

RESEARCH MONOGRAPH . COMPOUND PROFILE

Elafibranor

A first-in-class dual PPARalpha/delta agonist developed by Genfit for hepatic steatoinflammatory and cholestatic liver diseases, granted FDA accelerated approval in June 2024 as Iqirvo for the treatment of primary biliary cholangitis in adults with inadequate response or intolerance to ursodeoxycholic acid.

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COMPOUND CLASS	Dual peroxisome proliferator-activated receptor alpha/delta (PPARalpha/delta) agonist with additional PPARGgamma activity

ABSTRACT

Elafibranor (GFT505) is a synthetic phenoxyalkanoic acid derivative and dual agonist of the peroxisome proliferator-activated receptor alpha (PPARalpha) and peroxisome proliferator-activated receptor delta (PPARdelta), with additional lower-potency agonist activity at the peroxisome proliferator-activated receptor gamma (PPARGamma). The compound activates PPARalpha with an EC50 of approximately 45 nanomolar and PPARdelta with an EC50 of approximately 175 nanomolar, producing a composite pharmacological profile that modulates hepatic fatty acid beta-oxidation, triglyceride metabolism, high-density lipoprotein cholesterol, bile acid synthesis and transport, glucose homeostasis, and macrophage-mediated hepatic inflammation through coordinated transcriptional regulation at both receptor subtypes. Elafibranor and its principal active metabolite GFT1007, formed by hydrolysis of the parent compound, both contribute to the pharmacological activity. The compound was discovered and initially developed by Genfit S.A. (Lille, France) for the treatment of nonalcoholic steatohepatitis (NASH), advancing through a Phase 2b trial (GOLDEN-505) in 274 patients that produced a post-hoc signal for NASH resolution without fibrosis worsening at the 120 mg daily dose, and into the Phase 3 RESOLVE-IT trial in over 1,000 patients, which was terminated in 2020 following an interim futility analysis that failed to demonstrate statistically significant separation from placebo on the primary endpoint. Development subsequently pivoted to primary biliary cholangitis (PBC), where elafibranor received FDA Breakthrough Therapy Designation in 2019 and demonstrated robust efficacy in the Phase 3 ELATIVE

trial: 51 percent of patients receiving elafibranor 80 mg daily achieved a biochemical cholestasis response at week 52, compared to 4 percent on placebo, with alkaline phosphatase normalization in 15 percent of treated patients versus none on placebo. On June 10, 2024, the United States Food and Drug Administration granted accelerated approval to elafibranor (trade name Iqirvo, marketed by Ipsen) for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults with inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. European Union authorization followed in September 2024, and the United Kingdom National Institute for Health and Care Excellence (NICE) recommended elafibranor for National Health Service use in October 2024. Pharmacokinetics are characterized by high plasma protein binding (approximately 99.7 percent), a large apparent volume of distribution (approximately 4,731 liters), a long elimination half-life of the parent compound (approximately 60 to 70 hours), and metabolism of GFT1007 through CYP2C8, UGT1A3, and UGT2B7. The compound is generally well tolerated at the approved 80 mg daily dose; the principal adverse events in controlled trials were gastrointestinal (abdominal pain, diarrhea, nausea, and vomiting, each occurring in approximately 11 percent of treated patients versus 2 to 9 percent on placebo), weight gain, arthralgia, and musculoskeletal complaints including rare myopathy and rhabdomyolysis. Dose-dependent hepatotoxicity has been observed at supratherapeutic doses (exceeding 120 mg daily), with transaminase elevations above 5 times the upper limit of normal in approximately one-third of healthy volunteers at those exposures. The compound is contraindicated in decompensated cirrhosis and complete biliary obstruction and carries a warning for embryo-fetal toxicity. This monograph reviews the chemistry,

synthesis, and structural class of elafibranor; the PPAR-mediated molecular pharmacology; the comprehensive pharmacokinetic profile including the GFT1007 active metabolite; the preclinical evidence in rodent models of steatohepatitis, fibrosis, and cholestasis; the clinical evidence base across NASH and PBC indications; sourcing and quality verification; reconstitution and handling; stack interactions and combinations; adverse events and safety signals; and a comparative assessment of five alternative agents (obeticholic acid, seladelpar, bezafibrate, fenofibrate, and saroglitazar) against elafibranor on five competency standards.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

International Nonproprietary Name: Elafibranor.

Marketed name: Iqirvo (Ipsen; United States, European Union, United Kingdom).

Development code: GFT505 (Genfit S.A.). The development code is the canonical identifier in the early pharmacology and Phase 1/2 literature and the identifier under which the GOLDEN-505 and RESOLVE-IT trials were initiated [1, 2].

Chemical Abstracts Service registry number: 923978-27-2 (free acid form).

International Union of Pure and Applied Chemistry name: 2-[2,6-dimethyl-4-[(E)-3-[4-(methylsulfanyl)phenyl]-3-oxoprop-1-enyl]phenoxy]-2-methylpropanoic acid. The compound is a phenoxyisobutyric acid derivative bearing a (E)-chalcone substituent with a 4-(methylthio)phenyl ketone moiety.

Other identifiers: SureCN815512; UNII: ZL9C06E60Q.

1.2 Structural class and chemistry

Elafibranor belongs to the phenoxyalkanoic acid structural class, sharing the 2-aryloxy-2-methylpropanoic acid (fibrate) pharmacophore with the clinically established PPAR ligands fenofibrate, bezafibrate, and gemfibrozil. The compound is distinguished from first-generation fibrates by the (E)-chalcone linker connecting the 2,6-dimethylphenoxy core to a 4-(methylthio)phenyl ketone, a structural feature that confers dual PPAR α /delta selectivity and substantially higher receptor potency than the classical fibrate scaffold [3].

Molecular formula: C₂₂H₂₄O₄S.

Molecular weight: 384.49 g/mol.

Physical properties: White to off-white crystalline powder. The compound is practically insoluble in water owing to the lipophilic chalcone moiety and the free carboxylic acid; formulation for oral delivery employs standard solid oral dosage

form techniques (film-coated tablets). Soluble in dimethyl sulfoxide and in organic solvents including methanol and ethanol.

Stereochemistry: Elafibranor contains an (E)-configured alkene in the chalcone linker. There are no traditional stereocenters; the compound is achiral. The (E)-geometry is critical for receptor binding activity, and the (Z)-isomer is substantially less potent. Analytical confirmation of geometric isomer purity is appropriate for research-grade material.

1.3 Synthesis

The published medicinal chemistry of elafibranor proceeds through a convergent synthesis involving preparation of the 2,6-dimethyl-4-formylphenol (or equivalent aldehyde), aldol condensation or Claisen-Schmidt reaction with 4-(methylthio)acetophenone to generate the (E)-chalcone, and O-alkylation of the phenolic hydroxyl with methyl 2-bromoisobutyrate (or the corresponding alpha-bromoisobutyric acid derivative) to install the fibrate pharmacophore [3, 4]. The Claisen-Schmidt condensation is base-catalyzed (typically sodium hydroxide or potassium hydroxide in ethanol/water) and produces the thermodynamically favored (E)-isomer as the major product. Purification by recrystallization from ethanol or ethyl acetate provides the product at high geometric purity. Saponification of the methyl ester yields the free acid. The synthesis of structural analogs and derivatives of GFT505 has been reported by Wang et al. (2023), who explored modifications to the chalcone linker and the methylthiophenyl moiety for enhanced anti-NASH activity in vitro and in vivo [4]. Industrial manufacturing for the marketed 80 mg tablet formulation follows current Good Manufacturing Practice standards; the compound is formulated as a film-coated immediate-release tablet.

2. Abstract

Elafibranor (GFT505) is a dual peroxisome proliferator-activated receptor alpha and delta (PPARalpha/delta) agonist with additional low-potency PPARGgamma activity, developed as a first-in-class transcriptional regulator of hepatic lipid metabolism, bile acid homeostasis, glucose handling, and macrophage-mediated inflammation [1, 3]. The dual PPAR mechanism produces coordinated modulation of fatty acid beta-oxidation (PPARalpha), anti-inflammatory macrophage polarization (PPARdelta), and insulin sensitization (PPARalpha/delta/gamma composite), distinguishing elafibranor from selective single-PPAR agents and from the farnesoid X receptor (FXR) agonist obeticholic acid.

The compound was initially advanced by Genfit S.A. for the treatment of nonalcoholic steatohepatitis (NASH). The GOLDEN-505 Phase 2b trial (Ratziu et al. 2016) randomized 274 patients with NASH without cirrhosis to elafibranor 80 mg, 120 mg, or placebo daily for 52 weeks [1]. Although the protocol-defined primary endpoint was not met in the intention-to-treat population, a post-hoc analysis using a modified NASH resolution definition demonstrated that the 120 mg dose resolved NASH without fibrosis worsening in 19 percent of patients versus 12 percent on placebo (odds ratio 2.31; $P = 0.045$). Patients with NASH resolution showed a mean reduction in fibrosis stage of 0.65. These findings, combined with favorable metabolic effects on triglycerides, high-density lipoprotein cholesterol, and liver transaminases, supported advancement to the Phase 3 RESOLVE-IT trial. RESOLVE-IT enrolled 1,070 patients with NASH and fibrosis stages F2 to F3; in May 2020, an interim analysis demonstrated response rates of 19.2 percent on elafibranor 120 mg versus 14.7 percent on placebo, failing to achieve statistical significance, and the trial was terminated [2].

The PBC development program subsequently became the lead indication. A Phase 2 randomized placebo-controlled trial (Schattenberg et al. 2021) in 45 patients with PBC and inadequate response to UDCA demonstrated alkaline phosphatase reductions of 48.3 percent (80 mg) and 40.6 percent (120 mg) versus a 3.2 percent increase on placebo at 12 weeks [5]. The pivotal Phase 3 ELATIVE trial (Kowdley et al. 2024) in 161 patients demonstrated biochemical cholestasis re-

sponse in 51 percent of elafibranor-treated patients versus 4 percent on placebo at week 52, with alkaline phosphatase normalization in 15 percent versus 0 percent [6]. These results supported FDA accelerated approval on June 10, 2024.

Pharmacokinetics are characterized by rapid oral absorption (median T_{max} approximately 1.25 hours), very high plasma protein binding (approximately 99.7 percent, predominantly albumin), a large apparent volume of distribution (approximately 4,731 liters), and a long elimination half-life of the parent compound (approximately 60 to 70 hours) with a shorter half-life for the active metabolite GFT1007 (approximately 10 to 15 hours) [7]. Neither elafibranor nor GFT1007 undergoes major metabolism by cytochrome P450 or UDP-glucuronosyltransferase isoforms; the parent is hydrolyzed by 15-ketoprostaglandin delta-13 reductase (PTGR1) to GFT1007, which is further metabolized by CYP2C8, UGT1A3, and UGT2B7 [7, 8].

The compound is well tolerated at 80 mg daily. Principal adverse events are gastrointestinal (abdominal pain, diarrhea, nausea, vomiting), weight gain, and musculoskeletal complaints. Rare but serious adverse events include myopathy, rhabdomyolysis (especially with concurrent statin use), and dose-dependent hepatotoxicity at supratherapeutic doses [8, 9]. The compound is contraindicated in decompensated cirrhosis and complete biliary obstruction.

3. Discovery and Development History

3.1 Origin

Elafibranor (GFT505) was discovered at Genfit S.A., a biopharmaceutical company headquartered in Lille, France, as part of a medicinal chemistry program exploring dual PPARalpha/delta agonists for metabolic liver disease. The compound was designed to retain the lipid-modulating and insulin-sensitizing properties of first-generation fibrates (PPARalpha agonists) while incorporating PPARdelta agonism for anti-inflammatory activity in hepatic macrophages and Kupffer cells [3]. The structural innovation was the introduction of an (E)-chalcone linker connecting the classical fibrate pharmacophore to a 4-(methylthio)phenyl ketone, producing a compound with substantially higher potency (EC₅₀ 45 nM at PPARalpha, 175 nM at PPARdelta) than fenofibrate or bezafibrate at both receptor subtypes.

3.2 Early clinical development in metabolic disease

Genfit initially advanced GFT505 through Phase 1 and early Phase 2 studies in hyperlipidemia and type 2 diabetes, where the compound demonstrated dose-dependent reductions in plasma triglycerides, increases in high-density lipoprotein cholesterol, improvements in insulin sensitivity, and reductions in liver transaminases [10]. The liver transaminase improvements, combined with the emerging recognition of NASH as a major unmet medical need, prompted Genfit to pivot the lead indication to NASH.

3.3 GOLDEN-505 Phase 2b trial in NASH

The GOLDEN-505 trial (Ratziu et al. 2016) was a multicenter, randomized, double-blind, placebo-controlled Phase 2b study conducted at sites in Europe and the United States [1]. The trial enrolled 274 patients with biopsy-confirmed NASH without cirrhosis and randomized them to elafibranor 80 mg daily (n = 93), elafibranor 120 mg daily (n = 91), or placebo (n = 92) for 52 weeks. The protocol-defined primary outcome was NASH resolution without worsening of fibrosis on end-of-treatment liver biopsy. In the intention-to-treat population, the primary endpoint was not met. A post-hoc analysis using a modified NASH resolution definition (based on a

subsequently revised FDA consensus definition) demonstrated that elafibranor 120 mg resolved NASH in 19 percent of patients versus 12 percent on placebo (odds ratio 2.31; 95 percent confidence interval 1.02 to 5.24; $P = 0.045$). In patients with a nonalcoholic fatty liver disease activity score of 4 or greater ($n = 234$), the response rate was 20 percent versus 11 percent (odds ratio 3.16; $P = 0.018$). Responders demonstrated a mean fibrosis stage reduction of 0.65, compared to a mean increase of 0.10 in nonresponders. Elafibranor 120 mg also produced a mild, reversible increase in serum creatinine (mean increase 4.31 micromol/L versus placebo; $P < 0.001$) that was attributed to inhibition of renal tubular creatinine secretion rather than true nephrotoxicity [1].

3.4 RESOLVE-IT Phase 3 trial in NASH and termination

On the basis of the GOLDEN-505 post-hoc analysis, Genfit initiated the RESOLVE-IT Phase 3 trial (NCT02704403) in late 2016, enrolling patients with NASH and liver fibrosis stages F2 to F3 at approximately 250 sites globally. The trial randomized patients to elafibranor 120 mg daily or placebo, with a primary endpoint of NASH resolution without worsening of fibrosis on liver biopsy at 72 weeks and a composite long-term clinical outcome endpoint. In May 2020, Genfit announced the results of a pre-specified interim analysis on 1,070 patients: the response rate was 19.2 percent on elafibranor versus 14.7 percent on placebo, a difference that did not achieve statistical significance [2]. The fibrosis secondary endpoint showed similarly non-significant separation (24.5 percent versus 22.4 percent). The unusually high placebo response rate (approximately threefold higher than the 5 to 9 percent observed in prior NASH trials) was noted as a contributing factor. Genfit terminated the RESOLVE-IT trial in July 2020, concluding that the investment required to continue was not justified given the low probability of achieving a positive registration outcome.

3.5 Pivot to primary biliary cholangitis

Genfit had initiated parallel development of elafibranor in PBC, recognizing that the PPAR α -mediated modulation of bile acid synthesis (suppression of CYP7A1), bile acid detoxification (induction of CYP3A4, SULT2A1, UGT2B4), and bile acid transport (upregulation of BSEP and MRP2), combined with the PPAR δ -mediated anti-inflammatory activity, constituted a mechanistically coherent approach

to cholestatic liver disease [5, 11]. The FDA granted Breakthrough Therapy Designation in 2019 on the basis of Phase 2 data. Genfit subsequently entered a licensing agreement with Ipsen for global commercialization rights.

3.6 Regulatory approval

On June 10, 2024, the FDA granted accelerated approval to elafibranor 80 mg tablets (trade name Iqirvo, marketed by Ipsen) for the treatment of PBC in combination with UDCA in adults with inadequate response to UDCA, or as monotherapy in adults unable to tolerate UDCA [9, 12]. The approval was based on reduction of alkaline phosphatase as a surrogate endpoint; improvement in survival or prevention of liver decompensation has not been demonstrated, and continued approval is contingent upon verification of clinical benefit in confirmatory trials. The European Medicines Agency adopted a positive opinion in July 2024, with European Union marketing authorization following in September 2024. The United Kingdom National Institute for Health and Care Excellence (NICE) recommended elafibranor for National Health Service use in October 2024 [12].

4. Mechanism of Action

Elafibranor is a transcriptional regulator that acts through activation of the peroxisome proliferator-activated receptor (PPAR) family of nuclear hormone receptors. The compound and its active metabolite GFT1007 activate PPARalpha, PPARDelta, and PPARGgamma in vitro, with the alpha and delta subtypes representing the principal pharmacologically relevant targets at therapeutic concentrations [3, 11].

4.1 PPARalpha-mediated effects

PPARalpha is a ligand-activated nuclear transcription factor expressed at high levels in hepatocytes, cardiomyocytes, renal proximal tubular cells, and enterocytes. Upon ligand binding, PPARalpha heterodimerizes with the retinoid X receptor (RXR) and binds to peroxisome proliferator response elements (PPREs) in the promoter regions of target genes, recruiting coactivator complexes to drive transcription [3, 11].

In the liver, PPARalpha activation by elafibranor produces several coordinated effects relevant to cholestatic and steatoinflammatory disease. First, it modulates the lipid flux by inducing genes involved in fatty acid transport (FATP, FABPpm), mitochondrial and peroxisomal beta-oxidation (CPT1A, ACOX1, ACAD family members), and ketogenesis, thereby reducing hepatic triglyceride accumulation and steatosis. Second, PPARalpha activation inhibits bile acid synthesis through suppression of CYP7A1 (cholesterol 7-alpha-hydroxylase, the rate-limiting enzyme of the classical bile acid synthesis pathway). Third, it enhances bile acid detoxification by inducing phase I and phase II metabolizing enzymes (CYP3A4, SULT2A1, UGT2B4). Fourth, it increases bile acid output by upregulating the canalicular bile salt export pump (BSEP/ABCB11) and multidrug resistance-associated protein 2 (MRP2/ABCC2). Fifth, it reduces bile toxicity by inducing MDR3 (ABCB4) and ABCG5/G8, which promote phospholipid and cholesterol secretion into bile to form protective mixed micelles [11]. Additionally, PPARalpha activation inhibits proinflammatory gene expression driven by nuclear factor-kappaB (NF-kappaB) and suppresses acute-phase response genes, contributing to anti-inflammatory activity.

The lipid-modulating effects produce clinically measurable reductions in plasma triglycerides and increases in high-density lipoprotein (HDL) cholesterol, effects shared with the classical fibrate class.

4.2 PPARdelta-mediated effects

PPARdelta (also designated PPARbeta/delta) is ubiquitously expressed, with particularly high levels in macrophages, skeletal muscle, adipose tissue, and hepatic Kupffer cells. Activation of PPARdelta by elafibranor produces anti-inflammatory effects in macrophages and Kupffer cells through inhibition of NF-kappaB and AP-1 signaling pathways and through induction of the BCL6-dependent anti-inflammatory transcriptional program [3, 11]. BCL6 is a transcriptional repressor that, when desequestered from PPARdelta upon ligand binding, suppresses proinflammatory cytokine expression including tumor necrosis factor alpha (TNFalpha), interleukin-1 beta (IL-1beta), and monocyte chemoattractant protein-1 (MCP-1).

PPARdelta activation additionally enhances fatty acid transport and oxidation in skeletal muscle, increases HDL cholesterol levels, and improves glucose homeostasis by enhancing insulin sensitivity and inhibiting hepatic glucose output [3]. These metabolic effects complement the PPARalpha-mediated lipid modulation and contribute to the composite metabolic improvement observed in clinical trials.

4.3 PPARgamma-mediated effects

Elafibranor and GFT1007 activate PPARgamma at higher concentrations than PPARalpha or PPARdelta in vitro. PPARgamma is the molecular target of the thiazolidinedione class of insulin sensitizers (pioglitazone, rosiglitazone). At the therapeutic dose of 80 mg daily, the contribution of PPARgamma activation to the overall pharmacological effect is likely modest relative to the alpha and delta contributions, but may contribute to insulin sensitization in adipose tissue and to anti-inflammatory macrophage polarization (M2 phenotype) [11].

4.4 Composite pharmacology in PBC

In primary biliary cholangitis, the composite PPARalpha/delta mechanism of elafibranor addresses multiple nodes of disease pathophysiology. The PPARalpha-mediated suppression of bile acid synthesis, enhancement of bile acid detoxification, and augmentation of bile acid transport directly reduce the cholestatic burden. The

PPARdelta-mediated anti-inflammatory activity suppresses the biliary and portal inflammatory infiltrate. The combination produces the clinically observed reduction in alkaline phosphatase, gamma-glutamyltransferase, and markers of hepatic inflammation and cholestasis [5, 6, 11].

4.5 Composite pharmacology in NASH

In nonalcoholic steatohepatitis, the PPARalpha-mediated reduction in hepatic steatosis through enhanced fatty acid oxidation, the PPARdelta-mediated anti-inflammatory activity in Kupffer cells and recruited macrophages, and the composite insulin-sensitizing effect address the steatosis, inflammation, and metabolic dysregulation components of NASH pathophysiology. The anti-fibrotic effects observed in preclinical models are secondary to the reduction in inflammation and hepatocyte injury rather than a direct effect on hepatic stellate cell activation [1, 3, 13].

5. Pharmacokinetics and Routes of Administration

5.1 Absorption

Elafibranor is administered orally as an 80 mg film-coated tablet. Following oral administration, the compound is rapidly absorbed with a median time to peak plasma concentration (T_{max}) of approximately 1.25 hours for elafibranor and approximately 2 to 3 hours for the active metabolite GFT1007 [7, 8]. Administration with a high-fat, high-calorie meal delays the T_{max} by approximately 30 minutes for elafibranor and approximately 1 hour for GFT1007 relative to fasted conditions. The effect of food on total exposure (AUC) is not considered clinically significant, and the prescribing information permits administration with or without food [8].

5.2 Distribution

Plasma protein binding of both elafibranor and GFT1007 is approximately 99.7 percent, predominantly to serum albumin [7, 8]. The very high protein binding limits the free fraction available for receptor binding and for distribution into tissues. The mean apparent volume of distribution (V_d/F) of elafibranor is approximately 4,731 liters following a single 80 mg dose in fasted healthy subjects, indicating extensive tissue distribution despite the high protein binding [7]. The large apparent volume of distribution, combined with the lipophilic character of the molecule, suggests substantial hepatic and adipose tissue partitioning.

5.3 Metabolism

Following oral administration, elafibranor undergoes hydrolysis to its principal active metabolite GFT1007. The hydrolysis is catalyzed by 15-ketoprostaglandin delta-13 reductase (PTGR1) [7, 8]. In vitro, neither elafibranor nor GFT1007 shows major metabolism by the principal cytochrome P450 (CYP) or UDP-glucuronosyltransferase (UGT) isoforms. GFT1007 is further metabolized by CYP2C8, UGT1A3, and UGT2B7. The mean systemic exposure (AUC) to GFT1007 is approximately 3.2-fold

higher than that of elafibranor at steady state, indicating that GFT1007 is the predominant circulating species and the principal contributor to the sustained pharmacological activity [7].

Elafibranor and GFT1007 did not exhibit time-dependent CYP inhibition in vitro. Neither compound induced CYP1A2, CYP2B6, or CYP3A4, and neither was considered a clinically relevant inhibitor of the major CYP isoforms [8]. The absence of major CYP-mediated metabolism distinguishes elafibranor from many hepatic therapeutics and simplifies the drug interaction profile.

5.4 Elimination

Following a single 80 mg dose under fasted conditions, the mean apparent total clearance of elafibranor is approximately 50 liters per hour and the mean elimination half-life is approximately 70.2 hours [7]. GFT1007 has a mean elimination half-life of approximately 10.7 to 15.4 hours, with variability across studies reflecting differences in patient populations (healthy volunteers versus PBC patients) and analytical methods [7, 8]. Population pharmacokinetic modeling describes both elafibranor and GFT1007 by two-compartmental models, with predicted time to steady state of approximately 12.4 days for elafibranor and approximately 2.2 days for GFT1007 [7]. Following once-daily dosing, steady state of elafibranor is achieved by approximately Day 14 and steady state of GFT1007 by approximately Day 7.

5.5 Routes of administration

Elafibranor is administered exclusively by the oral route. The approved formulation is an 80 mg film-coated tablet for once-daily administration. No parenteral, intravenous, or alternative route formulations have been developed for clinical use. Research-grade elafibranor for in vitro and animal studies is supplied as a powder and dissolved in dimethyl sulfoxide (DMSO) for cell-based assays or suspended in appropriate vehicles (methylcellulose, carboxymethylcellulose) for oral gavage in rodent studies [13, 14].

5.6 Special populations

Hepatic impairment has been studied. Mild hepatic impairment (Child-Pugh A) does not produce clinically meaningful changes in elafibranor or GFT1007 exposure. The compound is not recommended in patients with moderate (Child-Pugh B)

or severe (Child-Pugh C) hepatic impairment or decompensated cirrhosis owing to insufficient safety data and the theoretical concern that impaired hepatic metabolism could increase exposure [8, 9]. Renal impairment data are limited; given the predominantly hepatic metabolism and the minimal renal excretion of unchanged drug, dose adjustment in mild to moderate renal impairment is not expected to be required. The compound has not been studied in pediatric PBC patients in the approved indication. A Phase 2 open-label study of elafibranor in pediatric NASH (ages 8 to 17 years) has been conducted, but results are not part of the approved labeling [15]. The compound is classified as embryo-fetal toxic; pregnancy testing is required before initiation, and effective contraception is mandated in women of childbearing potential during treatment and for one week after discontinuation [8, 9].

6. Preclinical Pharmacology

6.1 Rodent models of NASH and hepatic steatosis

The preclinical pharmacology of elafibranor (GFT505) has been characterized in multiple rodent models of nonalcoholic fatty liver disease and steatohepatitis [13, 14, 16]. Staels et al. (2013) assessed GFT505 in three complementary models: Western diet-fed human apolipoprotein E2 (apoE2) transgenic mice, methionine- and choline-deficient (MCD) diet-fed db/db mice, and carbon tetrachloride (CCl₄)-induced liver fibrosis in rats [13]. In all three models, GFT505 demonstrated hepatoprotective effects, reducing steatosis, hepatic inflammation, and fibrosis. The effects were mediated through both PPAR α -dependent mechanisms (fatty acid oxidation, lipid clearance) and PPAR α -independent mechanisms (anti-inflammatory and anti-fibrotic signaling).

Morrison et al. (2021) evaluated elafibranor in APOE*3Leiden.CETP mice fed a high-fat, high-cholesterol diet for 15 to 25 weeks [16]. Elafibranor treatment significantly reduced hepatic steatosis and inflammation and prevented fibrosis progression. The study also identified species differences in PPAR-mediated transcriptional responses between mice and humans, noting that some hepatic gene expression changes in mice were not fully predictive of human responses.

Lee et al. (2021) characterized the pharmacodynamics and differential gene expression of GFT505 in the choline-deficient, L-amino acid-defined, high-fat diet (CDAHFD) mouse model of NASH [14]. GFT505 ameliorated hepatic steatosis, inflammation, and fibrosis, with transcriptomic analysis confirming engagement of PPAR α and PPAR δ target gene networks.

6.2 Alcohol-associated liver disease models

Recent preclinical work has extended the elafibranor pharmacology to alcohol-associated liver disease. Gao et al. (2025) demonstrated that elafibranor attenuated hepatic steatosis, apoptosis, and fibrosis in an ethanol plus CCl₄-induced mouse model, with effects mediated through promotion of lipolysis, beta-oxidation, and

autophagy [17]. A companion study by the same group (2024) showed that elafibranor alleviated alcohol-related liver fibrosis by restoring intestinal barrier function [18].

6.3 Combination studies

Roth et al. (2019) evaluated the combination of obeticholic acid (an FXR agonist) and elafibranor in a diet-induced ob/ob mouse model of NASH and reported additive histological improvements [19]. The combination reduced steatosis, inflammation, and fibrosis to a greater degree than either agent alone, supporting the mechanistic rationale for combination approaches targeting different nuclear receptor pathways in liver disease.

7. Clinical Evidence Base

7.1 NASH: GOLDEN-505 Phase 2b

The GOLDEN-505 trial (Ratziu et al. 2016; Gastroenterology) randomized 274 patients with biopsy-confirmed NASH without cirrhosis to elafibranor 80 mg (n = 93), 120 mg (n = 91), or placebo (n = 92) once daily for 52 weeks [1]. The primary endpoint was NASH resolution without fibrosis worsening on end-of-treatment biopsy using a protocol-defined histological scoring system.

In the intention-to-treat analysis, the primary endpoint was not met (P = not significant for either dose versus placebo). A post-hoc analysis using the subsequently revised FDA consensus definition for NASH resolution demonstrated that elafibranor 120 mg resolved NASH in 19 percent versus 12 percent on placebo (odds ratio 2.31; 95 percent CI 1.02 to 5.24; P = 0.045). In the subgroup with nonalcoholic fatty liver disease activity score of 4 or greater (n = 234), the response rate was 20 percent versus 11 percent (odds ratio 3.16; P = 0.018). Patients who achieved NASH resolution on elafibranor showed a mean reduction in fibrosis stage of 0.65, compared to a mean increase of 0.10 in nonresponders (P < 0.001) [1].

Metabolic endpoints favored elafibranor 120 mg: significant reductions in triglycerides, LDL cholesterol, and liver enzymes (ALT, AST, GGT), with increases in HDL cholesterol. The compound produced a mild reversible increase in serum creatinine (4.31 micromol/L versus placebo; P < 0.001) attributed to inhibition of tubular creatinine secretion rather than glomerular filtration reduction. No weight gain was observed, and no cardiac events were reported [1].

7.2 NASH: RESOLVE-IT Phase 3

The RESOLVE-IT trial (NCT02704403) was a multinational, randomized, double-blind, placebo-controlled Phase 3 study enrolling patients with NASH and liver fibrosis stages F2 to F3 at approximately 250 sites globally [2]. Patients were randomized to elafibranor 120 mg or placebo once daily. The primary endpoint was NASH resolution without worsening of fibrosis at 72 weeks; a composite clinical outcome endpoint (progression to cirrhosis, liver-related events, and all-cause mortality) was a key secondary endpoint.

The pre-specified interim analysis conducted in May 2020 on 1,070 patients demonstrated a response rate of 19.2 percent on elafibranor versus 14.7 percent on placebo, a difference that did not achieve statistical significance [2]. The fibrosis improvement secondary endpoint showed 24.5 percent versus 22.4 percent, also non-significant. The placebo response rate was substantially higher than in previous NASH trials (historically 5 to 9 percent), complicating interpretation. Genfit terminated the trial in July 2020.

7.3 PBC: Phase 2 trial

Schattenberg et al. (2021) reported a 12-week, randomized, double-blind, placebo-controlled Phase 2 trial in 45 adults with PBC who had an inadequate response to UDCA [5]. Patients were randomized to elafibranor 80 mg (n = 15), elafibranor 120 mg (n = 15), or placebo (n = 15). At 12 weeks, alkaline phosphatase (ALP) was reduced by 48.3 percent in the 80 mg group and by 40.6 percent in the 120 mg group, compared to a 3.2 percent increase in the placebo group. Both elafibranor doses produced significant reductions in gamma-glutamyltransferase (GGT), total bilirubin, immunoglobulin M, and C-reactive protein. The compound was well tolerated; no serious adverse events related to study drug were reported [5].

7.4 PBC: ELATIVE Phase 3 trial

The ELATIVE trial (Kowdley et al. 2024; New England Journal of Medicine) was a multicenter, randomized, double-blind, placebo-controlled Phase 3 study in 161 patients with PBC who had an inadequate response to or were intolerant of UDCA [6]. Patients were randomized 2:1 to elafibranor 80 mg (n = 108) or placebo (n = 53) once daily. The primary endpoint was a composite biochemical cholestasis response at week 52, defined as ALP below 1.67 times the upper limit of normal (ULN), a reduction in ALP of at least 15 percent from baseline, and total bilirubin at or below the ULN.

At week 52, 51 percent of patients in the elafibranor group achieved the primary endpoint versus 4 percent in the placebo group ($P < 0.001$). ALP normalization was achieved in 15 percent of elafibranor-treated patients versus 0 percent on placebo. Elafibranor produced significant reductions in GGT, total bilirubin, direct bilirubin, conjugated bile acids, and markers of hepatic inflammation. Pruritus was not worsened (in contrast to obeticholic acid); some patients reported improvement in pruritus scores [6].

Adverse events occurring more frequently with elafibranor than placebo included abdominal pain (11 versus 6 percent), diarrhea (11 versus 9 percent), nausea (11 versus 6 percent), and vomiting (11 versus 2 percent). ALT elevations above 5 times the ULN occurred in 1 to 2 percent of patients. Serious adverse events were reported in 7 percent of elafibranor patients and 8 percent of placebo patients [6].

7.5 PBC: ongoing confirmatory trials and PSC

Confirmatory trials required for conversion of the accelerated approval to full approval are ongoing. In addition, Genfit reported positive late-breaking Phase 2 data for elafibranor in primary sclerosing cholangitis (PSC) presented at the European Association for the Study of the Liver (EASL) Congress in 2025, extending the cholestatic liver disease portfolio [20].

7.6 Metabolic disease studies

Earlier Phase 1 and Phase 2 studies evaluated GFT505 in patients with dyslipidemia and type 2 diabetes, demonstrating dose-dependent reductions in triglycerides, increases in HDL cholesterol, improvements in insulin sensitivity markers, and reductions in liver enzymes [10]. These metabolic indications are not in active commercial development.

8. Sourcing and Quality Verification

Pharmaceutical-grade elafibranor is available as the marketed product Iqirvo (Ipsen), supplied as 80 mg film-coated tablets for oral administration. The pharmaceutical product is the highest quality source for clinical research applications. Sourcing through clinical pharmacy channels is feasible in the United States, European Union, and United Kingdom following regulatory approval [9, 12].

Research-grade elafibranor is supplied by multiple chemical and pharmaceutical research suppliers (MedChemExpress, Selleckchem, Cayman Chemical, Sigma-Aldrich/MilliporeSigma, TargetMol, BioVision, others) at greater than 98 percent purity by HPLC. Supply is typically in milligram to gram quantities as the free acid form. Pricing is moderate for the research-grade compound; larger quantities may require custom synthesis arrangements.

Investigators should confirm compound identity and purity on every research-grade lot through:

- High-performance liquid chromatography (HPLC) area-percent purity, ideally greater than 98 percent
- Mass spectrometry confirmation of molecular weight (385.50 [M+H]⁺ for the protonated free acid)
- Nuclear magnetic resonance (NMR) spectroscopy (¹H and ¹³C) to confirm the (E)-chalcone geometry and overall structural integrity
- Geometric isomer analysis to confirm (E)-configuration purity, as the (Z)-isomer has substantially reduced receptor potency
- Karl Fischer or loss-on-drying analysis for residual water content
- Residual solvent analysis by gas chromatography

Third-party analytical laboratories provide independent confirmation of vendor certificates of analysis. The research-grade elafibranor market is well established given the compound's extensive clinical development history. Lot-to-lot variability should be assessed, and on-receipt analytical confirmation is appropriate for dose-response and mechanistic studies where pharmacological precision is important.

9. Reconstitution and Handling

Elafibranor free acid is practically insoluble in water. For in vitro research applications, the compound is typically dissolved in dimethyl sulfoxide (DMSO) to prepare concentrated stock solutions (typically 10 to 100 mM). The DMSO stock should be stored at minus 20 degrees Celsius in amber glass vials or polypropylene tubes, protected from light and moisture. DMSO stock solutions are stable for at least 6 months at minus 20 degrees Celsius when properly stored.

For cell-based assays, the DMSO stock is diluted into culture medium at the desired final concentration; the final DMSO concentration should be maintained below 0.1 to 0.5 percent to avoid vehicle cytotoxicity. Vehicle controls with matched DMSO concentration are essential.

For in vivo rodent studies, elafibranor is typically suspended in 1 percent methylcellulose or 0.5 percent carboxymethylcellulose in water for oral gavage administration [13, 14]. Suspensions should be prepared fresh daily or stored at 2 to 8 degrees Celsius for no more than 7 days with vigorous vortexing before each administration to ensure uniform suspension.

The solid compound (powder or crystalline form) should be stored at room temperature (15 to 25 degrees Celsius) in a desiccated container, protected from light and moisture. The compound is stable under these conditions for at least 2 years per typical vendor specifications.

The marketed pharmaceutical product (Iqirvo 80 mg tablets) should be stored at controlled room temperature (20 to 25 degrees Celsius, with excursions permitted to 15 to 30 degrees Celsius) per prescribing information [8, 9].

Aliquoting of DMSO stock solutions into single-use volumes is recommended to avoid repeated freeze-thaw cycles, which may promote precipitation or degradation. The compound is not known to be light-sensitive under normal laboratory conditions, but light protection during long-term storage is prudent practice.

10. Stack Interactions and Combinations

Elafibranor has a relatively favorable drug interaction profile owing to its primary metabolism through PTGR1-mediated hydrolysis rather than CYP450-dependent pathways [7, 8]. Investigators conducting research with elafibranor, especially in chronic dosing or combination regimens, should consider the following interactions:

Statins: Concurrent use of elafibranor with statins (HMG-CoA reductase inhibitors) warrants caution. The prescribing information reports increased risk of myalgia, myopathy, and rhabdomyolysis when elafibranor is co-administered with statins [8, 9]. Creatine phosphokinase (CPK) monitoring is recommended before initiation and periodically during concurrent therapy. The mechanism is not fully characterized but may involve additive effects on skeletal muscle or pharmacokinetic interactions at the level of hepatic uptake transporters (OATP1B1, OATP1B3).

CYP2C8 substrates and inhibitors: GFT1007, the active metabolite, is metabolized by CYP2C8. Strong CYP2C8 inhibitors (gemfibrozil, clopidogrel glucuronide) may increase GFT1007 exposure. Concurrent gemfibrozil is specifically noted in the prescribing information as a potential interaction [8]. Investigators should avoid combining elafibranor with gemfibrozil unless the pharmacokinetic interaction has been characterized.

Other fibrates: Concurrent use with other fibrates (fenofibrate, bezafibrate, ciprofibrate) is pharmacologically redundant for the PPARalpha agonist component and may produce additive risks for myopathy and hepatotoxicity. The combination is not recommended.

Ursodeoxycholic acid (UDCA): The approved indication specifies use in combination with UDCA. No clinically significant pharmacokinetic interaction between elafibranor and UDCA has been identified [5, 6, 8]. The combination is pharmacologically complementary: UDCA provides cytoprotective and choleretic effects through bile acid pool modification, while elafibranor modulates bile acid synthesis, detoxification, and transport through PPAR-mediated transcriptional regulation.

Obeticholic acid (OCA): The combination of elafibranor and OCA has been studied in preclinical models, where additive liver histological improvements were observed [19]. No clinical combination data are available. OCA was withdrawn from the United States market in September 2025 following postmarketing liver injury signals in non-cirrhotic PBC patients.

Oral contraceptives: Elafibranor may reduce the efficacy of hormonal contraceptives. The prescribing information recommends adding a non-hormonal method of contraception during treatment and for one week after discontinuation [8, 9].

Hepatotoxic agents: Concurrent administration with other hepatotoxic medications should be approached with caution given the dose-dependent hepatotoxicity observed at supratherapeutic elafibranor doses.

Bile acid sequestrants: Cholestyramine, colestipol, and colesevelam may reduce elafibranor absorption if co-administered. Separation of dosing by at least 4 hours is advisable, consistent with standard practice for fibrate-class compounds.

11. Adverse Events and Safety

11.1 Common adverse events

The principal adverse events at the approved 80 mg daily dose, as characterized in the ELATIVE Phase 3 trial, are [6, 8, 9]:

- Abdominal pain (11 percent versus 6 percent placebo)
- Diarrhea (11 percent versus 9 percent placebo)
- Nausea (11 percent versus 6 percent placebo)
- Vomiting (11 percent versus 2 percent placebo)
- Weight gain (reported as common; magnitude not specified in pivotal trial)
- Arthralgia (common)
- Constipation (common)
- Gastroesophageal reflux (common)
- Dry mouth (common)
- Rash (common)

The gastrointestinal adverse events are generally mild to moderate in severity, dose-dependent, and tend to diminish with continued therapy. The adverse event profile is consistent across the PBC and NASH clinical programs.

11.2 Musculoskeletal events

Myalgia, muscle injury, and elevated creatine phosphokinase (CPK) have been reported [8, 9]. Rare cases of rhabdomyolysis have occurred, particularly in patients with predisposing factors including concurrent statin therapy, renal impairment, hypothyroidism, or advanced age. One serious case in the clinical program involved a cirrhotic patient on concurrent statins who developed jaundice (total bilirubin 5.5 mg/dL), markedly elevated transaminases (ALT 300 U/L, AST 828 U/L), and rhabdomyolysis (CPK 12,647 U/L) with subsequent hepatic decompensation [9]. CPK monitoring before initiation and periodically during therapy is recommended, particularly with concurrent statin use.

11.3 Hepatotoxicity

The hepatotoxicity profile of elafibranor is dose-dependent. At the approved 80 mg dose, ALT elevations above 5 times the upper limit of normal occurred in approximately 1 to 2 percent of patients in clinical trials [6, 9]. Most elevations were transient and self-resolving without drug interruption or jaundice. At supratherapeutic doses exceeding 120 mg daily in healthy volunteers, ALT elevations above 5 times normal occurred in approximately one-third of subjects, establishing a clear dose-response relationship for hepatotoxicity [9].

The LiverTox assessment classified elafibranor with a likelihood score of E* (unproven but suspected rare cause of clinically apparent liver injury) [9]. Three cases of possible drug-induced liver injury were identified across the clinical program: two among 138 PBC patients and one among 1,433 NASH patients. The prescribing label recommends assessment of liver-related symptoms, signs, and laboratory values before initiation and periodically during treatment, with interruption if liver tests worsen and permanent discontinuation if injury recurs upon rechallenge [8].

11.4 Serum creatinine elevation

Elafibranor produces a mild, reversible increase in serum creatinine (approximately 4 micromol/L above placebo in the GOLDEN-505 trial) [1]. This effect is attributed to inhibition of renal tubular creatinine secretion rather than reduction in glomerular filtration rate, analogous to the creatinine effect observed with cimetidine and trimethoprim. The finding is not considered indicative of true nephrotoxicity but should be interpreted in context when assessing renal function during treatment.

11.5 Bone fractures

Bone fractures have been reported in clinical trials and are listed as an adverse event of interest [8, 9]. The mechanism, frequency, and clinical significance are not fully characterized. PPARgamma activation is known to reduce osteoblast differentiation and promote osteoclastogenesis, as demonstrated with the thiazolidinedione class; the low-potency PPARgamma agonism of elafibranor could theoretically contribute to bone effects on chronic dosing.

11.6 Embryo-fetal toxicity

Elafibranor is contraindicated in pregnancy. Animal reproductive toxicity studies demonstrated adverse developmental effects. Pregnancy testing is required before initiation, and effective contraception is mandated during treatment and for one week following discontinuation. The compound may reduce the efficacy of hormonal contraceptives [8, 9].

11.7 Contraindications

Elafibranor is contraindicated in patients with decompensated cirrhosis (Child-Pugh B or C), complete biliary obstruction, and known pregnancy. The compound is not recommended in patients with moderate or severe hepatic impairment [8, 9].

12. Comparable Compounds Assessment

This section presents a structured comparative assessment of five alternative agents against elafibranor for the treatment of primary biliary cholangitis, evaluated against five competency standards: novelty, effect size, promising potential (current clinical state and trajectory), side-effect profile, and overall validation. The five agents were selected as the principal pharmacological alternatives with substantive clinical evidence in PBC or closely related cholestatic liver disease.

12.1 Obeticholic acid (Ocaliva)

Mechanism: Selective farnesoid X receptor (FXR) agonist. FXR activation suppresses bile acid synthesis (CYP7A1), promotes bile acid export (BSEP upregulation), and modulates hepatic inflammation [21].

Development trajectory: Intercept Pharmaceuticals advanced obeticholic acid (OCA) through the Phase 3 POISE trial in PBC patients with inadequate UDCA response, demonstrating significant ALP reduction. OCA received FDA accelerated approval in 2016 as the first second-line agent for PBC. A confirmatory outcomes trial (COBALT) was required. However, postmarketing surveillance identified cases of liver injury and hepatic decompensation, including fatalities, in patients without pre-existing cirrhosis [21, 22]. In September 2025, the FDA requested and obtained voluntary withdrawal of OCA from the United States market based on these safety concerns.

Novelty: Moderate. FXR agonism is a well-characterized mechanism for cholestatic disease, mechanistically distinct from the PPAR pathway.

Effect size: The POISE trial demonstrated ALP reduction meeting the composite response endpoint in approximately 46 percent of patients at the 10 mg dose versus 10 percent on placebo. The effect size is broadly comparable to elafibranor (51 percent response in ELATIVE) [6, 21].

Promising potential: Very low. The compound has been withdrawn from the United States market. European marketing authorization was previously declined. Active commercial development has essentially terminated.

Side-effect profile: The principal limitation was pruritus, which occurred in up to 70 percent of patients and was dose-limiting in a substantial fraction. Hepatotoxicity, including hepatic decompensation and death in non-cirrhotic patients, led to market withdrawal. The side-effect profile is substantially worse than elafibranor at comparable efficacy [21, 22].

Overall validation: The compound produced strong Phase 3 efficacy data and was the first approved second-line PBC agent, conferring high initial validation. The market withdrawal and safety signal have substantially diminished the validation status. The compound serves as an important historical reference but is no longer a viable clinical comparator.

Comparison to elafibranor: Elafibranor has a markedly superior safety profile, does not worsen pruritus, and achieves comparable or slightly superior biochemical response rates. The withdrawal of OCA has strengthened the clinical positioning of elafibranor.

12.2 Seladelpar (Livdelzi)

Mechanism: Selective PPARdelta agonist. Seladelpar activates PPARdelta with high selectivity over PPARalpha and PPARGgamma, producing anti-inflammatory and anticholestatic effects [23].

Development trajectory: CymaBay Therapeutics (subsequently acquired by Gilead Sciences) advanced seladelpar through the Phase 3 RESPONSE trial in PBC patients with inadequate UDCA response. The trial demonstrated significant ALP reduction meeting the composite biochemical response endpoint. Seladelpar received FDA accelerated approval in 2024, the same year as elafibranor [23].

Novelty: Moderate. Selective PPARdelta agonism is mechanistically related to but narrower than the dual PPARalpha/delta approach of elafibranor.

Effect size: The RESPONSE trial demonstrated comparable biochemical response rates to the ELATIVE trial for elafibranor. Network meta-analyses have suggested that elafibranor may be slightly more effective than seladelpar in obtaining bio-

chemical response, though direct head-to-head comparison data are not available [22].

Promising potential: High. The compound is approved and actively marketed. Confirmatory trials are ongoing.

Side-effect profile: Seladelpar is the only PBC agent associated with a lower incidence of pruritus relative to placebo, representing a meaningful advantage in a disease where pruritus is a major symptom burden. Gastrointestinal adverse events are present but generally mild. The overall tolerability profile is favorable and broadly comparable to elafibranor, with the pruritus improvement being a distinguishing feature [22, 23].

Overall validation: High. Phase 3 positive, FDA-approved, actively marketed.

Comparison to elafibranor: Elafibranor and seladelpar are the two leading approved PPAR-based therapies for PBC. Elafibranor provides dual PPARalpha/delta agonism (broader transcriptional coverage), while seladelpar provides selective PPARdelta agonism (potentially cleaner on-target pharmacology). Seladelpar has an advantage in pruritus improvement; elafibranor may have a slight advantage in biochemical response magnitude. The choice between them is clinically nuanced and may depend on individual patient symptom burden and comorbidities.

12.3 Bezafibrate

Mechanism: Pan-PPAR agonist (PPARalpha, PPARdelta, PPARGgamma) with relatively balanced activity across the three subtypes [24].

Development trajectory: Bezafibrate is an established lipid-lowering fibrate marketed in Europe and Asia for dyslipidemia. It is not FDA-approved for any indication in the United States. The BEZURSO trial (Corpechot et al. 2018) evaluated bezafibrate 400 mg daily as add-on to UDCA in 100 PBC patients with inadequate UDCA response in a randomized, double-blind, placebo-controlled design for 24 months [24]. Bezafibrate achieved the primary endpoint of biochemical response (ALP normalization or reduction below 1.5 times ULN with normal bilirubin) in 31 percent of patients versus 0 percent on placebo. ALP normalization was achieved in 67 percent versus 2 percent.

Novelty: Low. Bezafibrate is a decades-old fibrate compound repurposed for PBC.

Effect size: The ALP normalization rate of 67 percent in BEZURSO is numerically higher than the 15 percent normalization rate reported for elafibranor in ELATIVE. However, direct comparison is confounded by differences in trial design, patient populations, response definitions, and trial duration (24 months versus 12 months) [6, 24].

Promising potential: Moderate. The compound is used off-label for PBC in Europe and Asia. It is not FDA-approved for PBC and is unlikely to be pursued for regulatory approval given its generic status. The BEZURSO results have established a clinical rationale for fibrate use in PBC but without regulatory pathway support.

Side-effect profile: Generally well tolerated. The principal concerns are myopathy (class effect of fibrates), hepatotoxicity, and renal effects. Long-term safety in PBC is established through decades of clinical experience in the dyslipidemia indication, though formal PBC-specific long-term safety data are limited [24].

Overall validation: Moderate. Positive Phase 3 results in PBC but no regulatory approval for this indication. Extensive real-world experience in lipid-lowering.

Comparison to elafibranor: Elafibranor has the regulatory advantage of FDA and EU approval specifically for PBC. Bezafibrate has the advantage of decades of clinical experience, generic availability, and possibly superior ALP normalization rates. Bezafibrate is a pan-PPAR agonist with PPARGgamma activity that may contribute to weight gain and thiazolidinedione-like effects; elafibranor has lower PPARGgamma engagement at therapeutic doses.

12.4 Fenofibrate

Mechanism: PPARalpha agonist. Fenofibrate is a prodrug hydrolyzed to fenofibric acid, which activates PPARalpha with selectivity over PPARDelta and PPARGgamma [25].

Development trajectory: Fenofibrate is a widely marketed lipid-lowering agent approved for hypertriglyceridemia and mixed dyslipidemia. It has been studied for PBC in multiple small, mostly uncontrolled studies. The evidence base comprises retrospective analyses, open-label series, and small randomized trials demonstrating ALP reduction when added to UDCA in patients with inadequate response. No large Phase 3 randomized controlled trial in PBC has been completed. The compound is not FDA-approved for PBC [25].

Novelty: Very low. Fenofibrate is a decades-old compound used off-label.

Effect size: ALP reductions of 20 to 40 percent have been reported in small series and retrospective analyses when added to UDCA. The effect size is smaller than that observed with elafibranor, bezafibrate, or seladelpar in controlled trials, consistent with the absence of PPARdelta-mediated anti-inflammatory activity [25].

Promising potential: Low. No regulatory pathway for PBC approval. Used off-label in clinical practice.

Side-effect profile: Established safety profile from decades of use in dyslipidemia. The principal concerns are myopathy (especially in combination with statins), hepatotoxicity, renal effects (creatinine elevation, cholelithiasis), and gastrointestinal intolerance [25].

Overall validation: Low for PBC. High for dyslipidemia. The PBC evidence base is small and uncontrolled.

Comparison to elafibranor: Elafibranor is substantially more potent at PPARalpha and additionally engages PPARdelta, producing greater ALP reduction and anti-inflammatory effects. Elafibranor has FDA approval for PBC; fenofibrate does not. Fenofibrate has the advantages of generic availability, decades of safety experience, and low cost.

12.5 Saroglitazar (Lipaglyn)

Mechanism: Dual PPARalpha/gamma agonist. Saroglitazar activates PPARalpha with high potency and PPARgamma with moderate potency [26].

Development trajectory: Saroglitazar was developed by Zydus Cadila and is approved in India for diabetic dyslipidemia and NASH. It is not approved by the FDA or EMA. A Phase 2 trial (EVIDENCES II) evaluated saroglitazar 4 mg daily in PBC patients with inadequate UDCA response, reporting significant ALP reduction [26]. Phase 3 development in PBC in major regulatory markets has not been initiated.

Novelty: Moderate. The PPARalpha/gamma dual agonism is mechanistically distinct from the PPARalpha/delta agonism of elafibranor; the gamma contribution targets insulin sensitization and adipocyte biology rather than macrophage anti-inflammatory programming.

Effect size: Phase 2 PBC data show meaningful ALP reduction, though the trial was small and uncontrolled relative to the ELATIVE standard.

Promising potential: Moderate in India (where it is approved for metabolic indications). Low in the United States and European Union (no regulatory pathway for PBC).

Side-effect profile: Generally well tolerated. The PPARGamma contribution may produce weight gain and fluid retention. Long-term safety data are limited outside the Indian market [26].

Overall validation: Low for PBC globally. Moderate for metabolic indications in India.

Comparison to elafibranor: Elafibranor has FDA and EU approval for PBC, Phase 3 data, and a broader evidence base. Saroglitazar targets a different PPAR combination (alpha/gamma rather than alpha/delta) and has a different metabolic and anti-inflammatory profile. The PPARdelta activity of elafibranor is likely more relevant to cholestatic liver disease anti-inflammatory programming than the PPARGamma activity of saroglitazar.

12.6 Comparator summary

The five comparator agents occupy distinct positions in the PBC pharmacotherapy landscape. **Obeticholic acid** was the historical first-mover with strong Phase 3 data but has been withdrawn from the United States market owing to hepatotoxicity and pruritus concerns. **Seladelpar** is the closest competitor to elafibranor, sharing PPAR-based mechanism and contemporaneous FDA approval, with a pruritus improvement advantage and comparable biochemical efficacy. **Bezafibrate** has produced the highest ALP normalization rates in a randomized trial but lacks regulatory approval for PBC. **Fenofibrate** provides modest ALP reduction through selective PPARalpha agonism and is used off-label but has a weak evidence base. **Saroglitazar** is approved in India for metabolic indications and has early PBC data but no major-market regulatory pathway.

Elafibranor occupies a strong position in this comparator landscape: it is one of only three agents with FDA approval for PBC (alongside UDCA and seladelpar, given OCA withdrawal), it has the broadest PPAR coverage among the approved agents (dual PPARalpha/delta versus selective PPARdelta for seladelpar), and it demonstrates robust biochemical response rates without pruritus worsening. The princi-

pal practical questions for clinical and research use are the relative positioning of elafibranor versus seladelpar (the closest competitor in mechanism and evidence) and the long-term clinical outcomes data that remain to be generated in confirmatory trials. The withdrawal of obeticholic acid has removed the principal non-PPAR competitor and has consolidated the second-line PBC treatment landscape around PPAR-based therapies, with elafibranor and seladelpar as the leading approved options.

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