GASTROENTEROLOGY & HEPATOLOGY
The Independent Peer-Reviewed Journal

December 2024 Volume 20, Issue 12, Supplement 12

A SPECIAL MEETING REVIEW EDITION

Highlights in Primary Biliary Cholangitis From the AASLD 2024 Liver Meeting

A Review of Selected Presentations From the American Association for the Study of Liver Diseases 2024 Liver Meeting • November 15-19, 2024 • San Diego, California

Special Reporting on:

- Efficacy and Safety of Seladelpar in Patients With Primary Biliary Cholangitis and Compensated Cirrhosis in the Phase 3 Placebo-Controlled RESPONSE Trial
- Elafibranor Long-Term Efficacy and Safety and Impact on Fatigue in Primary Biliary Cholangitis: Interim Results From the Open-Label Extension of the ELATIVE Trial Up to 3 Years
- Attenuation, Near Resolution, and Prevention of Pruritus in Patients With Primary Biliary Cholangitis Treated With Seladelpar: A Secondary Analysis of Patterns of Pruritus Change in the RESPONSE Trial
- Fibrate-OCA (Fi-OCA) Study – A Global Snapshot of PBC Practice Around the Globe
- Long-Term Efficacy and Safety of Open-Label Seladelpar Treatment in Patients With Primary Biliary Cholangitis: Pooled Interim Results for Up to 3 Years From the ASSURE Study
- One-Year Treatment With Elafibranor in the Phase 3 ELATIVE Trial Improves GLOBE and UK-PBC Prognostic Scores
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PLUS Meeting Abstract Summaries

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Efficacy and Safety of Seladelpar in Patients With Primary Biliary Cholangitis and Compensated Cirrhosis in the Phase 3 Placebo-Controlled RESPONSE Trial

Primary biliary cholangitis (PBC) is a chronic autoimmune cholestatic disease that primarily affects women 40 to 70 years of age.[1] The current standard initial treatment of PBC is ursodeoxycholic acid (UDCA). Timely diagnosis and appropriate treatment can prevent progression of PBC to cirrhosis and liver failure. However, for patients with PBC who do not attain a complete response to UDCA or develop intolerance and for patients who progress to cirrhosis, there is a need for safe and effective second-line therapies.[1]

Peroxisome proliferator-activated receptor (PPAR) agonists, which signal through specific intranuclear receptors to control metabolic processes, have demonstrated activity as second-line therapies for patients with PBC.[1] In August 2024, the oral selective PPAR-delta agonist seladelpar received accelerated approval from the US Food and Drug Administration (FDA) for the treatment of PBC in combination with UDCA in adults with an inadequate response to UDCA or as monotherapy in patients unable to tolerate UDCA, based on the results of the RESPONSE study.[2]

The 12-month placebo-controlled phase 3 RESPONSE study compared seladelpar with placebo in patients who had an inadequate response or intolerance to UDCA. A total of 193 patients were stratified by alkaline phosphatase (ALP) level (<350 vs ≥350 U/L) and pruritus numerical rating scale (NRS) score (<4 vs ≥4) and were randomly assigned 2:1 to seladelpar 10 mg daily (n=128) or placebo (n=65).[2]

The study met its primary endpoint, demonstrating a significant improvement in the proportion of patients attaining a composite biochemical response, defined as an ALP level less than 1.67 × upper limit of normal (ULN), with a decrease of 15% or more from baseline, and a normal bilirubin level at 12 months (61.7% vs 20.0% with placebo; P<.001).[3]

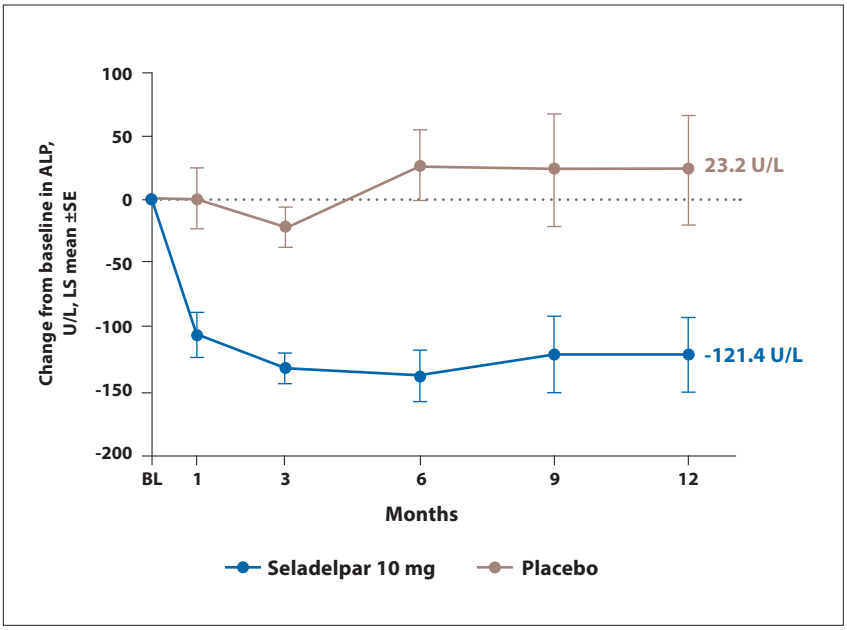

Figure 1. Reduction in ALP in patients with primary biliary cholangitis and cirrhosis treated with seladelpar vs placebo in the RESPONSE study. ALP, alkaline phosphatase; BL, baseline; LS, least squares. Adapted from Villamil A, et al. AASLD abstract 700. *Hepatology.* 2024;80(suppl 1).[3]

At the American Association for the Study of Liver Diseases (AASLD) 2024 Liver Meeting, outcomes in the subset of patients with PBC and cirrhosis from the RESPONSE trial were presented.[3] Overall, 27 patients with cirrhosis were enrolled in the trial, accounting for 14% of patients in each arm. No patients met the criteria for cirrhosis based on laboratory findings alone, and 60% of patients met at least 2 criteria. Baseline characteristics showed higher liver stiffness values in patients with cirrhosis vs those without cirrhosis, lower platelet counts, and higher ALP levels. Two patients in the seladelpar arm had a Child-Pugh score 6.

The efficacy analysis showed rapid, sustained declines in ALP with seladelpar regardless of cirrhosis status. In patients with cirrhosis, the mean change in ALP from baseline to 12 months was -121.4 U/L in the seladelpar arm and +23.2 U/L in the placebo arm (Figure 1). In patients without cirrhosis, the mean change in ALP with seladelpar and placebo was -134.8 U/L and -18.0 U/L, respectively.

Seladelpar was also associated with sustained declines in gamma-glutamyl transferase (GGT) levels. Total bilirubin measurements remained stable regardless of the presence of cirrhosis; mean international normalized ratio and Model for End-Stage Liver Disease scores were similar between groups over the 12-month period. Transient elastography showed stable liver stiffness across study groups.

The safety profile of seladelpar in patients with cirrhosis was similar to that in the overall population. In patients with cirrhosis receiving seladelpar, no adverse events (AEs) led to

The additional analyses of the RESPONSE study will allow health care professionals to safely utilize seladelpar in the setting of cirrhosis. Although OCA has a black box warning and a new FDA safety alert on OCA was issued earlier this month, OCA remains available as second-line treatment for patients without cirrhosis/clinically significant portal hypertension. Seladelpar is now a safe option for patients with PBC who have portal hypertension and a history or presence of decompensation.

— Robert G. Gish, MD

discontinuation of treatment. There were no treatment-related serious AEs. Two patients with cirrhosis receiving seladelpar developed liver-related AEs: 1 patient had grade 1 hepatomegaly, and 1 patient had grade 1 ascites and then experienced a serious AE of esophageal varices hemorrhage. Muscular-related AEs were mild and not associated with creatinine phosphokinase increases. Laboratory events in patients with cirrhosis included alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations in 1 patient receiving seladelpar and 2 patients receiving placebo, and total bilirubin elevations in 1 patient receiving seladelpar and 2 patients receiving placebo. The investigators concluded that seladelpar was safe and well tolerated in patients with compensated cirrhosis.

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Elafibranor Long-Term Efficacy and Safety and Impact on Fatigue in Primary Biliary Cholangitis: Interim Results From the Open-Label Extension of the ELATIVE Trial Up to 3 Years

Elafibranor is an oral PPAR agonist that exerts effects on both PPAR-alpha and PPAR-gamma. In 2024, elafibranor received FDA approval for the treatment of PBC in combination with UDCA or as monotherapy for adults who have an inadequate response to UDCA or are unable to tolerate it, based on the results of the ELATIVE trial.[1] In the multinational, phase 3, double-blind, placebo-controlled ELATIVE trial, elafibranor administered at 80 mg once daily was associated with significantly greater improvements in biochemical indicators of cholestasis at week 52 compared with placebo in patients with PBC with an inadequate response to or unacceptable side effects with UDCA.[1]

Interim results from the open-label extension (OLE) of the ELATIVE trial were presented in posters at the AASLD 2024 Liver Meeting.[2,3] For patients who received placebo during the double-blind period and crossed

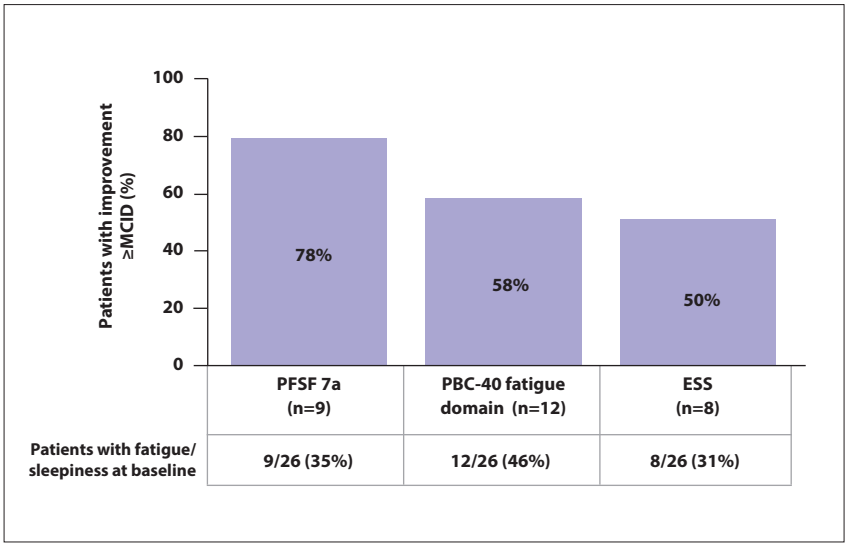

Figure 2. Proportion of patients with primary biliary cholangitis receiving elafibranor in the phase 3 ELATIVE trial who had moderate to severe fatigue or excessive sleepiness at baseline with improvements greater than or equal to the MCID at week 130. ESS, Epworth Sleepiness Scale; MCID, minimal clinically important difference; PBC-40, 40-item scale on health-related quality of life in primary biliary cholangitis; PFSF 7a, Patient-Reported Outcome Measurement Information System (PROMIS) Fatigue Short Form 7a. Adapted from Swain MG, et al. AASLD abstract 5042. Presented at: The Liver Meeting; November 15-19, 2024; San Diego, CA.[3]

over to elafibranor, the OLE baseline was considered the last available measurement before the first OLE elafibranor dose; data are available for this cohort with a maximum follow-up of 52 weeks.[2] For patients who received elafibranor in the double-blind period, OLE baseline was defined as the time of initial randomization; data are available with up to 156 weeks of follow-up for this cohort.[3]

An analysis by Kowdley and colleagues reported interim results after up to 3 years in the ongoing OLE of the ELATIVE trial.[2] The analysis included 138 patients of whom 45 were in the placebo arm and crossed over to elafibranor. Overall, elafibranor was associated with sustained improvements in biomarkers of cholestasis, including ALP and total bilirubin. Although mean reductions in ALP remained stable during the OLE, biochemical responses fluctuated over time. Approximately 30% of patients with a biochemical response at the beginning of the OLE had at least 1 study visit during the OLE in which they did not achieve a biochemical response, and 37% of the patients who were nonresponders at the beginning of the OLE had at least 1 study visit in which they achieved a biochemical response. Surrogates for fibrosis, including the median change in liver stiffness measurement and enhanced liver fibrosis score, were also sustained over the OLE period up to week 156. Measures of pruritus improved over time in patients who crossed over from placebo, with an improvement similar to patients initially assigned to elafibranor. No new safety findings were noted. The most frequent treatment-emergent AEs in the OLE were abdominal pain, diarrhea, nausea, and vomiting.

Given the significant impact of fatigue on patients with PBC, Swain and colleagues conducted an analysis evaluating the effects of elafibranor on fatigue-related outcome in the OLE.[3] Among patients with moderate to severe fatigue or excessive sleepiness at baseline, 50% to 69% had clinically meaningful improvements in fatigue and sleep from baseline to week 104, and 50% to 78% had improvements from baseline to week 130 (Figure 2). Improvements in fatigue and sleep were also observed in the overall population but were more pronounced in those with moderate to severe fatigue or excessive sleepiness at baseline.

> Three-year data from the ELATIVE trial on elafibranor provide great confidence in the ability of the treatment to provide stable improvements in liver enzymes and function in patients with PBC, without breakthrough increases of ALP, AST, ALT, bilirubin, or GGT.
>
> — Robert G. Gish, MD

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Attenuation, Near Resolution, and Prevention of Pruritus in Patients With Primary Biliary Cholangitis Treated With Seladelpar: A Secondary Analysis of Patterns of Pruritus Change in the RESPONSE Trial

Cholestatic pruritus is a significant consequence of PBC, occurring in approximately 80% of patients and causing substantial reductions in quality of life (QOL).[1] Cholestatic pruritus can even become an indication for liver transplant in the most severe cases.[2] Off-label treatment options for cholestatic pruritus include rifampicin and fibrates, although there are limitations with these options.[2] There is a need for therapies for PBC that improve both biochemical disease markers and pruritus.

In the phase 3 placebo-controlled RESPONSE trial, in which seladelpar demonstrated significant reductions in itch compared with placebo as measured by the pruritus NRS after 6 months, the secondary endpoint of PBC-40 Itch domain and the exploratory endpoint of 5-D Itch scale showed similar improvements in pruritus with seladelpar.[3]

In a secondary analysis from the RESPONSE trial, Kremer and colleagues reported more detailed outcomes regarding changes in pruritus and QOL.[4] Among the 49 patients in the seladelpar arm with an NRS of 4 or higher at baseline, the mean itch intensity declined to a mild level (NRS score >0 to <4) by month 12. In contrast, of the 23 patients in the placebo arm with an NRS of 4 or higher at baseline, mean itch inten-

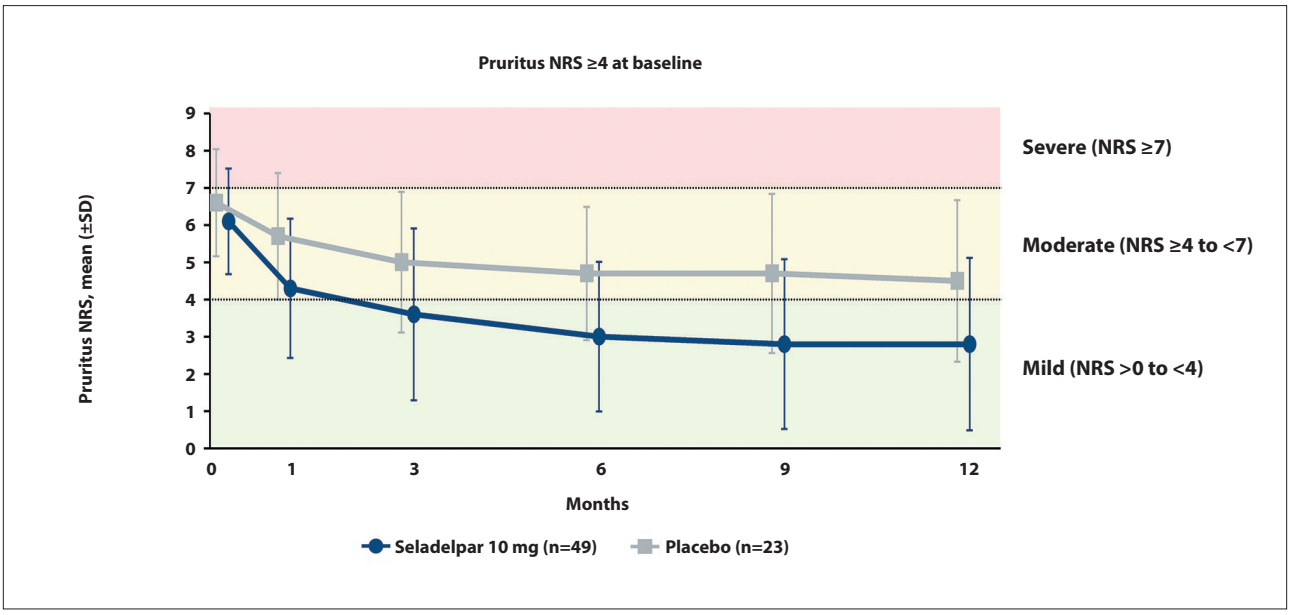

Figure 3. Reduction in mean pruritus NRS from moderate to mild by month 12 in patients with primary biliary cholangitis treated with seladelpar who had moderate to severe pruritus at baseline in the RESPONSE study. NRS, numerical rating scale. Adapted from Kremer AE, et al. AASLD abstract 703. *Hepatology.* 2024;80(suppl 1).[4]

sity remained in the moderate range (Figure 3).

Seladelpar was also associated with a higher likelihood of attaining reductions in NRS by month 12 than placebo, including reductions of at least 3 points (46.9% vs 21.7%) and reductions of at least 4 points (30.6% vs 8.7%). In the seladelpar arm, reductions in NRS to a score of 0 or 1, indicating near resolution of itch, were attained by month 12 in 26.5% of patients with moderate to severe pruritus at baseline (NRS ≥4), and 18.8% of patients with severe pruritus at baseline (NRS ≥7). No patients in the placebo arm with a baseline NRS of 4 or higher attained an NRS of 0 or 1.

Patients with severe itch at baseline also reported reductions in itch, sleep disturbance, and fatigue as assessed by the PBC-40. Among patients with clinically significant itch at baseline (defined as a PBC-40 ≥7), seladelpar was associated with improvements in itch, sleep, and fatigue. The PBC-40 was less than 7 in 40% of patients in the seladelpar arm with a PBC-40 of 7 or higher at baseline, compared with 20% of patients in the placebo arm.

There are different pruritus scoring systems that can be used in PBC. With the pruritus NRS (the preferred scale of regulatory agencies), itch intensity can be categorized as none (0), mild (1-3), moderate (4-6), severe (7-8), or very severe (≥9). Other scales include the PBC-40 patient-reported questionnaire; the Visual Analog Scale, which assesses patients' subjective sensation of their itch; the verbal rating scale, which categorizes patient itch as no itch to severe itch on a Likert scale; the 12-Item Pruritus Severity Scale, which categorizes pruritus severity as mild, moderate, or severe; and ItchyQuant, an illustrated numeric rating scale that rates the severity of itch over the past 7 days. The pruritus NRS is an excellent option and fully validated, as demonstrated in patients on seladelpar in the RESPONSE study.

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Finally, no new itching developed in patients in the seladelpar arm without itching at baseline, whereas 26.7% of patients in the placebo arm developed itch at 12 months. Safety analyses found no difference in the incidence of AEs based on baseline itch severity.

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Fibrate-OCA (Fi-OCA) Study – A Global Snapshot of PBC Practice Around the Globe

Until 2023, the main options for the second-line treatment of PBC after first-line UDCA were obeticholic acid (OCA) and bezafibrate. OCA was evaluated in the randomized, placebo-controlled, phase 3 POISE trial, demonstrating improvements in ALP and total bilirubin at 12 months.[1] Bezafibrate was evaluated in combination with UDCA as second-line therapy in the BEZURSO trial, demonstrating higher complete biochemical response rates over placebo plus UDCA.[2]

Use of these second-line therapies is limited by differential access worldwide, a lack of real-world data regarding outcomes with these therapies, and a lack of tools to effectively individualize therapy. To better understand the use of current second-line therapies worldwide, Ronca and colleagues with the Global PBC Study Group conducted a retrospective multicenter cohort study evaluating real-world use of these agents as second-line therapy worldwide in patients with PBC.[3]

Centers from the United States, Canada, Argentina, Europe, Israel, and Japan enrolled patients with PBC with at least 12 months of follow-up on second-line treatment with fenofibrate, bezafibrate, or OCA. Patients with overlap syndromes with autoimmune hepatitis or concomitant chronic liver disease were excluded.

The analysis included 1825 patients, of whom 887 received fibrates and 938 received OCA. Overall, the median age was 49.0 years at the time of diagnosis and 56.6 years at the time of second-line treatment. Males accounted for 11.6% of the population. Cirrhosis was present at diagnosis in 25.5% of patients and present at the time of second-line treatment in 25.2%. Second-line treatment changes included switching agents in 7.6% and adding treatment in 8.7%. The median time from second-line to third-line

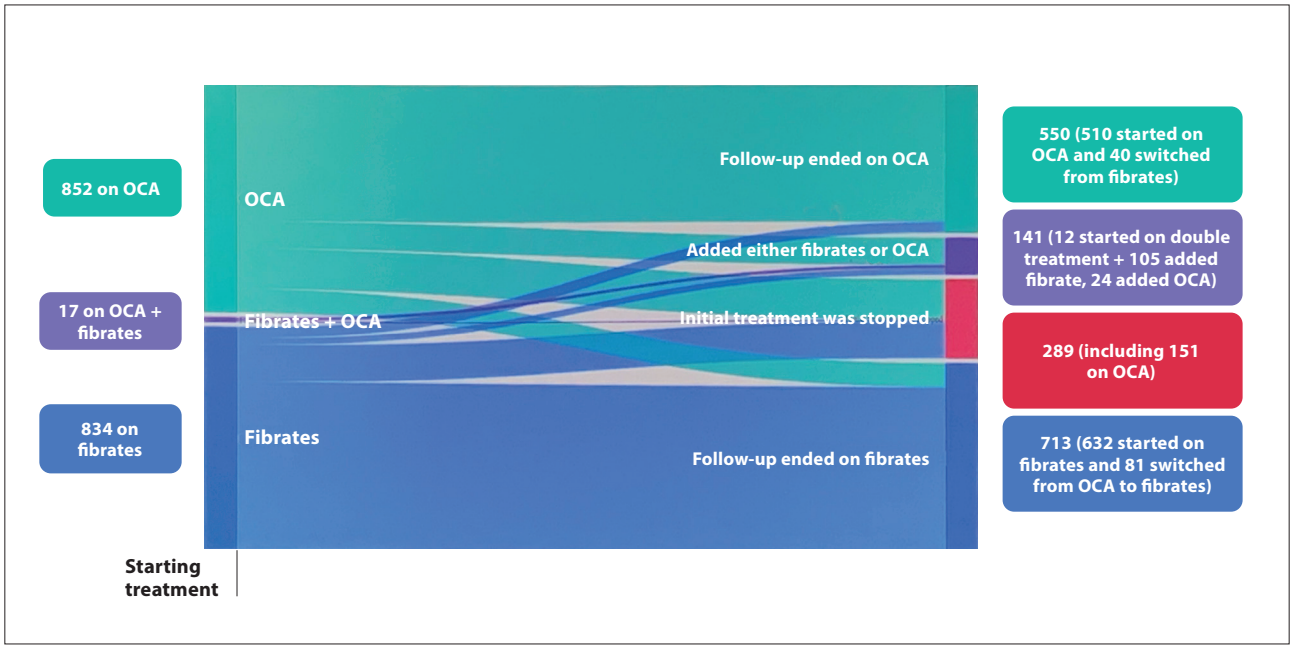

Figure 4. Sankey plots summarizing the journey of a cohort of 1825 patients from around the world with primary biliary cholangitis not responding to ursodeoxycholic acid on second-line treatment with OCA or fibrates. OCA, obeticholic acid. Adapted from Ronca V, et al. AASLD abstract 724. *Hepatology.* 2024;80(suppl 1).[3]

Fibrates are very commonly used off-label in the European Union and Canada for PBC. This use is very interesting because there are no global phase 3, placebo-controlled studies with the fibrate family of medications for PBC. In the United States, fibrates—particularly fenofibrate—are occasionally used off-label for PBC treatment in spite of a black box warning for liver and renal toxicity and possible severe muscle problems. The fenofibrate label states that it should not be used in patients with chronic liver disease.

— Robert G. Gish, MD

treatment was 24.0 months. Orthotopic liver transplant was performed in 4.6% of patients, and 4.6% of patients had died at the time of analysis.

Compared with patients receiving fibrates (n=887), patients receiving OCA (n=938) had higher rates of cirrhosis at baseline (30% vs 12.4%; *P*<.001) and at the time of second-line treatment (28.4% vs 19.5%; *P*<.0001), higher rates of switching second-line treatment (9.8% vs 5.4%) or adding treatment (14.4% vs 3.0%) (*P*<.001), a shorter median time before stopping treatment (18.0 vs 26.0 months; *P*=.012), a shorter time from first-line to second-line treatment (72.0 vs 51.0 months; *P*<.001), and shorter follow-up on second-line treatment (*P*<.001).

An analysis of cohort features found geographic differences based on whether patients were in America (n=432), Europe (n=1143), or Japan (n=214). Patients in Japan tended to be older (*P*<.001) and had a higher proportion of males (24.3% vs 6.7% in America and 10.9% in Europe) (*P*<.001). Patients in America were significantly more likely than patients in Europe to change treatment (*P*<.001). Rates of pruritus and fatigue were higher in American and European patients than in Japanese patients.

A comparison of clinical features in patients receiving bezafibrate (n=500) or fenofibrate (n=175) found no significant differences in choice of fibrate based on age, rate of cirrhosis, liver transplant, and death. The patients on fenofibrate had a longer time before starting the second-line treatment, 77 months compared with 41 months on bezafibrate, and also had a higher rate of switching treatment to bezafibrate or to OCA.

In an analysis of treatment sequences, 852 patients started on OCA, 17 started on OCA plus fibrates, and 834 started on fibrates. By the end of follow-up, 550 patients were receiving OCA, including 40 who switched from fibrates, 141 were receiving combination (12 who started double treatment, 105 who added a fibrate, and 24 who added OCA), 289 had stopped treatment (including 151 patients who had started with OCA), and 713 were still receiving fibrates (including 81 patients who switched from OCA to fibrates) (Figure 4).

The most frequent reasons for interrupting OCA were pruritus (31.8%), hepatic events (9.6%), gastrointestinal symptoms (6.3%), insufficient response (5%), and an FDA warning (2.9%). The most frequent

ABSTRACT SUMMARY Alkaline Phosphatase Changes With Seladelpar Across Subgroups of Primary Biliary Cholangitis Patients in the RESPONSE Trial

An analysis from the RESPONSE trial focused on changes in ALP levels across patient subgroups (Abstract 2410). At baseline, ALP levels were 350 U/L or higher in 27% of patients in the seladelpar arm and 28% of patients in the placebo arm. By month 12, seladelpar was associated reductions in ALP levels in key subgroups including by age, sex, race, baseline ALP level, total bilirubin, use of UDCA, use of prior OCA and/or fibrates, and the presence of cirrhosis. Reductions in ALP levels in the seladelpar arm were similar across baseline ALP quartiles. Although the greatest change in mean ALP level occurred in the highest quartile, mean ALP remained above 1.67 × ULN after 12 months in these patients. Seladelpar was also associated with a higher proportion of patients attaining different ALP reduction thresholds, including 20% or higher (78.9% vs 23.1% with placebo), 30% or higher (71.9% vs 7.7%), and 40% or higher (59.4% vs 6.2%). Moreover, 80% of patients in the seladelpar arm who did not meet the composite endpoint for biochemical response at 12 months experienced declines in ALP. In contrast, ALP increases occurred in 29.2% of patients in the placebo group vs 5.5% in the seladelpar group by 12 months. The safety profile was similar with seladelpar and placebo whether patients had a baseline ALP of less than 350 U/L or greater than or equal to 350 U/L.

reasons for interrupting fibrates were high transaminases (17.5%), renal dysfunction (9.8%), muscle pain (7.6%), gastrointestinal symptoms (7%), insufficient response (6.0%), and hepatic events (5.6%).

The investigators concluded that differences in access to therapy and selection of therapy yield differences in treatment pictures geographically. The high rate of treatment changes and discontinuation suggest suboptimal treatment selection. A more granular definition of international cohorts could provide greater information on patients' treatment trajectories, which could enable the development of treatment allocation tools.

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Long-Term Efficacy and Safety of Open-Label Seladelpar Treatment in Patients With Primary Biliary Cholangitis: Pooled Interim Results for Up to 3 Years From the ASSURE Study

The ongoing open-label phase 3 ASSURE trial is evaluating the long-term efficacy and safety of seladelpar 10 mg in patients with PBC who had received seladelpar in the placebo-controlled RESPONSE trial or in other earlier seladelpar trials.[1]

A total of 337 patients have been enrolled in the ASSURE study, including 179 patients from legacy studies, 104 patients from the seladelpar arm of the RESPONSE trial, and 54 patients from the placebo arm of the RESPONSE trial. As of the data cutoff, 124 patients had at least 24 months of seladelpar exposure. The mean age of patients at baseline was 58.1 years; 94% of patients were female and 16% had cirrhosis.

Interim results reported by Lawitz and colleagues show that the composite biochemical response endpoint (defined as an ALP <1.67 × ULN, an ALP decrease ≥15%, and a normal total bilirubin level) was met in 73% of patients at month 12, 73% of patients at week 24, and 81% of patients at month 30 (Figure 5). The ALP normalization rate at month 30 was 41% (15 of 37). At month 30, ALT had normalized in 90% (17 of 19) of patients with elevated ALT at baseline. Among 37 patients with month 30 data, the mean percentage change from baseline in ALT, total bilirubin, and GGT was -29%, -5%, and -42%, respectively. Among 99 patients with moderate to severe pruritus at baseline, the mean change in pruritus NRS from baseline

> The risk-benefit ratio for a treatment is important to all health care professionals, and data beyond the year 1 data used for licensing are an essential part of a clinician's assessment of the treatment risk-benefit ratio. As demonstrated in this interim analysis of the ASSURE study, which included patients with PBC who participated in prior clinical seladelpar studies, the 3 years of safety and efficacy data provide a marked increase in confidence for seladelpar use.
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> — Robert G. Gish, MD

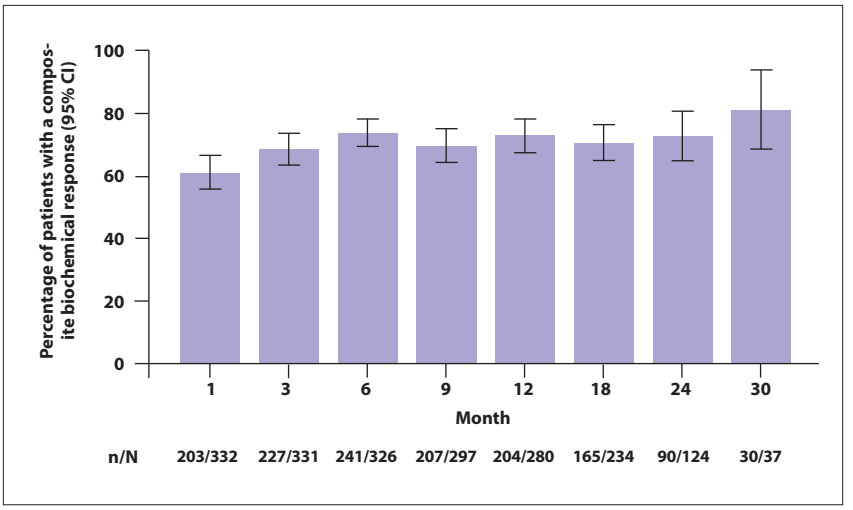

Figure 5. Composite biochemical response, a key efficacy endpoint, in patients with primary biliary cholangitis treated with seladelpar in the ASSURE study was met in 73% (204/280), 73% (90/124), and 81% (30/37) of patients at months 12, 24, and 30. Adapted from Lawitz EJ, et al. AASLD abstract 5044. Presented at: The Liver Meeting; November 15-19, 2024; San Diego, CA.[1]

to 6 months was -3.3.

No new safety issues or changes in AE frequency were observed after up to 3 years of treatment. The most common AEs were COVID-19, pruritus, and nausea; most AEs of interest were grade 1 or 2 in severity. No serious treatment-related AEs were reported. One death caused by autoimmune hemolytic anemia was considered unrelated to seladelpar use. Rates of exposure-adjusted liver, muscle, and renal AEs were stable or decreased over the 3-year period.

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One-Year Treatment With Elafibranor in the Phase 3 ELATIVE Trial Improves GLOBE and UK-PBC Prognostic Scores

The GLOBE and UK-PBC are scoring systems that were developed and validated independently to predict outcomes in patients with PBC.[1,2] The GLOBE formula incorporates age, total bilirubin, ALP, albumin, and platelet count, whereas the UK-PBC formula incorporates ALP, ALT or AST, total bilirubin, albumin, and platelet count.[1,2]

The GLOBE and UK-PBC models were developed in patients receiving UDCA but have demonstrated utility in patients receiving OCA.[3] The models demonstrate greater prognostic value than dichotomous response criteria.[3] Kowdley and colleagues reported outcomes of an analysis evaluating GLOBE and UK-PBC scores in patients receiving elafibranor or placebo in the phase 3 ELATIVE trial.[4]

Overall, baseline demographics and clinical and laboratory parameters that contribute to the GLOBE and UK-PBC scores were well balanced between the elafibranor and placebo arms. Both scores improved after 4 weeks in the elafibranor arm and continued to improve through 52 weeks (Figure 6). During the 52-week period, changes in all contributing laboratory parameters were observed in the elafibranor arm, including mean ALP (-117.7 U/L), mean total bilirubin (-0.04 mg/dL), mean AST (-2.5 U/L), mean ALT (-9.7 U/L), mean albumin (0.10 g/dL), and mean platelet count (7.5×10^9/L).

In the elafibranor arm, estimated transplant-free survival rates as calculated with the GLOBE score improved from baseline to week 52 by 2.9% at 10 years (from 91.2% to 94.1%) and by 4.9% at 20 years (from 84.8% to 89.7%). In the placebo arm, estimated transplant-free survival rates improved from baseline to week 52 by 0.4% at 10 years (from 92.2% to 92.6%) and by 0.7% at 20 years (from 86.5% to 87.2%). Similarly, estimated transplant-free survival rates based on UK-PBC scores at week 52 improved by 0.9% at 10 years and 1.6% at 15 years in the elafibranor arm, and decreased by 0.2% at 10 years and 0.4% at 15 years in the placebo arm. The improvement on estimated transplant-free survival based on the GLOBE score was observed regardless of disease stage (early vs advanced

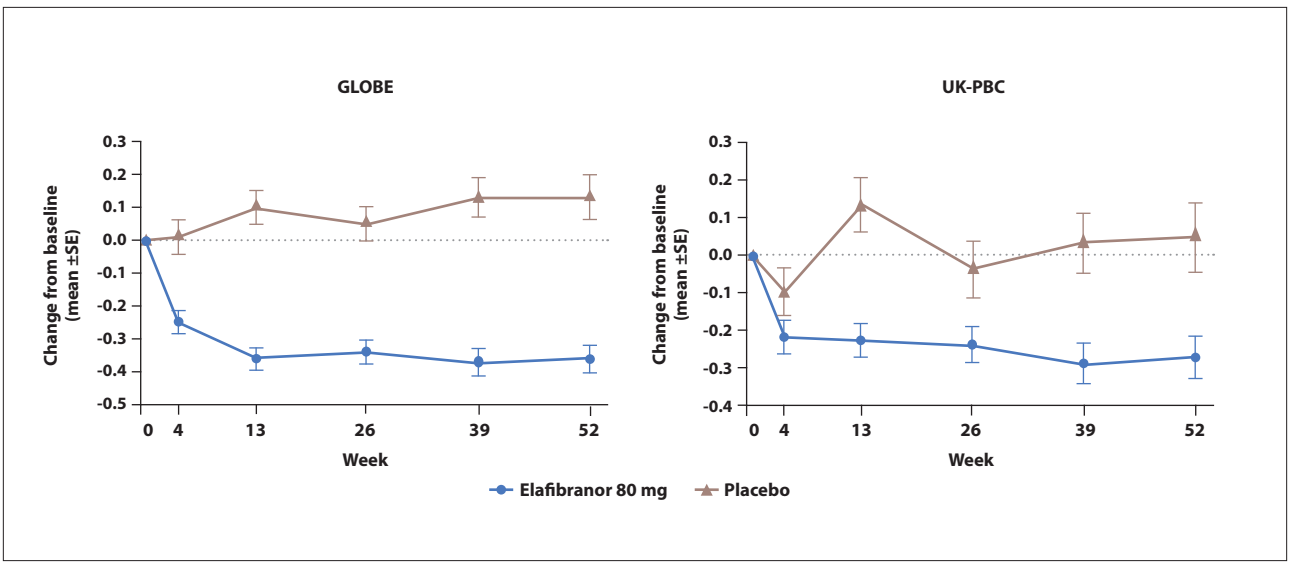

Figure 6. The risk of needing a liver transplant, measured by the GLOBE and UK-PBC scores, in patients with primary biliary cholangitis treated with elafibranor decreased from the start of the ELATIVE trial. Adapted from Kowdley KV, et al. AASLD abstract 2371. *Hepatology.* 2024;80(suppl 1).[4]

based on liver stiffness or histology) or biochemical response.

The investigators concluded that elafibranor was associated with greater improvements than placebo in GLOBE and UK-PBC prognostic scores, with improvements observed as early as week 4. These improvements translated to higher estimated transplant-free survival rates including in patients with advanced disease and those without a biochemical response.

Knowing the benefits with elafibranor use is key. The ultimate goal in the treatment of PBC is to prevent liver transplantation, cirrhosis, liver failure, and death, as well as to improve quality of life. The GLOBE and UK-PBC are real-world, evidence-based scores that help predict outcomes based on treatment response or nonresponse. The score improvements (lower scores) noted in this study give confidence in the use of elafibranor for patients with PBC.

— Robert G. Gish, MD

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Disparities in Primary Biliary Cholangitis: A Retrospective Study Using Real-World Data From a Single Hepatology Clinic in the Greater Los Angeles Area

Rates of metabolic dysfunction-associated steatotic liver disease (MASLD) and metabolic dysfunction-associated steatohepatitis (MASH) are higher in Hispanic adults in the United States than in non-Hispanic adults, and MASH is associated with a poorer prognosis in patients with PBC.[1,2]

Disparities in PBC severity in Hispanic/Latino adults have not been well characterized, particularly in a real-world setting. Alff and colleagues conducted a retrospective study evaluating demographic, clinical, and laboratory characteristics of patients with PBC receiving care at a nonacademic hepatology clinic in the Los Angeles area.[2]

The cohort included 184 patients with PBC for whom ethnic data were available, of whom 49.5% (n=91) were Hispanic/Latino and 50.5% (n=93) were non-Hispanic/Latino. Hispanic/Latino patients identified as White, whereas non-Hispanic/Latinos identified as White (56.5%), Asian (39.1%), and Black (4.4%). The median age of

ABSTRACT SUMMARY Long-Term Safety of Seladelpar 10 Mg With Up to 5 Years of Treatment in Patients With Primary Biliary Cholangitis

A pooled analysis evaluated the long-term safety of seladelpar 10 mg among 486 patients enrolled across 6 clinical trials (Abstract 2412). The largest cohort had received seladelpar for at least 1 year (n=355), followed by at least 2 years (n=170), 3 years (n=66), 4 years (n=36), or 5 years (n=10). Safety outcomes were compared for 152 patients who had received placebo, including 117 for at least 12 weeks and 94 for at least 26 weeks. Exposure-adjusted incidence (EAI) rates of AEs were lower with seladelpar and placebo for multiple parameters assessed, including rates of grade 3 or higher AEs (9.8 vs 12.2 per 100 patient-years [PY]), rates of serious AEs (8.0 vs 7.8 per 100 PY), and rates of AEs leading to treatment discontinuation (2.9 vs 5.6 per 100 PY). The most frequent exposure-adjusted AEs per 100 PY with seladelpar and placebo, respective, were pruritus (9.3 vs 26.7), COVID-19 (8.1 vs 11.1), nausea (7.7 vs 7.8), urinary tract infection (6.6 vs 4.5), fatigue (6.4 vs 13.3), diarrhea (6.2 vs 7.8), arthralgia (6.1 vs 10.0), headache (6.0 vs 3.3), and upper abdominal pain (5.3 vs 6.7). The exposure-adjusted rate of liver-related AEs per 100 PY was 6.1 with seladelpar and 13.3 with placebo. Exposure-adjusted rates of muscle-related AEs per 100 PY were 6.9 and 8.9, respectively, and exposure-adjusted rates of renal related AEs per 100 PY were 0.7 and 0, respectively. Specifically, elevations in liver enzymes and creatine kinase occurred more frequently in patients receiving placebo than in patients receiving seladelpar.

Table. Liver Disease Stage in Patients With PBC, Stratified by Ethnicity, From a Retrospective Study of Data From a Hepatology Clinic in the Greater Los Angeles Area

		Hispanic/Latino (n=91, 49.5%)			Non-Hispanic/Latino (n=93, 50.5%)	
Variable	**n**	**Prevalence**	**Median (range)**	**n**	**Prevalence**	**Median (range)**
Biopsy performed	19/89	21.4%		28/91	30.8%	
Scheuer stages	12			20		
Stage 0	0	0.0%		2	10.0%	
Stage 1	0	0.0%		9	45.0%	
Stage 2	3	25.0%		3	15.0%	
Stage 3	8	66.7%		6	30.0%	
Stage 4	1	8.3%		0	0.0%	
METAVIR stages	12			20		
Stage 0	1	8.3%		7	35.0%	
Stage 1	0	0.0%		4	20.0%	
Stage 2	4	33.3%		3	15.0%	
Stage 3	5	41.7%		6	30.0%	
Stage 4	2	17.7%		0	0.0%	
FibroScan kPa	36		10.1 (2.9-69.2)	41		7.5 (3.1-75.0)

METAVIR, Meta-analysis of Histological Data in Viral Hepatitis; PBC, primary biliary cholangitis.
Adapted from Alff S, et al. AASLD abstract 907. *Hepatology.* 2024;80(suppl 1).[2]

the cohort was 62 years (range, 20-90), and 83% were female.

Analyses using the Area Deprivation Index (ADI) showed significantly more disadvantage for Hispanic/Latinos than non-Hispanic/Latinos according to continuous and categorical ADI scores. White Hispanic/Latinos were significantly more likely to be in the 7-to-10 ADI category than Black non-Hispanic/Latinos (25.0%), White non-Hispanic/Latinos (14.6%), and Asian non-Hispanic/Latinos (9.1%).

Median body mass index (BMI) was significantly higher in Hispanic/Latinos than in non-Hispanic/Latinos (26.7 vs 22.4; *P*=.0025), and 22.4% of patients had a history of type 2 diabetes mellitus. In an assessment of PBC, MASLD, and autoimmune hepatitis, Hispanic/Latinos were significantly more likely than non-Hispanic/Latinos to have MASLD (45.6% vs 19.4%; *P*=.0001) and to have all 3 associated conditions (12.1% vs 2.2%; *P*=.0011). They were significantly less likely than non-Hispanic/Latinos to have only 1 liver condition (40.7% vs 63.4%; *P* =.0011).

An analysis of PBC severity showed higher degrees of fibrosis in Hispanic/Latinos vs non-Hispanic/Latinos as assessed by Scheuer stage (*P*=.0059), METAVIR stage (*P*=.0207), and FibroScan stiffness (10.1 vs 7.5 kPa; *P*=.0249) (Table), and by composite fibrosis score distribution (*P*=.0105) and prevalence of F2 to F4 disease (*P*=.0012).

In a multivariate analysis, being Hispanic/Latino, single, male, older, and having low plasma albumin levels was independently associated with F2 to F4 disease. Compared with having just PBC, having PBC plus either autoimmune hepatitis overlap or MASLD was associated with a significantly increased risk of having F2 to F4 fibrosis (odds ratio, 2.91; 95% CI, 1.23-7.16; *P*=.0143), and having all 3 conditions further increased the risk over having 2 conditions.

> Black and Hispanic patients have more aggressive PBC disease risk. As health care professionals, we need to show we abrogate disease in all ethnic groups. Focusing on diversity, equity, and inclusion in clinical trials is key to broad-based utilization of our PBC armamentarium.
>
> — Robert G. Gish, MD

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The Effect of Obeticholic Acid on Inflammatory Markers and Fibrosis Scores in POISE Incomplete Responders: A Retrospective Review of POISE, a Phase 3 Trial of Obeticholic Acid for the Treatment of Primary Biliary Cholangitis

OCA received FDA approval for the treatment of PBC based on results from the randomized, double-blind, phase 3 POISE trial, in which OCA was associated with significantly greater reductions in ALP and total bilirubin from baseline than placebo.[1] At 12 months, the proportion of patients achieving the composite endpoint (defined as an ALP <1.67 × ULN, with a reduction of ≥15% from baseline and normal total bilirubin) was significantly higher with either of the OCA doses evaluated (46% with 5-10 mg and 47% with 10 mg) than with placebo (10%; *P*<.001 for both).

Victor and colleagues reported results from a post-hoc analysis evaluating other outcomes, including markers of farnesoid X receptor (FXR) activation, inflammation, hepatocyte injury, and hepatic fibrosis, in patients without an incomplete response to OCA in the POISE trial.[2] Of the 217 patients randomized in the trial, 70 were assigned to OCA 5-10 mg, 73 were assigned to OCA 10 mg, and 73 were assigned to placebo. Incomplete responses occurred in 54.3% of patients receiving OCA titration, 53.4% receiving OCA 10 mg, and 90.4% of patients receiving placebo.

> For patients with PBC who are incomplete responders to OCA, clinicians should monitor more than ALP and evaluate bilirubin (total and direct), AST, ALT, and GGT as a cornerstone of patient analysis. In addition, noninvasive liver disease assessments at one time point, as well as longitudinal evaluation, should be used to determine patient trajectories and see if the liver enzyme curve is flat, worsening, or improving before changing second-line treatment or adding a third medication.
>
> — Robert G. Gish, MD

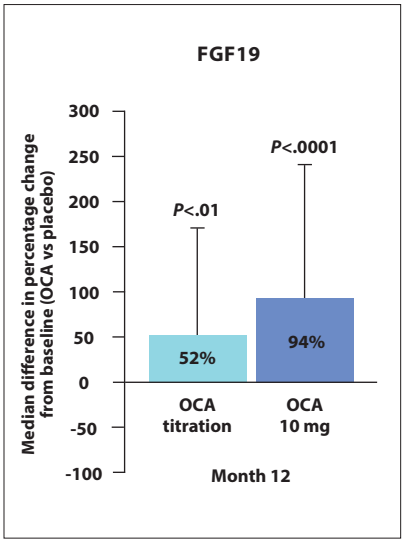

Figure 7. Difference in median percentage change from baseline of FGF19 in patients with primary biliary cholangitis who were incomplete responders to OCA vs placebo. FGF19, fibroblast growth factor 19; OCA, obeticholic acid. Adapted from Victor D, et al. AASLD abstract 949. *Hepatology.* 2024;80(suppl 1).[2]

Among the patients with an incomplete response, OCA was associated with a significant difference over placebo in the median percentage change from baseline in fibroblast growth factor 19 (FGF19), a marker of FXR activation. The difference in percentage change from baseline in FGF19 with OCA vs placebo was statistically significant at 12 months whether patients received OCA titration (52%) or OCA 10 mg (94%) (Figure 7). Differences were also observed for reductions in the immune-mediated inflammatory markers C-reactive protein, immunoglobulin M, and cytokeratin 18.

Finally, noninvasive estimates of hepatic fibrosis (Fibrosis-4 and AST to Platelet Ratio Index) indicated lower fibrosis scores in patients with incomplete responses to OCA compared with placebo. Investigators concluded that patients who did not achieve the composite endpoint of response assessed by ALP and bilirubin may still gain benefits from OCA as assessed by reductions in inflammation that could translate to reduced progression of fibrosis.

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