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ADISINSIGHT REPORT

Elafibranor: First Approval

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Abstract
Elafibranor (IQIRVO®) is a first-in-class peroxisome proliferator-activated receptor (PPAR) agonist being developed by Ipsen, under license from Genfit, for the treatment of primary biliary cholangitis (PBC) and primary sclerosing cholangitis (PSC). On 10 June 2024, elafibranor received accelerated approval based on reduction of alkaline phosphatase (ALP) in the USA for the treatment of PBC in combination with ursodeoxycholic acid (UDCA) in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA. Elafibranor has also received a positive opinion in the EU. This article summarizes the milestones in the development of elafibranor leading to this first approval for PBC.

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Elafibranor (IQIRVO®): Key Points

PPAR agonist being developed by Ipsen, under license from Genfit, for the treatment of PBC and PSC

Received its first approval on 10 June 2024 in the USA under accelerated approval based on reduction of ALP

Approved for the treatment of PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA

1 Introduction

Primary biliary cholangitis (PBC; previously known as primary biliary cirrhosis) is a chronic autoimmune disease of the liver that causes inflammation and progressive destruction of the bile ducts [1]. This leads to cholestasis which, if left untreated, progresses to liver fibrosis and cirrhosis. Clinically, PBC is characterized by fatigue, jaundice and pruritus. The disease is typically diagnosed between the ages of 40 and 60 years, with females being at greater risk than males [1].

Guidelines for the management of PBC recommend ursodeoxycholic acid (UDCA) as first-line therapy [2]. UDCA has been shown to improve liver biochemistry and slow disease progression in patients with PBC [1, 2]. However, between 30% and 40% of patients have a suboptimal response to UDCA and are at high risk for disease progression [2]. Obeticholic acid has been approved in the USA as a second-line therapy for PBC, but cannot be used in patients with advanced liver cirrhosis [1, 2]. Peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor family of ligand-activated transcription factors that heterodimerize with the retinoid X receptor to regulate the expression of genes involved in fatty acid metabolism, inflammation and glucose metabolism [1]. PPAR activation represents a therapeutic target for cholestatic liver diseases [1].

Elafibranor (IQIRVO®) is a first-in-class PPAR agonist that is being developed by Ipsen, under license from Genfit, for the treatment of PBC and primary sclerosing cholangitis (PSC).

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch and beyond.

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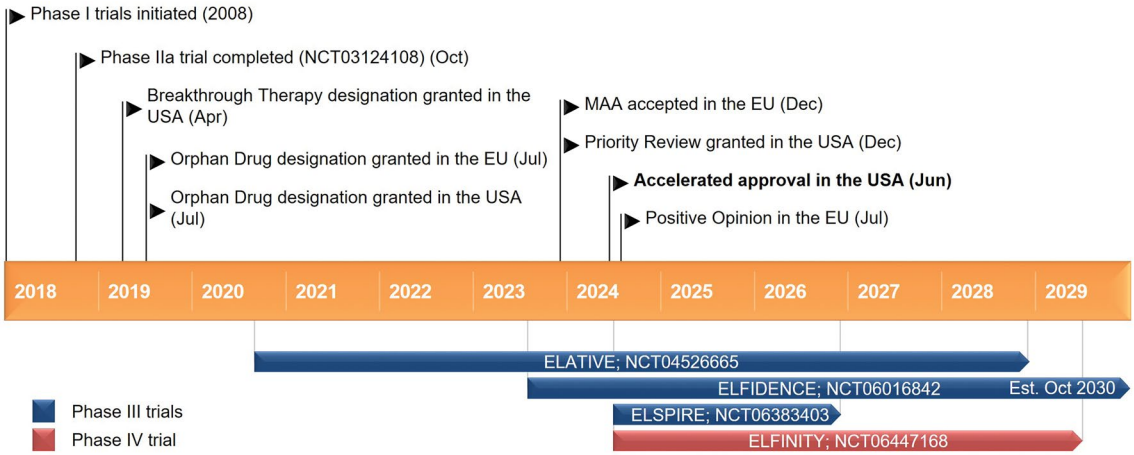


Key milestones in the development of elafibranor, focusing on its use in the treatment of primary biliary cholangitis. *MAA* marketing authorization application

Elafibranor was given orphan drug designation in the USA and the EU in July 2019 for the treatment of PBC [3]; prior to this, elafibranor had been granted breakthrough therapy designation [4]. In December 2023, the US FDA granted priority review for elafibranor in PBC [5]. On 10 June 2024, elafibranor received accelerated approval in the USA for the treatment of PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA [6, 7]. The approval was based on reduction of alkaline phosphatase (ALP) [6] in the phase III ELATIVE trial (Sect. 2.4.1) [7]. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s) [6]. The recommended dosage of elafibranor is 80 mg once daily, with or without food. Elafibranor should be administered ≥ 4 h before or 4 h after administration of a bile acid binding sequestrant (or at as great an interval as possible). The use of elafibranor in patients who have or who develop decompensated cirrhosis (e.g. ascites, variceal bleeding, hepatic encephalopathy) is not recommended. The use of elafibranor in patients with complete biliary obstruction should be avoided [6].

Elafibranor received a positive opinion the EU in July 2024 for the treatment of PBC [8]. Elafibranor is under regulatory review in the UK for the treatment of PBC [5]. The drug is in phase III development for PBC in multiple countries worldwide. Elafibranor is also being developed for the treatment of PSC (in phase II). Clinical development of elafibranor in non-alcoholic steatohepatitis was terminated after the phase II trial did not meet the primary endpoint due to lack of efficacy, but not for safety reasons. Clinical development of elafibranor for the treatment of non-alcoholic fatty liver disease, hepatic fibrosis, lipid metabolism disorders and type 2 diabetes mellitus has also been discontinued.

1.1 Company Agreements

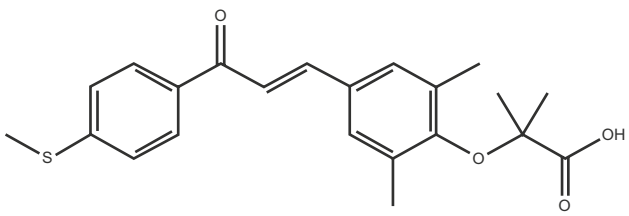
In June 2019, Terns Pharmaceuticals acquired rights to develop and commercialize elafibranor in Greater China from Genfit in exchange for upfront, milestone and royalty payments [9, 10].

Genfit and Ipsen entered into a long-term strategic global partnership in December 2021 [11]. Under the terms of the licensing agreement, Ipsen acquired exclusive worldwide rights to develop, manufacture and commercialize elafibranor from Genfit in exchange for upfront, milestone and royalty payments [11].

2 Scientific Summary

2.1 Pharmacodynamics

Elafibranor and its main active metabolite GFT1007 are PPAR agonists that activate PPAR-α, PPAR-γ and PPAR-δ in vitro [6]. Uncertainty exists regarding the exact mechanism by which elafibranor exerts its therapeutic effects in PBC. However, it is thought to involve inhibition of bile acid synthesis via activation of PPAR-α and PPAR-δ.



Chemical structure of elafibranor

The key enzyme involved in bile acid synthesis from cholesterol, CYP7A1, is thought to be downregulated by fibroblast growth factor 21 as part of the PPAR-δ signaling pathway [6].

Elafibranor and GFT1007 produced activation of PPAR-α in vitro, with half-maximal effective concentration (EC_{50}) values of 46 nM and 14 nM, respectively, and maximum effect (E_{max}) values of 56% and 61%, respectively, compared with reference PPAR agonists [6]. Elafibranor and GFT1007 were ≈3- to 8-fold more potent for PPAR-α than for PPAR-γ and PPAR-δ. Although the in vitro pharmacology studies detected PPAR–γ activation by elafibranor and GFT1007, animal toxicology studies demonstrated no adverse effects associated with activation of PPAR-γ [6].

In a phase IIa trial in patients with PBC (Sect. 2.4.2), elafibranor was associated with significant ($p < 0.05$ vs placebo) reductions from baseline in various disease and inflammatory markers, including γ-glutamyltransferase, immunoglobulin M, 5'-nucleotidase, high-sensitivity C-reactive protein and haptoglobin [12].

No clinically significant QTc interval prolongation was observed after administration of an elafibranor dose 3.75 times the recommended dose [6].

2.2 Pharmacokinetics

Elafibranor demonstrated time-dependent pharmacokinetics following 16 days of repeated once-daily administration [6]. Steady-state plasma concentrations of GFT1007 and elafibranor were achieved after 7 and 14 days, respectively. The area under the concentration-time curve (AUC) over the last 24-h dosing interval increased dose-proportionally across the dose range of 40–300 mg. Following repeated administration of elafibranor 80 mg once daily in patients with PBC, peak plasma concentrations (C_{max}) of elafibranor were reached after a median of 1.25 h (T_{max}). When a single dose of elafibranor was administered with a high-fat and -calorie meal, the T_{max} of elafibranor increased by 30 min and elafibranor C_{max} and AUC decreased by 50% and 15%, respectively, compared with fasted conditions. Elafibranor is highly (≈99.7%) bound to plasma proteins (mainly serum albumin). Elafibranor has a mean apparent volume of distribution of 4731 L following a single dose of 80 mg in healthy fasted volunteers [6].

Elafibranor is extensively metabolized by the cytosolic enzyme 15-ketoprostaglandin 13-Δ reductase to form the major active metabolite GFT1007 [6]. GFT3351 is a major inactive metabolite. The metabolism of elafibranor is also mediated by CYP2J2, UGT1A3, UGT1A4 and UGT2B7. GFT1007 is further metabolized by CYP2C8, UGT1A3 and UGT2B7. Following a single radiolabeled oral dose of elafibranor 120 mg (1.5 times the recommended dose) in healthy volunteers, ≈77% of the administered dose was recovered in faeces, primarily as unchanged drug (57%) and GFT1007 (6%). Approximately 19% of the administered dose was recovered in urine, primarily as GFT3351 (12%). Following a single dose of 80 mg under fasted conditions, the mean apparent total clearance of elafibranor is 50 L/h and the mean elimination half-life is 70.2 h. GFT1007 has a mean elimination half-life of 15.4 h [6].

Sex, body weight (43 kg to 120 kg), body mass index (14.5 kg/m^2 to 53.5 kg/m^2), renal impairment and hepatic impairment have no clinically relevant effects on the pharmacokinetics of elafibranor [6]. Following a single dose of 120 mg (1.5 times the recommended dose), the exposure of elafibranor was 23% higher in healthy elderly volunteers aged 75–80 years than in healthy younger volunteers aged 26–42 years [6].

Features and properties of elafibranor

Alternative names	GFT505; IPN60190; IQIRVO
Class	Anti-inflammatories; antifibrotics; antihyperglycaemics; antihyperlipidaemics; hepatoprotectants; organic sulfur compounds; phenyl ethers; propionic acids; small molecules
Mechanism of action	PPAR-α agonists; PPAR-δ agonists
Route of administration	Oral
Pharmacodynamics	Mechanism by which elafibranor exerts its therapeutic effects in PBC appears to involve inhibition of bile acid synthesis via activation of PPAR-α and PPAR-δ
Pharmacokinetics	Time-dependent pharmacokinetics; median T_{max} 1.25 h; ≈99.7% bound to plasma proteins; mean apparent volume of distribution 4731 L; mean apparent total clearance 50 L/h; mean elimination half-life 70.2 h
Most frequent adverse events	COVID-19, pruritus, abnormal weight gain, abdominal pain, diarrhoea, nausea, UTI, vomiting
WHO ATC codes	A05AX06 (Other Drugs for Bile Therapy)
Chemical name	2-[2,6-dimethyl-4-[(E)-3-(4-methylsulfanylphenyl)-3-oxoprop-1-enyl]phenoxy]-2-methylpropanoic acid

PBC primary biliary cholangitis, *PPAR* peroxisome proliferator-activated receptor, T_{max} time to peak plasma concentration, *UTI* urinary tract infection

Key clinical trials of elafibranor

Drug(s)	Indication	Phase	Status	Location(s)	Identifier	Company
Elafibranor	PBC	IIa	Completed	Multinational	NCT03124108	Genfit
Elafibranor	PBC	III	Active, no longer recruiting	Multinational	NCT04526665; ELATIVE	Genfit, Ipsen
Elafibranor	PBC	III	Recruiting	Multinational	NCT06016842; ELFIDENCE	Ipsen
Elafibranor	PBC	III	Not yet recruiting	Multinational	NCT06383403; ELSPIRE	Ipsen
Elafibranor	PBC	IV	Not yet recruiting	Multinational	NCT06447168; ELFINITY	Ipsen
Elafibranor	PSC	II	Recruiting	Multinational	NCT05627362; ELMWOOD	Ipsen

PBC primary biliary cholangitis, *PSC* primary sclerosing cholangitis

2.3 Drug Interactions

Elafibranor is a substrate of CYP2J2, UGT1A3, UGT1A4, UGT2B7, PTGR1, MRP2 and BCRP, a weak inducer of CYP3A4 and an inhibitor of BSEP and BCRP [6]. Therefore, clinically significant drug interactions may occur when elafibranor is coadministered with other drugs. Coadministration of elafibranor with hormonal contraceptives may reduce the systemic exposure of ethinyl estradiol and progestin (both CYP3A4 substrates) and lead to contraceptive failure and/or increased breakthrough bleeding. The risk of myopathy may be increased when elafibranor is coadministered with HMG-CoA reductase inhibitors. Coadministration of elafibranor with rifampin (an enzyme inducer) may reduce the systemic exposure of elafibranor and lead to a delayed or suboptimal biochemical response. Coadministration of elafibranor with bile acid binding sequestrants (Sect. 1) may reduce the absorption and systemic exposure of elafibranor and lead to reduced efficacy. Consult local prescribing information for specific recommendations [6].

2.4 Therapeutic Trials

2.4.1 Phase III ELATIVE Trial

Elafibranor significantly improved biochemical indicators of cholestasis in patients with PBC participating in the randomized, double-blind, multinational, phase III ELATIVE trial (NCT04526665) [13]. The proportion of patients achieving a biochemical response at week 52, defined as an ALP level < 1.67 x upper limit of normal (ULN), with a 15% reduction from baseline, and a total bilirubin level ≤ ULN, was 51% in the elafibranor group and 4% in the placebo group (primary endpoint; $p < 0.0001$). The proportion of patients with normalization of ALP at week 52 was 15% with elafibranor and 0% with placebo ($p = 0.0019$). Among patients with moderate to severe pruritus at baseline ($n = 66$), the least squares mean change in score on the Worst Itch Numeric Rating Scale [WI-NRS; scores range from 0 (no itch) to 10 (worst itch imaginable)] was not significantly different between the elafibranor and placebo groups from baseline through week 52 (–1.93 vs –1.15) and from baseline through week 24 (–1.60 vs –1.26). However, the change from baseline to week 52 on the itch domain of the PBC-40 quality of life (QOL) questionnaire (scores range from 0/1 to 5, with higher scores indicating worse QOL) and the 5-D itch scale total score (scores range from 5 to 25, with higher scores indicating worse itch-related QOL) appeared to favour elafibranor over placebo [13].

ELATIVE enrolled patients aged 18–75 years with a diagnosis of PBC, an inadequate response to or unacceptable adverse events (AEs) with UDCA, an ALP level ≥1.67 x ULN and a total bilirubin level ≤2 x ULN [13]. Patients were randomized to receive oral elafibranor 80 mg ($n = 108$) or placebo ($n = 53$) once daily. Randomization was stratified by ALP > 3 x ULN or total bilirubin > ULN (yes or no) and a WI-NRS score of ≥4 (yes or no). At the end of the double-blind treatment period, patients were eligible to enter an open-label extension during which they received elafibranor for up to 5 additional years [13].

2.4.2 Phase IIa Trial

Elafibranor significantly improved markers of liver injury in patients with PBC and an incomplete response to UDCA participating in a randomized, double-blind, multicentre, phase IIa trial (NCT03124108) [12]. The relative reduction in ALP levels from baseline to week 12 (primary endpoint) was –48.3% in the elafibranor 80 mg group and –40.6% in the elafibranor 120 mg group, compared with a 3.2% increase in the placebo group (both $p < 0.001$). Significantly ($p < 0.001$) more elafibranor than placebo recipients achieved the composite secondary endpoint of ALP ≤1.67 x ULN, total bilirubin < ULN and > 15% reduction in

ALP (67% with elafibranor 80 mg and 79% with elafibranor 120 mg vs 7% with placebo). Similar results were seen for the more stringent composite endpoint of ALP < 1.5 x ULN, total bilirubin < ULN and > 40% reduction in ALP (53% and 36% vs 0%; $p < 0.001$) [12].

This study included patients aged 18–75 years with PBC, defined as the presence of at least two of the following: ≥ 6-month history of elevated ALP levels; positive anti-mitochondrial antibody titre or positive PBC specific anti-nuclear antibodies; liver biopsy consistent with PBC [12]. All patients had been treated with UDCA for ≥ 12 months (on a stable dose for ≥ 6 months) and had ALP levels ≥ 1.67 x ULN (ULN = 104 U/L for females and 129 U/L for males). Patients were randomized to receive elafibranor 80 mg ($n = 15$), elafibranor 120 mg ($n = 15$) or placebo ($n = 15$) once daily for 12 weeks. All patients continued to receive UDCA during the study [12].

2.5 Adverse Events

Elafibranor was generally well tolerated in patients with PBC [13]. In the phase III ELATIVE trial, treatment-related adverse events (AEs) occurred in 39% of patients receiving elafibranor and 40% of patients receiving placebo. The most common treatment-emergent AEs (TEAEs) occurring in ≥ 10% of patients in either treatment group were COVID-19 (29% with elafibranor vs 38% with placebo), pruritus (20% vs 26%), abnormal weight gain (19% vs 19%), abdominal pain (11% vs 6%), diarrhoea (11% vs 9%), nausea (11% vs 6%), urinary tract infection (11% vs 19%), vomiting (11% vs 2%), fatigue (9% vs 13%), headache (8% vs 11%) and back pain (4% vs 11%). Most TEAEs were of mild or moderate severity; severe AEs occurred in 11% of patients in both treatment groups. TEAEs led to discontinuation of treatment in 10% of elafibranor recipients and 9% of placebo recipients. Fatal AEs occurred in two elafibranor recipients, neither of which was considered to be treatment-related [13].

Elafibranor has been associated with cases of myalgia, myopathy and rhabdomyolysis [6]. Elevated creatine phosphokinase (CPK) levels and muscle injury were more common with elafibranor than with placebo in ELATIVE [13]. Four elafibranor recipients (vs no placebo recipients) discontinued treatment due to CPK levels > 5 x ULN with or without associated symptoms or > 3 x ULN with symptoms; of these patients, two had myalgia and one had rhabdomyolysis [13].

There have been reports of drug-induced liver injury with elafibranor [6]. In ELATIVE, one elafibranor recipient and two placebo recipients had elevated aminotransferase levels (> 3 x baseline value if baseline value was elevated or 5 x ULN if baseline value was normal), elevated bilirubin levels (> 2 x ULN) or both that met protocol-defined thresholds for consideration of potential drug-induced liver injury [13]. The event in the elafibranor group was adjudicated as a possible drug-induced liver injury and the events in the placebo group were adjudicated as probable drug-induced liver injuries. One patient in each group discontinued treatment due to elevated aminotransferase levels. All cases of elevated aminotransferase levels were reversible, with levels returning toward baseline after treatment discontinuation [13].

2.6 Ongoing Clinical Trials

In addition to the ongoing ELATIVE open-label extension (NCT04526665) described in Sect. 2.4.1, a number of other clinical trials are currently underway. The randomized, double-blind, multinational, phase III ELFIDENCE trial (NCT06016842) is currently recruiting patients and plans to evaluate the long-term efficacy of elafibranor in adults with PBC. The randomized, double-blind, phase III ELSPIRE trial (NCT06383403) will evaluate the effect of elafibranor on normalization of ALP in adults with PBC and an inadequate response or intolerance to UDCA. The prospective, multicentre, non-interventional, phase IV ELFINITY trial (NCT06447168) plans to assess the effectiveness, safety and tolerability of elafibranor in patients with PBC receiving treatment in a real-world setting.

A randomized, double-blind, multinational, phase II trial (ELMWOOD; NCT05627362) is also underway to evaluate the safety and efficacy of elafibranor in adults with PSC.

3 Current Status

Elafibranor received its first approval on 10 June 2024 (accelerated approval based on reduction of ALP) in the USA for the treatment of PBC in combination with UDCA in adults who have an inadequate response to UDCA, or as monotherapy in patients unable to tolerate UDCA [7]. Elafibranor received a positive opinion in the EU in July 2024 for the treatment of PBC [8].

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Declarations

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Ltd/Springer Nature, and declares no relevant conflicts of interest. All authors contributed to this article and are responsible for its content.

Ethical Approval, Consent to Participate, Consent to Publish, Availability of Data and Material, Code Availability Not applicable.

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