approval by the FDA of elafibranor and seladelpar as second-line agents for PBC has ushered in a new era in treating cholestatic liver diseases. Building on clinical and translational research,[95] these recent developments suggest that PPAR agonist therapies are an effective and safe approach to address cholestasis, with the additional potential to improve QOL through reduction in pruritus. This represents a powerful alignment of clinician and patient goals through a single pharmacotherapeutic approach. However, multiple challenges remain that have yet to be addressed.

First, it must be acknowledged that the efficacy of PPAR therapy is currently supported only by way of surrogate endpoints, namely improvement in serum markers of cholestasis. Furthermore, in the recently published phase 3 studies neither elafibranor or seladelpar significantly improved markers of fibrosis including liver stiffness measurement and the enhanced liver fibrosis score by 52 weeks.[75,77] Longer-term studies are therefore required to measure the effect of these drugs on markers of liver fibrosis and, ultimately, on clinical outcomes. The regulatory accelerated approval process highlights the importance of this need and serves as a reminder that full approval for these drugs is conditional on additional studies to determine the impact on patient outcomes such as transplant-free survival. The recent controversy surrounding OCA, where the pivotal confirmatory study was unable to document clinical outcome improvements,[16] resulting in the FDA's decision to decline full approval of OCA for the treatment of PBC in November 2024, reinforces the notion that reduction in serum markers of cholestasis must ultimately be followed by demonstrated improvement in hard endpoints. This reality is relevant not only for second-line drug considerations in PBC but also for PSC, where no effective therapy is known to date and where surrogate endpoints are currently the standard approach in clinical trials.

Second, a substantial minority of people receiving second-line PPAR agonists for PBC will not have an adequate response to dual therapy with UDCA, as measured by POISE criteria. This was noted in the elafibranor and seladelpar phase 3 trials, where the nonresponse rates ranged from 39-49% after a full year of treatment. In addition to the ongoing studies of triple therapy combining UDCA, OCA, and PPAR agonists, biomarkers to predict response to PPAR agonist therapy will be important to ascertain who will need additional therapeutic options. Prediction tools using existing clinical variables and innovative immune-based or genetic predictors should be explored and developed. For example, an early and significant decrease in serum ALP (eg, at 4 wk) should be further studied as a prediction tool for response to PPAR agonist therapy and may help guide the development of personalized treatment algorithms. Ultimately, such evidence-based treatment algorithms will be necessary to guide clinicians in this respect in PBC. Likewise, in PSC, novel candidate predictors of biochemical response to PPAR agonists should be studied and analyzed in the context of ongoing clinical trials. Improvements in surrogate indicators of fibrosis, including liver stiffness measurements by transient elastography and serum markers such as enhanced liver fibrosis and PRO-C3, should also be routinely reported.

Third, the immunomodulatory action of PPAR agonists is not fully understood and will benefit from significant additional research, particularly given the autoimmune and immune-mediated nature of PBC and PSC, respectively.[95,96] The degree to which current PPAR agonists, each with a different receptor subunit activity profile, can effectively modulate immune cytokine pathways will be highly informative and help determine the impact of these drugs on inflammation and fibrosis, as well as potential extrahepatic manifestations of these cholestatic diseases.

CONCLUSIONS

PPAR agonists are a major new second-line treatment approach for treating PBC and a potential novel treatment approach for PSC. Although the primary endpoint of reduction in serum biochemical cholestatic markers has been achieved in multiple trials for PBC, it is important to note that such serum markers are surrogate endpoints of efficacy. While elevated serum ALP levels are associated with a 2- to 2.5-fold higher risk of liver transplantation or death,[97] long-term studies will be required to carefully assess the impact of PPAR agonists on clinical events such as transplant-free survival, particularly given the accelerated approval framework currently employed by regulatory agencies such as the FDA. In addition, measuring the impact of PPAR agonists in PSC through phase 3 studies remains challenging due to the lack of accepted clinical trial endpoints. Furthermore, the comparative efficacy of each PPAR agonist on bile acid metabolism, cholestatic markers, clinical outcomes, and QOL remains to be determined. Nonetheless, the results of published clinical studies to date are very encouraging and demonstrate a marked impact of PPAR agonists, findings that strengthen the role of this drug category in chronic cholestasis.

CONFLICTS OF INTEREST

Gina Gallucci is employed by Boehringer Ingelheim. James Boyer serves on clinical events committees for IPSEN. He received grants from Mirum Pharmaceuticals.

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