PPAR Agonists in PBC: Understanding Their Efficacy and Safety



PPAR Agonists Have Emerged as Promising New Second-line Therapies in PBC Management

In the United States, only **elafibranor** and **seladelpar** are conditionally approved by the FDA as PPAR agonists in PBC:

- Fenofibrate is not approved
- As monotherapy or in combination with UDCA

No evidence supports the superiority of one PPAR agonist over another.

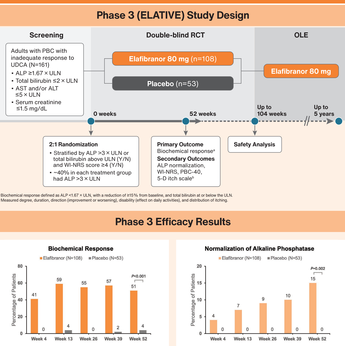
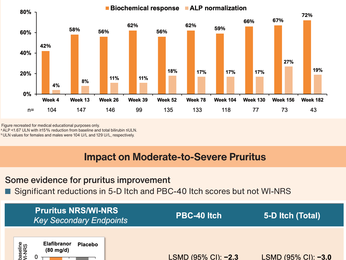


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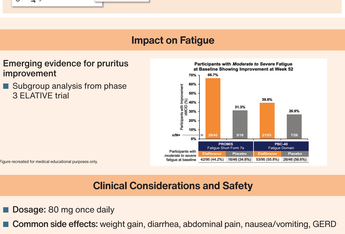
Elafibranor

Phase 3 (ELATIVE) Study Design



*Biochemical response defined as ALP <1.67 × ULN, with a reduction of ≥15% from baseline, and total bilirubin at or below the ULN.
†Measured degree, duration, direction (improvement or worsening), disability (effect on daily activities), and distribution of itching.

Phase 3 Efficacy Results



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Long-term Extension Data

Sustained biochemical responses and ALP normalization up to week 182

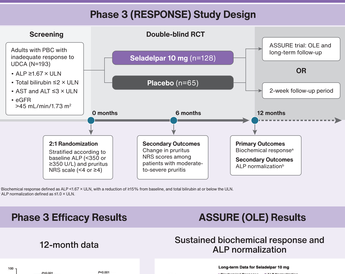
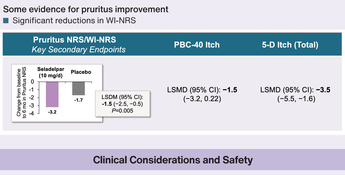


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*Data for females and males were 104 (42%) and 147 (58%) and total bilirubin ≤ULN.
†ULN values for females and males were 104 (4), and 129 (4), respectively.

Impact on Moderate-to-Severe Pruritus

Some evidence for pruritus improvement

- Significant reductions in 5-D Itch and PBC-40 Itch scores but not Wi-NRS



Impact on Fatigue

Emerging evidence for pruritus improvement

- Subgroup analysis from phase 3 ELATIVE trial

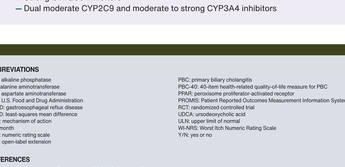


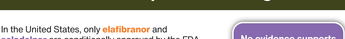
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Clinical Considerations and Safety

- **Dosage:** 80 mg once daily
- **Common side effects:** weight gain, diarrhea, abdominal pain, nausea/vomiting, GERD
- **Potential risk for bone fractures:** 6% (vs 0% in placebo)
- **Drug-drug interactions**
  - Monitor if on a concomitant statin (potential risk for rhabdomyolysis/myositis)
  - Interacts with hormonal contraception

Seladelpar

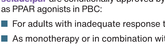
Phase 3 (RESPONSE) Study Design



*Biochemical response defined as ALP <1.67 × ULN, with a reduction of ≥15% from baseline, and total bilirubin at or below the ULN.
†ALP normalization defined as ≤1.0 × ULN.

Phase 3 Efficacy Results

12-month data



ASSURE (OLE) Results

Sustained biochemical response and ALP normalization



Figures recreated for medical educational purposes only.

Impact on Moderate-to-Severe Pruritus

Some evidence for pruritus improvement

- Significant reductions in Wi-NRS

Clinical Considerations and Safety

- **Dosage:** 10 mg once daily
- **Common side effects:** headache, abdominal pain/distension, nausea, diarrhea
- **Potential risk for bone fractures:** 4% (vs 0% in placebo)
- **Drug-drug interactions**
  - Strong CYP2C9 inhibitors
  - Dual moderate CYP2C9 and moderate to strong CYP3A4 inhibitors

ABBREVIATIONS

ALP: alkaline phosphatase
ALT: alanine aminotransferase
AST: aspartate aminotransferase
FDA: U.S. Food and Drug Administration
GERD: gastroesophageal reflux disease
LSMD: least-squares mean difference
MoA: mechanism of action
mo: month
NRS: numeric rating scale
OLE: open-label extension
PBC: primary biliary cholangitis
PBC-40: 40-item health-related quality-of-life measure for PBC
PPAR: peroxisome proliferator-activated receptor
PROMIS: Patient Reported Outcomes Measurement Information System
RCT: randomized controlled trial
UDCA: ursodeoxycholic acid
ULN: upper limit of normal
Wi-NRS: Worst Itch Numeric Rating Scale
Y/N: yes or no

REFERENCES

Elafibranor (package insert). Revised June 2024. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/218860s000lbl.pdf. Accessed April 2026.

Hirschfield GM, Bowlus CL, Mayo MJ, et al. A phase 3 trial of seladelpar in primary biliary cholangitis. *N Engl J Med.* 2024;390(9):783–794. doi:10.1056/NEJMoa2312100.

Jones DE, Carbone M, Kremer AE, et al. Long-term treatment with elafibranor leads to biochemical and symptomatic improvements for at least 3 years in patients with primary biliary cholangitis. Presented at: American Association for the Study of Liver Diseases, The Liver Meeting 2025; November 7–11, 2025; Washington, DC.

Jones DE, Carbone M, Kremer AE, et al. P726: Elafibranor improves fatigue versus placebo in patients with primary biliary cholangitis (PBC), with limited correlation with pruritus: analyses from the phase III ELATIVE trial. *Gut.* 2025;74:A30–A31.

Kowdley KV, Levy C, Lee YJ, et al. Efficacy and safety of elafibranor in primary biliary cholangitis. *N Engl J Med.* 2024;390(9):795–805. doi:10.1056/NEJMoa2306185.

Kremer AE, Kowdley KV, Levy C, et al. LPB-028 Effect of elafibranor on pruritus in primary biliary cholangitis: symptom severity and quality of life measurements from the phase III ELATIVE trial. *J Hepatol.* 2024;80:S91–S92.

Long-term treatment with elafibranor leads to biochemical and symptomatic improvements for at least 3 years in patients with PBC. *Gastroenterol Hepatol (NY).* 2025;21(12 Suppl 10):3–4.

Pratt D, Lewitz EJ, Bowlus CL, et al. Seladelpar is associated with a sustained reduction in cholestatic markers and a consistent safety profile in patients with primary biliary cholangitis treated up to 48 months in the ongoing, open-label ASSURE study. *Dig Liver Dis.* 2026;58(Suppl 1):566–567. doi:10.1016/j.dld.2026.01.111.

Seladelpar (package insert). Revised January 2026. U.S. Food and Drug Administration website. https://www.accessdata.fda.gov/drugsatfda_docs/label/2026/217189s002lbl.pdf. Accessed April 2026.

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Wetten A, Jones DEJ, Dyson JK. Seladelpar: an investigational drug for the treatment of early-stage primary biliary cholangitis (PBC). *Expert Opin Investig Drugs.* 2022;31(10):1101–1107. doi:10.1080/13543784.2022.2109750.