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ADISINSIGHT REPORT

Seladelpar: First Approval

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Abstract
Seladelpar (LIVDELZI®) is an oral delpar [i.e. a selective peroxisome proliferator-activated receptor (PPAR)δ agonist] being developed by Gilead Sciences for the treatment of primary biliary cholangitis (PBC). On 14 August 2024, based on a reduction in alkaline phosphatase (ALP), it received accelerated approval 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. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory studies. A regulatory assessment for seladelpar for the treatment of PBC is underway in the EU and the UK. This article summarizes the milestones in the development of seladelpar leading to this first approval.

Digital Features for this AdisInsight Report can be found at https://doi.org/10.6084/m9.figshare.27229650.

Seladelpar (LIVDELZI®): Key Points

A PPARδ agonist being developed by Gilead Sciences for the treatment of PBC

Received its first approval on 14 August 2024 in the USA under accelerated approval based on a reduction in 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

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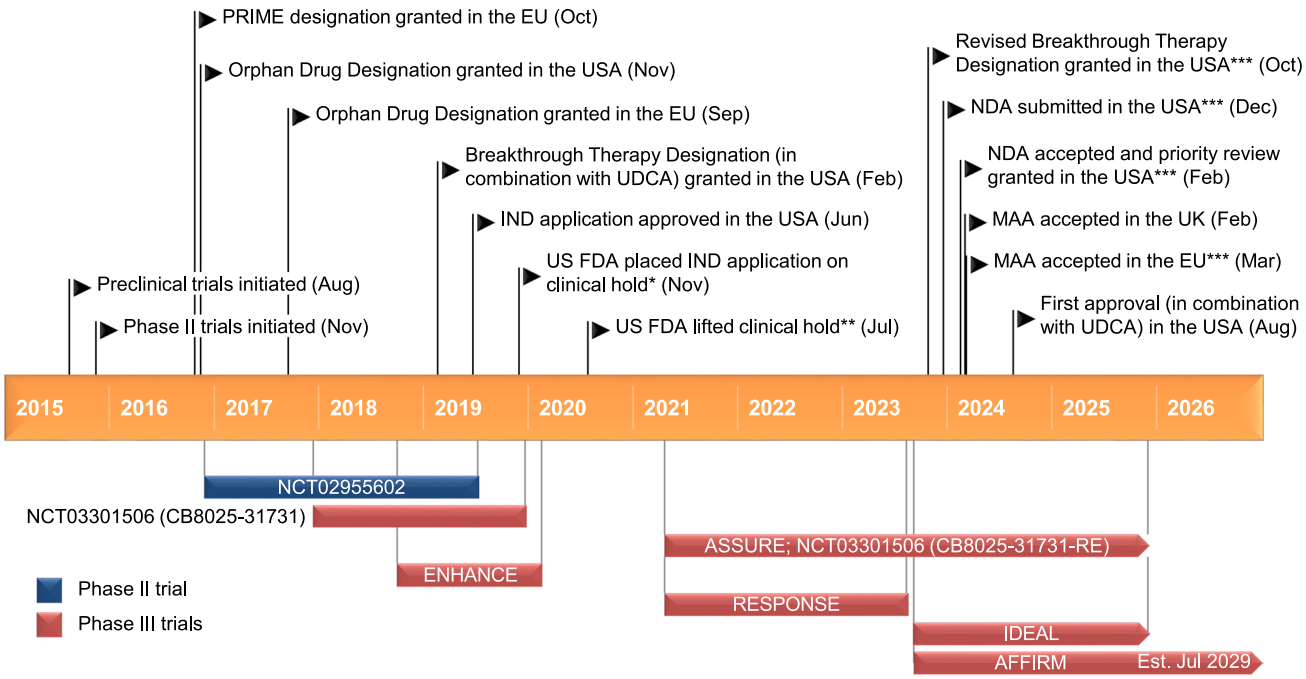
1 Introduction

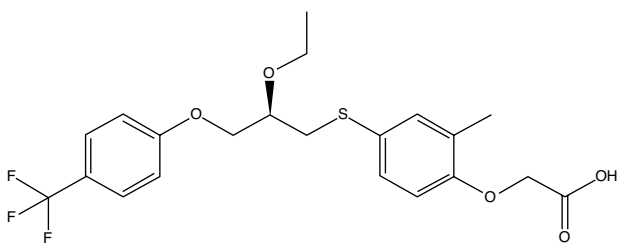
Primary biliary cholangitis (PBC; formerly known as primary biliary cirrhosis) is a chronic, autoimmune cholestatic liver disease in which immune dysregulation provokes biliary epithelial cell injury and the subsequent destruction of small- and medium-sized intrahepatic bile ducts [1–3]. This leads to cholestasis, which, if left untreated, can progress to biliary fibrosis and cirrhosis [1–4]. Complications of biliary cirrhosis include portal hypertension, hepatocellular carcinoma and liver failure, which may be fatal without a liver transplant [1–4]. PBC mostly affects women aged 40–70 years, with its predominance in this population reported to be mainly caused by sex hormones, environmental circumstances and epigenetic changes [5, 6]. Patients may present asymptomatically or with a variety of subjective symptoms (e.g. fatigue and pruritus) that affect quality of life (QOL) [2, 3]. However, a diagnosis of PBC is incidental in most patients with consistently elevated cholestatic liver enzymes [e.g. alkaline phosphatase (ALP)] [2, 7].

The aim of PBC treatment is to obtain a biochemical response, thereby slowing or even preventing the development of biliary fibrosis, and manage the patient's symptoms and thus improve their QOL [4]. Ursodeoxycholic acid (UDCA) was the first drug approved for the treatment of PBC in the USA and is considered the first line of therapy for PBC by the American Association for the Study of Liver Diseases [8]. It is the only first-line therapy currently approved by the US FDA [9]. However, up to 40% of patients with PBC will not achieve a complete biochemical response after 12 months of UDCA therapy [4],



Key milestones in the development of seladelpar for the treatment of primary biliary cholangitis. *Est.* estimated, *IND* Investigational New Drug, *MAA* Marketing Authorization Application, *NDA* New Drug Application, *PBC* primary biliary cholangitis, *PRIME* PRIority MEdicines, *UDCA* ursodeoxycholic acid. *Based on atypical histological findings with no clinical or laboratory correlates that were identified in a phase II study in nonalcoholic steatohepatitis [39] **Lifted following an in-depth investigation of the findings and a comprehensive safety evaluation that concluded with an independent expert panel review [39] *** For the treatment of PBC including pruritus in adults without cirrhosis or with compensated cirrhosis (Child-Pugh A)

with the biochemical response to UDCA strongly predicting long-term outcome [10]. Obeticholic acid (OCA), in combination with UDCA, or as monotherapy, was approved by the US FDA in 2016 for the treatment of PBC [8]. The 2018 practice guidance for primary biliary cholangitis from the American Association for the Study of Liver Diseases recommends that patients who are inadequate responders to UDCA should be considered for OCA therapy [8]. In 2021, a warning was issued by the US FDA restricting the use of OCA in patients with PBC and advanced cirrhosis owing to the risk of serious liver injury [11, 12]. In September 2024, the Gastrointestinal Drugs Advisory Committee of the US FDA voted against recommending full approval of OCA in PBC [13].



Chemical structure of seladelpar

Peroxisome proliferator-activated receptor (PPAR) is a nuclear receptor that exists in three isoforms (α, δ and γ) [8]. The isoforms play a role in a variety of metabolic processes, including bile acid homeostasis [8], making them a potential therapeutic target for cholestatic liver diseases. Seladelpar (LIVDELZI®) is an oral delpar (i.e. a selective PPARδ agonist) being developed by Gilead Sciences for the treatment of PBC [14, 15]. It received its first approval on 14 August 2024 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 [14, 15]. This was an accelerated approval based on a reduction in ALP [14] in the multinational phase III RESPONSE (NCT04620733) study (Sect. 2.4). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory studies [14].

The recommended dosage of seladelpar is 10 mg once daily; the capsules may be administered with or without food [14]. Seladelpar should be administered ≥ 4 h before or 4 h after consuming bile acid sequestrants (or at as great an interval as possible). The recommended dosage of seladelpar for patients with mild, moderate or severe renal impairment is the same as that recommended for patients with normal renal function.

There is no dosage adjustment recommended for patients with PBC and mild hepatic impairment (Child-Pugh A). Discontinuing seladelpar should be considered if the patient progresses to moderate or severe hepatic impairment (Child-Pugh B or C). The use of seladelpar is not recommended in patients who have or develop decompensated cirrhosis (e.g. ascites, hepatic encephalopathy, variceal bleeding) and should be avoided in patients with complete biliary obstruction. Patients with cirrhosis who are receiving seladelpar should be monitored for evidence of decompensation [14].

A regulatory assessment for seladelpar for the treatment of PBC is underway in the EU [16] and the UK [17]. The hyperlipidaemia, hyperlipoproteinaemia type IIa, non-alcoholic steatohepatitis (NASH), and primary sclerosing cholangitis indications for seladelpar are not present in the Gilead Sciences pipeline (as of August 2024) [18].

1.1 Company Agreements

In June 2006, Metabolex (renamed as CymaBay Therapeutics) and Ortho-McNeil, a Johnson & Johnson company, entered into a comprehensive global strategic agreement for the development and commercialization of multiple programmes addressing metabolic diseases [19]. Under the terms of the agreement, CymaBay Therapeutics was granted an exclusive, worldwide, royalty bearing license to seladelpar and certain other PPARδ compounds, and the right to grant sublicenses to third parties to make, use and sell such products [20]. In January 2023, CymaBay Therapeutics and Kaken Pharmaceutical entered into a collaboration and license agreement under which Kaken will be responsible for the development, regulatory approval and commercialization of seladelpar for the treatment of PBC in Japan [21]. In March 2024, Gilead Sciences acquired CymaBay Therapeutics [22]. In July 2024, Gilead Sciences paid US$320 million to Janssen Pharmaceutica NV, a Johnson & Johnson company, to terminate a future royalty obligation related to seladelpar [23].

2 Scientific Summary

2.1 Pharmacodynamics

PPARδ is found in various tissues including the liver, where it is expressed on cholangiocytes, hepatic stellate cells, hepatocytes and Kupffer cells [3, 4]. Its activation in hepatocytes and cholangiocytes improves cholestasis [via the downregulation of CYP7A1 (the rate-limiting enzyme for the synthesis of bile acids from cholesterol [24])] and reduces cholesterol synthesis and dietary absorption, resulting in a reduction in bile acid pools [3]. The activation of PPARδ expressed on hepatic stellate cells and Kupffer cells has been shown to induce anti-inflammatory and antifibrotic effects on these cells [3]. Seladelpar demonstrated selectivity for PPARδ (half-maximal effective concentration of 20.2 nmol/L and an efficacy of 99.3%) over PPARα (1.64 µmol/L and 41.0%) and PPARγ (3.53 µmol/L and 58.5%) in vitro [25].

It is not yet clear how seladelpar exerts its therapeutic effects in patients with PBC [14]. However, it appears to reduce CYP7A1 and thus bile acid synthesis through a fibroblast growth factor 21 (FGF21)-dependent mechanism that signals at least partially through c-Jun N-terminal kinase (JNK; which plays a role in reducing CYP7A1 in hepatocytes) [24]. PPARδ activation by seladelpar increased *FGF21* expression and reduced *CYP7A1* expression in hepatocytes. This downregulation in *CYP7A1* expression was independent of the farnesoid X receptor pathway (which plays an essential role in regulating bile acid synthesis in the liver). However, the FGF21-induced reduction of *CYP7A1* expression in hepatocytes was abolished by a JNK inhibitor [24].

In the multinational phase III ENHANCE (NCT03602560) study (Sect. 2.4) in patients with PBC, changes in serum metabolites (many of which are downstream of the known effects of *PPARδ* activation) [26] and increases in serum carnitine (which plays a key role in carrying out the beta-oxidation of long-chain fatty acids for energy production) [27] were observed following the administration of oral seladelpar 5 mg or 10 mg once daily.

In cholangiocytes, seladelpar was associated with the upregulation of various genes essential to lipid pathways, including *PPARδ*-activated genes [28]. In pooled data from ENHANCE and a phase II study (NCT02955602) in patients with PBC, oral seladelpar 5 mg or 10 mg once daily, with or without UDCA, was associated with significant ($p < 0.05$ vs placebo) reductions from baseline in total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol (HDL-C), non-HDL-C and/or total triglycerides in patients with PBC [29]. Moreover, in patients with PBC participating in ENHANCE (Sect. 2.4), mean serum IL-31 (a cytokine known to mediate pruritus) levels were significantly reduced from baseline in seladelpar 5 mg and 10 mg, but not placebo, recipients, respectively, at month 3 [3.8 to 1.7 pg/mL ($p = 0.0002$), 4.2 to 1.7 pg/mL ($p = 0.0003$) and 4.3 to 3.9 pg/mL] ($n = 53$, 53 and 55) [30]. The effect of oral seladelpar on ALP in clinical studies is reported in Sect. 2.4.

At a supratherapeutic dose (i.e. 20-fold the recommended dose), seladelpar did not prolong the corrected QT interval to any clinically relevant extent [14].

2.2 Pharmacokinetics

Following a single dose of seladelpar, systemic exposure increased dose proportionally across a 2–15 mg (0.2–1.5-fold the recommended dose) dose range and more than dose proportionally at higher doses [14]. With a 20-fold dose increase (i.e. from 10 mg to 200 mg), mean maximum concentration (C_{max}) and mean area under the concentration–time (AUC) values of seladelpar increased 70-fold and 27-fold, respectively. Following once-daily seladelpar dosing, steady state was reached by day 4 and the increase in AUC was < 30%. The median time to C_{max} was 1.5 h for seladelpar. In healthy individuals, no clinically relevant differences in the pharmacokinetics of seladelpar were seen following the administration of a high-fat meal [14].

Seladelpar is > 99% bound to plasma proteins [14]. In vitro, it is predominately metabolized by CYP2C9 and, to a lesser extent, by CYP2C8 and CYP3A4; the resulting major metabolites do not have pharmacological activity. Seladelpar is mostly eliminated in urine as metabolites. Following the administration of a single oral 10 mg dose of radiolabelled seladelpar, ≈ 73.4% and 19.5% of the dose was recovered in the urine (< 0.01% unchanged) and faeces (2.02% unchanged) within 216 h. Seladelpar has an elimination half-life of 6 h (mean value; following administration of a single 10 mg dose) in healthy individuals and 3.8–6.7 h in patients with PBC [14].

The pharmacokinetics of seladelpar are not affected to a clinically relevant extent by age (19–79 years), sex, race (White, Black or other), body weight (45.8–127.5 kg) or body mass index (17.6–45.0 kg/m^2) [14].

Patients with mild, moderate or severe renal impairment do not require adjustments in the dose of seladelpar (Sect. 1) [14]. The pharmacokinetics of seladelpar have not been studied in patients requiring haemodialysis [14]. Following a single oral 10 mg dose of seladelpar, seladelpar exposure was 1.7–1.8-fold higher in patients with PBC and mild hepatic impairment with portal hypertension and 1.6–1.9-fold higher in patients with PBC and moderate hepatic impairment (Child-Pugh B) compared with patients with PBC and mild hepatic impairment (Child-Pugh A) without portal hypertension [14]. After the administration of seladelpar 10 mg once daily for 28 days, accumulation ratios were < 1.2-fold in patients with PBC and mild hepatic impairment with portal hypertension and those with PBC and moderate hepatic impairment [14].

2.3 Drug Interactions

Seladelpar is a substrate of CYP2C8, CYP2C9 and CYP3A4, and the transporters BCRP, OAT3 and P-gp in vitro [14]. The concomitant use of seladelpar with an OAT3 inhibitor (e.g. probenecid) or a strong CYP2C9 inhibitor (e.g. sulphaphenazole) may increase the exposure of seladelpar and should therefore be avoided. Patients should be closely monitored for adverse events (AEs) when seladelpar is coadministered with a drug that is a dual moderate CYP2C9 inhibitor and moderate to strong CYP3A4 inhibitor (as increases in seladelpar exposure have been observed with this combination). The monitoring of patients who are CYP2C9 poor metabolizers is also advised when they are receiving concomitant seladelpar and a moderate to strong CYP3A4 inhibitor (as this combination may increase seladelpar exposure and thus the risk of AEs). Coadministration of seladelpar with a BCRP inhibitor (e.g. cyclosporine) may increase the exposure of seladelpar; therefore, patients receiving both these agents should be closely monitored for AEs.

Features and properties of seladelpar

Alternative names	LIVDELZI; MBX 8025; RWJ 800025; Seladelpar lysine
Class	Acetates; Anti-inflammatories; Antifibrotics; Antihyperlipidaemics; Hepatoprotectants; Small molecules
Mechanism of action	Peroxisome proliferator-activated receptor delta agonist
Route of administration	Oral
Pharmacodynamics	Mechanism by which seladelpar exerts its therapeutic effects in patients with primary biliary cholangitis may involve the inhibition of bile acid synthesis via the activation of peroxisome proliferator-activated receptor δ
Pharmacokinetics	Systemic exposure increased dose proportionally across a 2–15 mg dose range and more than dose proportionally at higher doses; median time to maximum concentration of 1.5 h; elimination half-life of 3.8–6.7 h in patients with primary biliary cholangitis
Most frequent adverse events	Headache, abdominal pain, nausea and abdominal distension
ATC codes	
WHO ATC code	A05A-X07 (Seladelpar); C10 (Lipid Modifying Agents)
EphMRA ATC code	A5 (Cholagogues and Hepatic Protectors); C10 (Lipid-Regulating/Anti-Atheroma Preparations)
Chemical name	(2S)-2,6-diaminohexanoic acid;2-[4-[(2R)-2-ethoxy-3-[4-(trifluoromethyl)phenoxy]propyl]sulfanyl-2-methyl-phenoxy]acetic acid;dihydrate

Biochemical response (e.g. ALP and bilirubin) should be monitored when rifampin therapy is initiated in patients receiving seladelpar as this combination may reduce systemic seladelpar exposure and thus lead to a delayed or suboptimal biochemical response. As bile acid sequestrants may reduce the absorption and systemic exposure of seladelpar, which may reduce its efficacy, seladelpar should be administered ≥ 4 h before or 4 h after consuming a bile acid sequestrant (or at as great an interval as possible). There were no clinically relevant differences in the pharmacokinetics of tolbutamide (a CYP2C9 substrate), midazolam (a CYP3A4 substrate), simvastatin and atorvastatin (CYP3A4 and OATP substrates) and rosuvastatin (a BCRP and OATP substrate) when they were each used concomitantly with seladelpar in clinical studies. Consult local prescribing information for further details [14].

2.4 Therapeutic Trials

2.4.1 Phase III RESPONSE Study

In the 12-month, randomized, double-blind, multinational, phase III RESPONSE (NCT04620733) study, a significantly greater proportion of adults with PBC receiving oral seladelpar 10 mg once daily than those receiving placebo achieved a biochemical response (primary endpoint) and ALP normalization (key secondary endpoint) [31]. At month 12, 61.7% of 128 seladelpar recipients and 20.0% of 65 placebo recipients [between-group difference (BGD) 41.7% (95% CI 27.7–53.4); $p < 0.001$] met the primary endpoint of biochemical response [defined as an ALP of < 1.67 × upper limit of normal (ULN), with a reduction from baseline of ≥ 15%, and a total bilirubin of ≤ 1.0 × ULN]. The biochemical response benefit of seladelpar over placebo was generally consistent across subgroups including the presence or absence of cirrhosis and whether concomitant UDCA was administered. ALP normalization (defined as an ALP of ≤ 1.0 × ULN) at month 12 was achieved by 25.0% and 0% of patients receiving seladelpar and placebo [BGD 25.0% (95% CI 18.3–33.2); $p < 0.001$]. Among patients with a pruritus numerical rating scale (NRS) score ≥ 4 [indicating moderate-to-severe pruritus; scores range from 0 (no itch) to 10 (worst itch imaginable)] at baseline ($n = 49$ and 23 in the seladelpar and placebo groups), the pruritus NRS score (key secondary endpoint) was lowered by a significantly greater extent with seladelpar than placebo [change from baseline to month 6 − 3.2 vs − 1.7 points; least-squares mean (LSM) BGD − 1.5 points (95% CI − 2.5, − 0.5); $p = 0.005$]. In the overall population, the change from baseline to month 6 in the pruritus NRS score was − 1.3 points and − 0.4 points in the respective groups [LSM BGD − 0.9 points (95% CI − 1.4, − 0.5)] [31].

In RESPONSE, eligible patients had a diagnosis of PBC, an ALP of ≥ 1.67 × ULN, AST and ALT up to 3 × ULN, a total bilirubin up to 2 × ULN and an estimated glomerular filtration rate (eGFR) > 45 mL/min/1.73 m^2, and had received treatment with UDCA for ≥ 12 months or had a history of unacceptable AEs with UDCA (with their last dose administered > 3 months before screening) [31]. Among the exclusion criteria were advanced PBC (defined as an albumin level below the lower limit of normal and a total bilirubin level > 1.0 × ULN), hepatic decompensation, and any other chronic liver disease. Randomization was stratified by baseline ALP (< 350 U/L or ≥ 350 U/L) and pruritus NRS score (< 4 or ≥ 4). Patients received UDCA as a standard-of-care background treatment unless they had a history of unacceptable AEs with this therapy. At baseline ($n = 193$), mean ALP and total bilirubin were 314.3 U/L (2.7 × ULN) and 0.76 mg/dL (0.69 × ULN); 27.5% and 13.0% of patients had an ALP of ≥ 350 U/L (3 × ULN) and a total bilirubin > ULN. The mean baseline pruritus NRS score was ≥ 4 in 37.3% of patients; 14.0% of patients had cirrhosis and 93.8% were taking UDCA (mean total daily dose 15.0 mg/kg) [31]. The ULN for ALP and total bilirubin was defined as 116 U/L and 1.1 mg/dL [14].

2.4.2 Phase III ENHANCE Study

In the randomized, double-blind, placebo-controlled, multinational, phase III ENHANCE (NCT03602560) study, oral seladelpar 10 mg once daily significantly improved biochemical responses and pruritus in adults with PBC who had had an inadequate response or intolerance to UDCA [32]. ENHANCE originally aimed to evaluate treatment through 12 months; however, it was terminated early following an erroneous safety signal in a concurrent seladelpar study in patients with NASH. Thus the timepoints for primary and secondary efficacy endpoint analyses were adjusted (from 12 months for biochemical responses and 6 months for pruritus) to 3 months. At month 3, seladelpar 5 mg and 10 mg once daily were significantly ($p < 0.0001$) more effective than placebo with regard to the proportion of patients meeting the primary endpoint (defined as an ALP of < 1.67 × ULN, with a reduction from baseline of ≥ 15%, and a total bilirubin of ≤ 1.0 × ULN) [57.1% and 78.2% vs 12.5%]. Notably, the response rate in the seladelpar 10 mg group was significantly more effective than that in the seladelpar 5 mg group ($p = 0.02$). A significant ($p < 0.05$) difference in this endpoint was seen early (at month 1) in both seladelpar groups versus placebo and between the seladelpar 10 mg group versus the seladelpar 5 mg group, and maintained (at month 6) in both seladelpar groups versus placebo. ALP normalization (key secondary endpoint; defined as an ALP of ≤ 1.0 × ULN) occurred in significantly more seladelpar 5 mg and 10 mg recipients than placebo recipients (5.4% and 27.3% vs 0%; $p = 0.002$ and < 0.0001) at

month 3. Among patients with a pruritus NRS score ≥ 4 at baseline (seladelpar 5 mg: $n = 17$; seladelpar 10 mg: $n = 18$; placebo $n = 18$), the mean reduction from baseline at month 3 was significantly greater with seladelpar 10 mg (− 3.14 vs − 1.55; $p = 0.02$), but not seladelpar 5 mg (− 2.01 vs − 1.55), than placebo [32].

ENHANCE enrolled patients with a diagnosis of PBC, an ALP of ≥ 1.67 × ULN and a total bilirubin ≤ 2 × ULN who had been receiving a stable and recommended dose of UDCA (generally 13–15 mg/kg/day) for the previous 12 months unless they were UDCA intolerant [32]. Patients who were receiving UDCA therapy prior to enrolment continued receiving UDCA. Among other criteria, patients were excluded if they had aspartate aminotransferase (AST) or alanine aminotransferase (ALT) of > 3 × ULN, advanced PBC (defined as an albumin level below the lower limit of normal and a total bilirubin of > 1.0 × ULN), an eGFR < 60 mL/min/1.73 m^2, and clinically significant hepatic decompensation or the presence of another chronic liver disease. At baseline, demographics and disease characteristics were well balanced across the treatment groups. Mean ALP and total bilirubin levels were 291.5 U/L (2.5 × ULN) and 0.73 mg/dL (0.66 × ULN); 31%, 24% and 12% of patients had a baseline pruritus NRS score ≥ 4, an ALP ≥ 350 U/L (3 × ULN) and a total bilirubin of > 1 × ULN, respectively [32].

2.4.3 Phase III NCT03301506 Studies

Continued therapy with oral seladelpar resulted in durable and progressive effects on serum biomarkers of cholestasis, and hepatocellular injury, according to data from an open-label, multinational, phase III, long-term safety study (NCT03301506; also known as CB8025-31731) in adults with PBC [33]. The study intended to enrol patients who had completed either a phase II dose-ranging study (NCT02955602) or ENHANCE and treat them for up to ≈ 5 years with either the dose of seladelpar they received in the parent study (2 mg, 5 mg or 10 mg) or an uptitrated dose. However, it was terminated early (at the same time that ENHANCE was terminated); thus, data from the patients enrolled up to that point were analysed. Among the 53 patients who had received therapy with seladelpar 5 mg ($n = 10$) or 10 mg ($n = 43$) once daily, with or without UDCA, for up to 2 years across the parent and extension studies, a biochemical response was achieved by 66% after 1 year of therapy and 79% after 2 years of therapy. ALP normalisation was reached by 26% of patients after 1 year and 42% of patients after 2 years. In patients with total bilirubin > ULN at baseline, total bilirubin ≤ ULN was achieved by 54% of 13 patients after 1 year of therapy and 43% of 7 patients after 2 years of therapy. A biochemical response was defined as an ALP < 1.67 × ULN, with a reduction from baseline of ≥ 15%, and a total bilirubin of ≤ ULN; ALP normalisation was defined as an ALP ≤ 1.0 × ULN (≤ 116 U/L) [33].

Along with the initiation of RESPONSE, NCT03301506 was restarted as the open-label, phase III, long-term ASSURE study (also known as CB8025-31731-RE) in adults with PBC [34, 35]. Preliminary data from this study demonstrated the longer-term efficacy of oral seladelpar [35]. Patients were eligible to enrol in ASSURE if they had previously participated in ENHANCE, NCT03301506 (CB8025-31731), NCT02955602 or the phase I NCT04950764 study (collectively known as legacy studies), or RESPONSE. Among patients from RESPONSE who had received up to 155 weeks of oral seladelpar 10 mg once daily across RESPONSE and ASSURE, a biochemical response was achieved by 62% (63/102) and 72% (21/29) of patients at 6 and 12 months. Among patients who received placebo during RESPONSE, a biochemical response was achieved by 75% (39/52) and 94% (15/16) of patients after 6 and 12 months' treatment with seladelpar 10 mg once daily in ASSURE. ALP normalization at 6 and 12 months of treatment in ASSURE was reached by 33% and 17% of patients who had received seladelpar in RESPONSE and 27% and

Key clinical trials of seladelpar (sponsored by Gilead Sciences)

Drug	Indication	Phase	Status	Location(s)	Identifier
Seladelpar	Primary biliary cholangitis	III	Recruiting	Multinational	NCT03301506 (ASSURE; EudraCT2020-005198-29; CB8025-31731-RE)
Seladelpar	Primary biliary cholangitis	III	Recruiting	Multinational	NCT06051617 (AFFIRM)
Seladelpar	Primary biliary cholangitis	III	Recruiting	USA	NCT06060665 (IDEAL)
Seladelpar	Primary biliary cholangitis	III	Completed	Multinational	NCT03301506 (EudraCT2017-003910-16; CB8025-31731)
Seladelpar	Primary biliary cholangitis	III	Completed	Multinational	NCT03602560 (ENHANCE)
Seladelpar	Primary biliary cholangitis	III	Completed	Multinational	NCT04620733 (RESPONSE)
Seladelpar	Primary biliary cholangitis	II	Completed	Multinational	NCT02955602
Seladelpar	Primary biliary cholangitis	II	Terminated	Multinational	NCT02609048

50% of those who had received placebo in RESPONSE. Among the patients from the legacy studies, a biochemical response was achieved by 73% (120/164) and 70% (69/99) of patients after 12 and 24 months' therapy in ASSURE. ALP normalization was achieved by 42% of patients after 12 months, a rate that was sustained through 24 months. A biochemical response was defined as an ALP of ≥ 1.67 × ULN, a reduction in ALP of 15% and a total bilirubin of ≤ ULN [35].

2.4.4 Phase II Studies

In a 52-week, open-label, multinational, phase II, dose-ranging study (NCT02955602), seladelpar dose-dependently improved biochemical markers of cholestasis in adults with PBC who were receiving or intolerant to UDCA [36]. At week 8, mean ALP (primary efficacy endpoint) was significantly ($p < 0.005$) reduced from baseline in all three seladelpar cohorts (2 mg: 26%; 5 mg: 33%; 10 mg: 41%) [$n = 11$, 49 and 52, respectively]. At week 52 in the seladelpar 2 mg, 5 mg and 10 mg groups, respectively, 64%, 53% and 67% of patients met the composite biochemical endpoint (defined as an ALP of < 1.67 × ULN, with a reduction from baseline of ≥ 15%, and a normal total bilirubin) and 9%, 13% and 33% achieved ALP normalization. Patients in NCT02955602 had a diagnosis of PBC and an ALP of > 1.67 × ULN and were either receiving stable recommended doses of UDCA for the prior 12 months or were intolerant to UDCA. At baseline, 71% of patients had pruritus and 21% had cirrhosis, and mean ALP in the seladelpar 2 mg, seladelpar 5 mg and seladelpar 10 mg groups ($n = 11$, 53 and 55), respectively, was 300 U/L, 345 U/L and 295 U/L [36].

Therapy with oral seladelpar 50 mg or 200 mg once daily for 12 weeks normalized ALP in patients with PBC who inadequately responded to UDCA treatment in a randomized, double-blind, placebo-controlled, phase II, dose-ranging, proof-of-concept study (NCT02609048) [37]. The mean reduction in ALP was significantly ($p < 0.0001$) greater with seladelpar 50 mg and seladelpar 200 mg than with placebo (− 53% and − 63% vs − 2%) [$n = 13$, 10 and 12, respectively]. Patients in NCT02609048 had a diagnosis of PBC, an ALP ≥ 1.67 × ULN and had been on a stable and recommended dose of UDCA for the past 12 months. At baseline, ALP was 312 U/L, 248 U/L and 233 U/L in the seladelpar 50 mg, seladelpar 200 mg and placebo groups, respectively. The study was terminated during ongoing recruitment (Sect. 2.5) [37].

2.5 Adverse Events

In adults with PBC participating in RESPONSE, the incidence of AEs, including serious AEs (SAEs), was generally similar between the seladelpar 10 mg once daily and placebo groups [31]. AEs were reported in 86.7% of 128 seladelpar recipients and 84.6% of 65 placebo recipients. COVID-19 (18.0% vs 15.4%), headache (7.8% vs 3.1%), abdominal pain (7.0% vs 1.5%), nausea (6.2% vs 4.6%) and abdominal distension (6.2% vs 3.1%) were the most frequently reported AEs (incidence ≥ 6.2% in either group and occurring more frequently in the seladelpar group than the placebo group) [31]. In the seladelpar and placebo groups, pruritus AEs occurred in 4.7% and 15.4% of patients [31] and fractures in 4% and 0% of patients [14]. After receiving seladelpar, the median time to fracture was 295 days [14]. SAEs were reported in 7.0% of seladelpar recipients and 6.2% of placebo recipients [31]. No SAEs occurred in more than one patient and none were deemed by the investigators to be related to seladelpar. AEs resulting in treatment discontinuation occurred in 3.1% and 4.6% of patients in the seladelpar and placebo groups. No deaths were reported in RESPONSE. The safety profile of seladelpar was similar between patients who had cirrhosis at baseline and those that did not [31].

Oral seladelpar appeared safe and well tolerated in adults with PBC participating in ENHANCE [mean (SD) exposure duration 17.7 (11.7) weeks]; it was not associated with emergent safety concerns [32]. At least one TEAE occurred in 62.9% of 89 seladelpar 5 mg recipients, 65.2% of 89 seladelpar 10 mg recipients and 73.6% of 87 placebo recipients. The most frequently reported (incidence ≥ 7.0% in any group and occurring more frequently in the seladelpar groups than the placebo group) TEAEs were upper abdominal pain (9.0% of seladelpar 5 mg recipients and 6.7% of seladelpar 10 mg recipients vs 3.4% of placebo recipients), nausea (5.6% and 7.9% vs 4.6%) and headache (5.6% and 7.9% vs 1.1%). Pruritus (qualitative) occurred in 3.4% of seladelpar 5 mg recipients and 11.2% of seladelpar 10 mg recipients compared with 12.6% of placebo recipients, and fatigue in 2.2% and 4.5% versus 9.2% of patients, respectively. In the seladelpar 5 mg, seladelpar 10 mg and placebo groups, respectively, at least 1 grade ≥ 3 TEAE occurred in 3.4%, 5.6% and 6.9% of patients, ≥ 1 treatment-related TEAE was reported in 28.1%, 16.9% and 18.4% of patients, and ≥ 1 serious TEAE was observed in 3.4%, 1.1% and 3.4% of patients. Approximately 2% of patients in each group experienced a TEAE resulting in study discontinuation. No treatment-related SAEs or treatment-related grade ≥ 3 TEAEs were reported, and no patients died [32].

Seladelpar was safe and well tolerated over the longer term in adults with PBC participating in NCT03301506 (CB8025-31731) [33]. Among the 106 patients treated with seladelpar 2 mg, 5 mg or 10 mg once daily for up to 2 years, 95% experienced ≥ 1 TEAE, with pruritus (24.5%), nausea (21.7%), fatigue (18.9%), arthralgia (17.9%), diarrhoea (17.9%) and urinary tract infection (17.9%) the most frequently reported (≥ 15%). Notably, the frequency of TEAEs

tended to decrease during the second year: from year 1 to year 2, there were decreases in the incidence of pruritus (22.6% to 2.8%), nausea (15.1% to 7.5%) and fatigue (12.3% to 9.4%). In the seladelpar 2 mg, 5 mg and 10 mg groups (n = 10, 46 and 50), respectively, the incidence of TEAEs was 100%, 91% and 98% and the incidence of treatment-related TEAEs was 60%, 37% and 32% over the 2-year treatment period. Only one grade ≥ 3 treatment-related TEAE was observed (in a seladelpar 10 mg recipient). Serious TEAES (none of which were considered to be related to treatment) occurred in 1 seladelpar 2 mg recipient, 9 seladelpar 5 mg recipients and 11 seladelpar 10 mg recipients. No serious liver-related TEAEs or grade ≥ 3 serious treatment-related TEAEs were reported. Four patients discontinued treatment prior to study termination due to safety-related reasons (one of which was possibly related to seladelpar). One patient (a seladelpar 5 mg recipient) died 7 months after discontinuing seladelpar [33].

As of 31 January 2024, preliminary data from the ASSURE (NCT03301506; CB8025-31731-RE) study demonstrated that the long-term use of oral seladelpar appeared safe and well tolerated in adults with PBC [35].

At dosages up to 10 mg once daily, seladelpar was safe and well tolerated, with no concerning safety signals reported, in the phase II NCT02955602 study [36]. The most frequently reported TEAEs in seladelpar 2 mg, seladelpar 5 mg and seladelpar 10 mg recipients (n = 11, 53 and 55), respectively, were pruritus (54.5%, 20.8% and 21.8%), diarrhoea (36.4%, 13.2% and 16.4%) and fatigue (27.3%, 17.0% and 10.9%). The incidences of TEAEs (100%, 88.7% and 85.5%), treatment-related TEAEs (54.5%, 39.6% and 27.3%), grade ≥ 3 TEAEs (9.1%, 15.1% and 9.1%) and SAEs (9.1%, 15.1% and 9.1%) were generally similar across the seladelpar 2 mg, seladelpar 5 mg and seladelpar 10 mg groups, respectively. No patient experienced treatment-related SAEs, and no patients died during the study [36].

During ongoing recruitment of the phase II NCT02609048 study, one patient receiving seladelpar 50 mg once daily and two patients receiving seladelpar 200 mg once daily developed asymptomatic and fully reversible (2–4 weeks post treatment discontinuation) grade 3 increases in ALT (≥ 5 × ULN to 20 × ULN) [37]. All three cases were deemed to be related to seladelpar; therefore the study was terminated (at which point 41 patients had been randomized). Apart from the aforementioned ALT events, no AEs in the study were considered severe. No serious AEs and no deaths were reported [37].

Therapy with seladelpar was well tolerated in patients with PBC and compensated liver cirrhosis, with its safety comparable to that seen in patients with PBC without cirrhosis, according to limited pooled data from ENHANCE and the phase II NCT02955602 study [38].

2.6 Ongoing Clinical Trials

The randomized, double-blind, placebo-controlled, multinational phase III AFFIRM (NCT06051617) study is currently recruiting adults with PBC and compensated cirrhosis. The open-label, multinational phase III ASSURE (NCT03301506; CB8025-31731-RE) study is currently recruiting patients and plans to evaluate the long-term efficacy and safety of seladelpar in adults with PBC. The randomized, double-blind, placebo-controlled, multicentre phase IIII IDEAL (NCT06060665) study will evaluate the effect of seladelpar on the normalization of ALP in adults with PBC and an incomplete response or intolerance to UDCA.

3 Current Status

Seladelpar received its first approval on 14 August 2024 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 [14, 15].

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