Primary Biliary Cholangitis (PBC): Diagnosing and Positioning New Treatments

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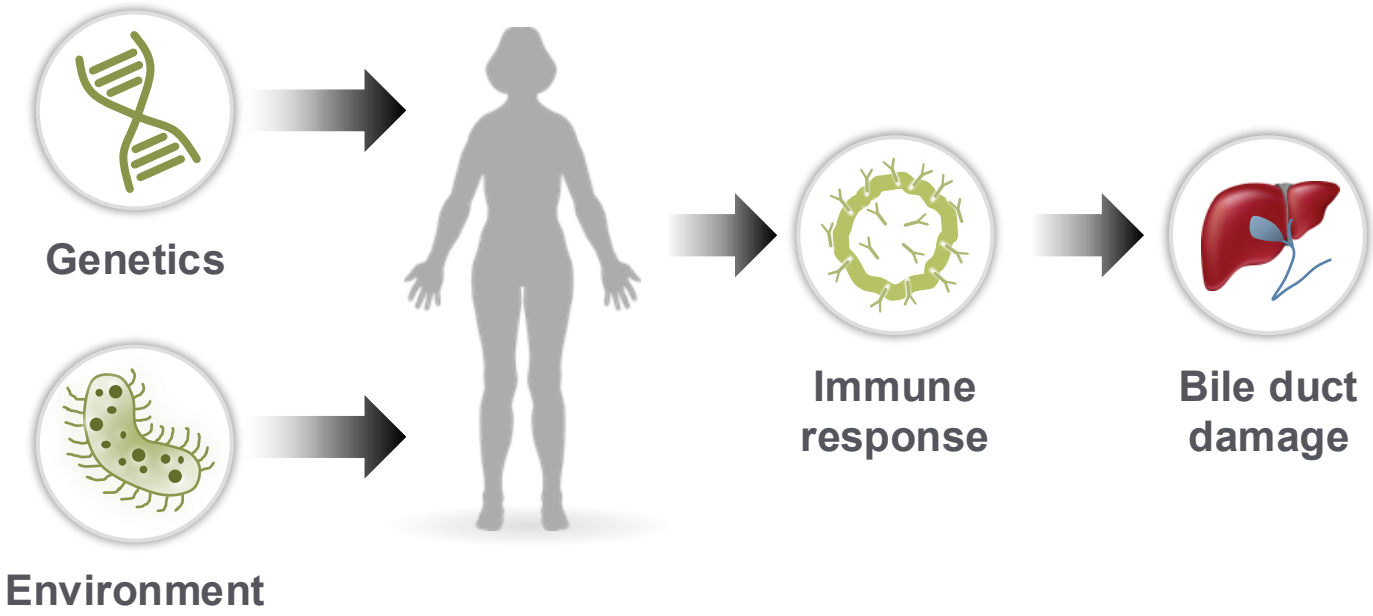
What is Primary Biliary Cholangitis (PBC)?

- Chronic, progressive, cholestatic autoimmune disease
- Lymphocytic destruction of intralobular bile ducts resulting in periportal inflammation, bile duct damage, fibrosis and progression to cirrhosis
- Previously referred to as “primary biliary cirrhosis”

PBC Is a Chronic, Progressive Autoimmune Disease[1-3]

- **Factors possibly associated with onset and perpetuation of bile-duct injury in PBC**



PBC is a progressive disease in which up to 50% of untreated patients develop cirrhosis after 4 years

PBC is characterized by destruction of the interlobular and septal bile ducts that may lead to cirrhosis

1. Poupon R. *J Hepatol*. 2010;52(5):745-758. 2. Selmi C, et al. *Lancet.* 2011;377(9777):1600-1609. 3. Carey EJ, et al. *Lancet.* 2015;386:1565-1575.

PBC Phenotype

Age	Typically >45 years
Gender	Female > Male (9:1)
Serology	AMA in ~95%; disease-specific ANA in ~30%-50%; ASMA may be present, ANA specific anti-GP210, anti-sp-100
Immunoglobulin	IgM typically elevated
MRCP	Normal
Liver Histology	Lymphocytic infiltrate; inflammatory duct lesion; granuloma may be present
Coexisting IBD	Not typical

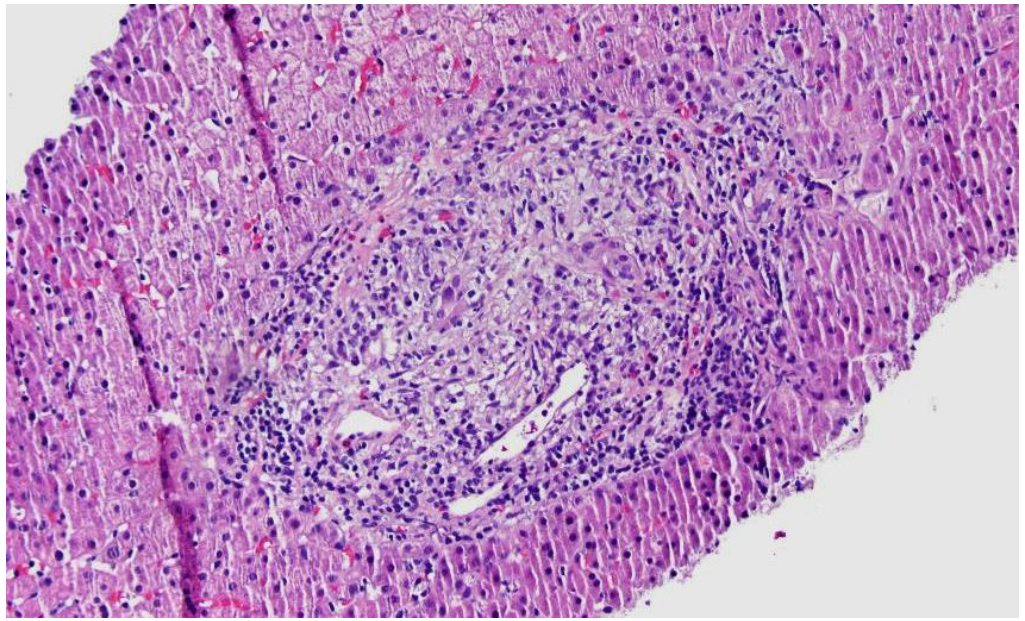
Abbreviations: AMA, antimitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth-muscle antibody; IBD, inflammatory bowel disease; MRCP, magnetic resonance cholangiography; PBC, primary biliary cholangitis.

Trivedi PJ et al. *Aliment Pharmacol Ther*. 2012; 36:517-533.

PBC Diagnostic Criteria

PBC Diagnosis

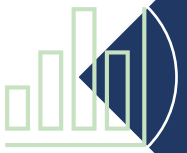
- Unexplained elevation of ALP ≥ 1.5x ULN
- Positive anti-mitochondrial antibody (AMA)
- Non-suppurative destructive cholangitis on histology



2 out of these 3 criteria are required for the diagnosis of PBC

AASLD Criteria

Epidemiology



Global prevalence: 35/100,000

The most common cholestatic disease of US middle-aged women

Affects about 1/1000 women age >40

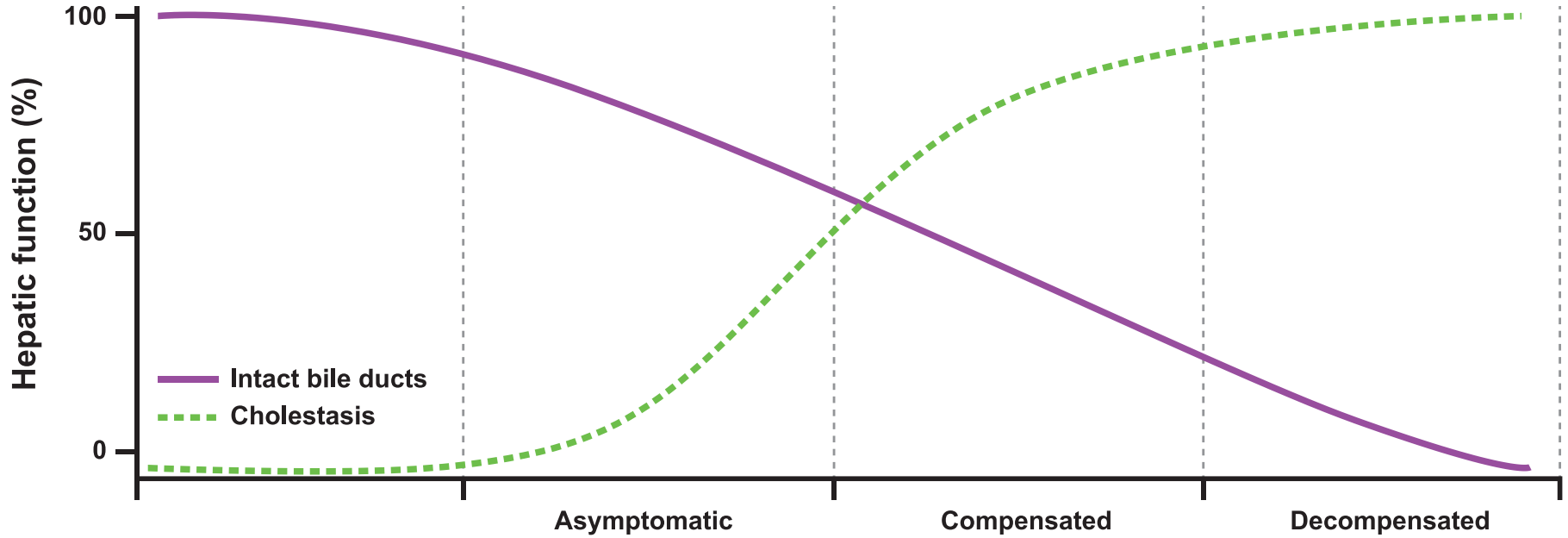
Median age at diagnosis ~ 50

More commonly diagnosed in Europe and North America

EASL. *J Hepatol.* 2017; 67(1):145-172; Lammers et al. 2014.

The Natural History of PBC

PBC is commonly characterized by slow progression of cholestasis, fibrosis, followed by hepatic dysfunction and decompensation

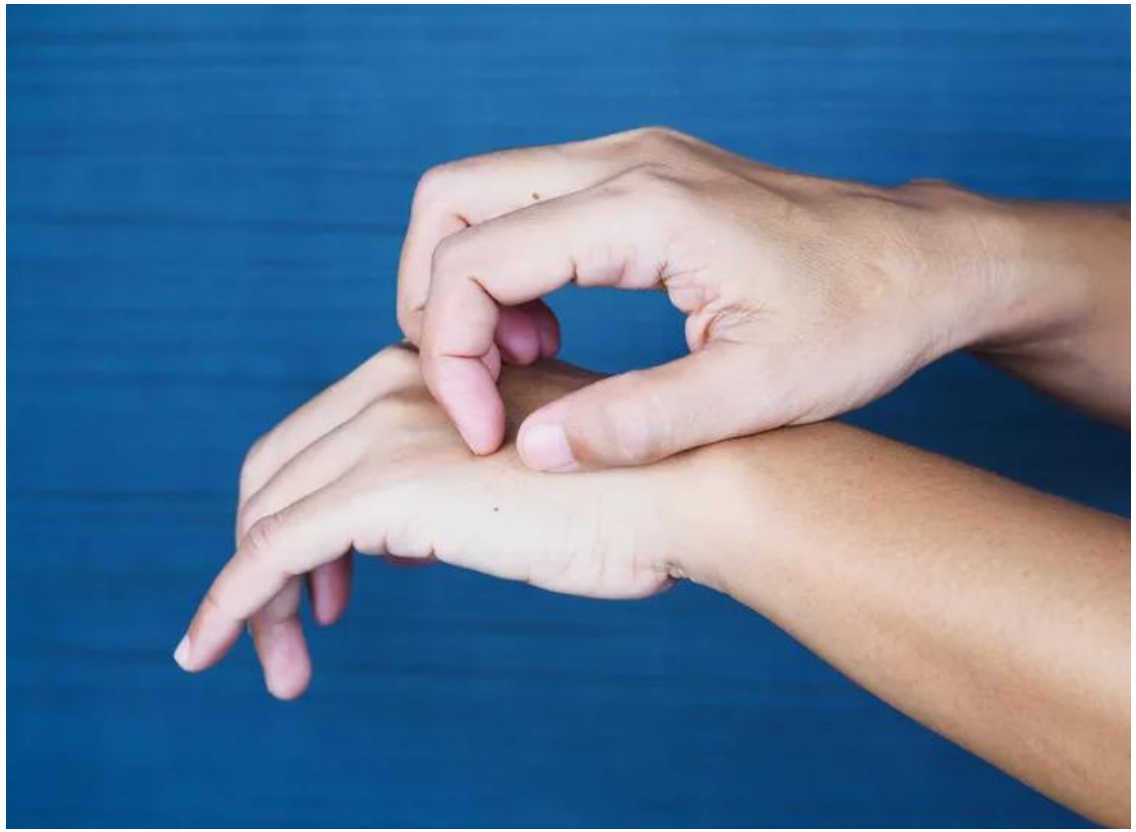


Widespread use of AMA testing enables the diagnosis of PBC patients before they develop symptoms of cholestasis or hepatic decompensation.

Younossi Z et al. *AJG*. 2019; 114:48-63.

Clinical Manifestations of PBC

- Fatigue
- Pruritus (hands &feet)
- RUQ abdominal pain
- Other autoimmune conditions
- Excoriations
- Xanthelasma
- Xanthoma



Fatigue in PBC

- Fatigue is the most common symptom reported by PBC pts.
- Moderate to severe in 40-80% of patients.
- Higher fatigue scores in women, younger patients, longer disease duration.
- More prevalent on questionnaire than telling MD.
- Leads to significant ↓ HRQoL, especially in those where it leads to social withdrawal.

Carbone M et al. *Hepatology*. 2013; Blackburn P et al. *Liver Int*. 2007; Swain and Jones. *Liver Int.* 2019; Dyson JK et al. *Aliment Pharmacol Ther.* 2016; Mells GF et al. *Hepatology*. 2013.

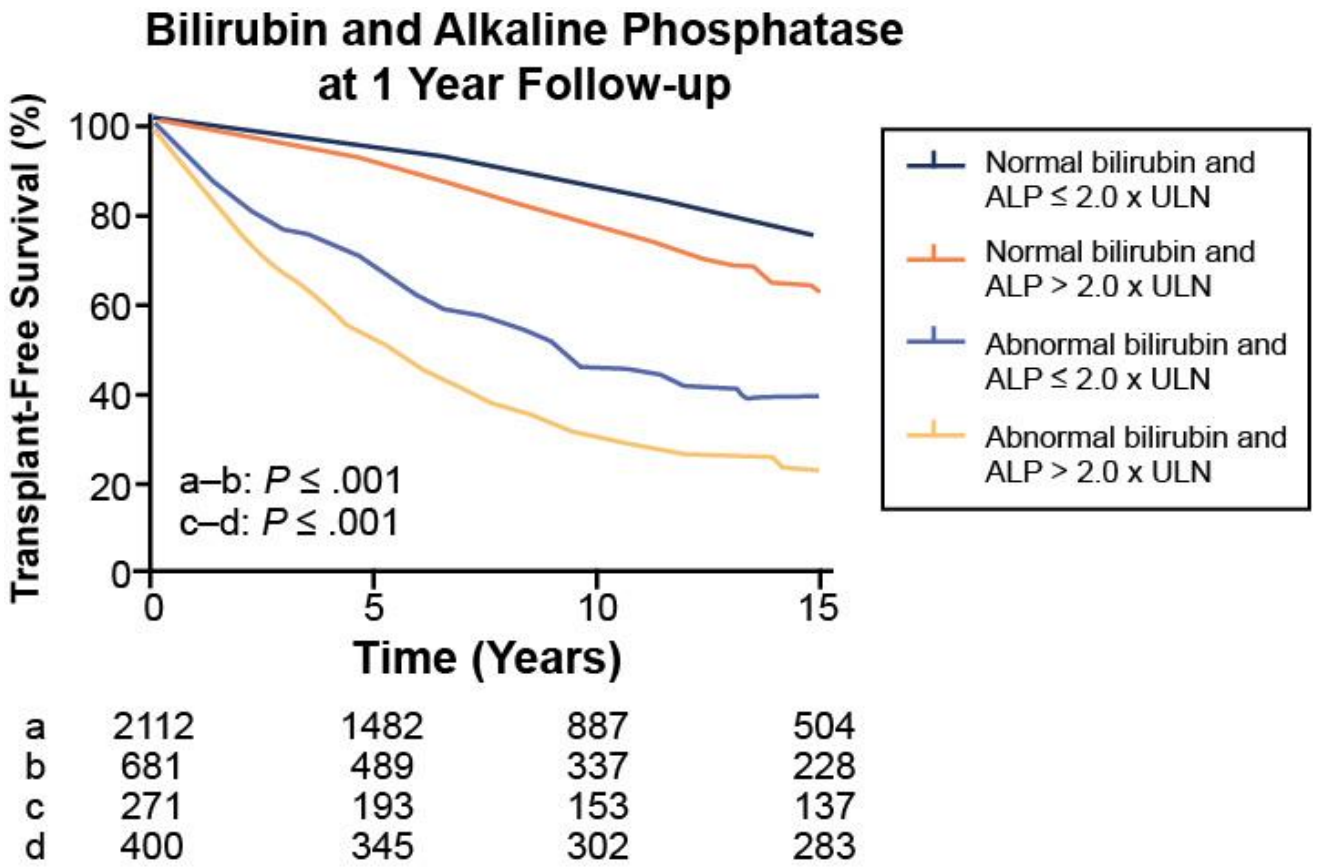
Pruritus in PBC

- Pruritus experienced by up to 75% of pts at some point post-Dx*.
  - Persistent in 35%
  - Severe in 12% (can reflect aggressive, ductopenic variant with poor prognosis, and decreased UDCA response)
- More severe in women and in pts at younger age of presentation.
- Typically ↑ during day, often worse at night, may impact sleep and HRQoL → often associated with fatigue.

Carbone M et al. *Hepatology*. 2013; Dyson JK et al. *Aliment Pharmacol Ther*. 2016; Mells GF et al. *Hepatology*. 2013; *Hegade VS et al. *Clin Gastroenterol Hepatol*. 2019; Hirschfield GM et al. *Exp Rev Gastroenterol Hep*. 2012.

Transplant-Free Survival of Patients

At 1 year after study enrollment, levels of alkaline phosphatase that were 2.0 times the upper limit of normal (ULN) best predicted patient outcome



Abbreviation: ALP, alkaline phosphatase.

Lammers WJ, van Buuren HR, Hirschfield GM, et al. Levels of Alkaline Phosphatase and Bilirubin are Surrogate End Points of Outcomes of Patients with Primary Biliary Cirrhosis: An International Follow-up Study. *Gastroenterology*. 2014; 147:1338-1349.

New Paradigm in PBC Evaluation and Goals

Old Paradigm (wait to fail)

Diagnosis
UDCA 13-15 mg/kg/d

↓

Assess response
At 12 mo

↓

Second-line therapy and manage symptoms

New Paradigm (Personalized Care)

- **Target therapy to patient profile:**
  - Liver tests
  - Liver fibrosis
  - Symptoms
  - Risk factors
- **Treat based on individual baseline risk and treatment response**

- **Aspirational goals:**
  - Patients informed of their risk
  - Normal serum liver levels
  - Ductopenia and liver fibrosis resolved
  - Normal QOL
  - Liver transplantation avoided
  - Hope for an eventual cure for PBC

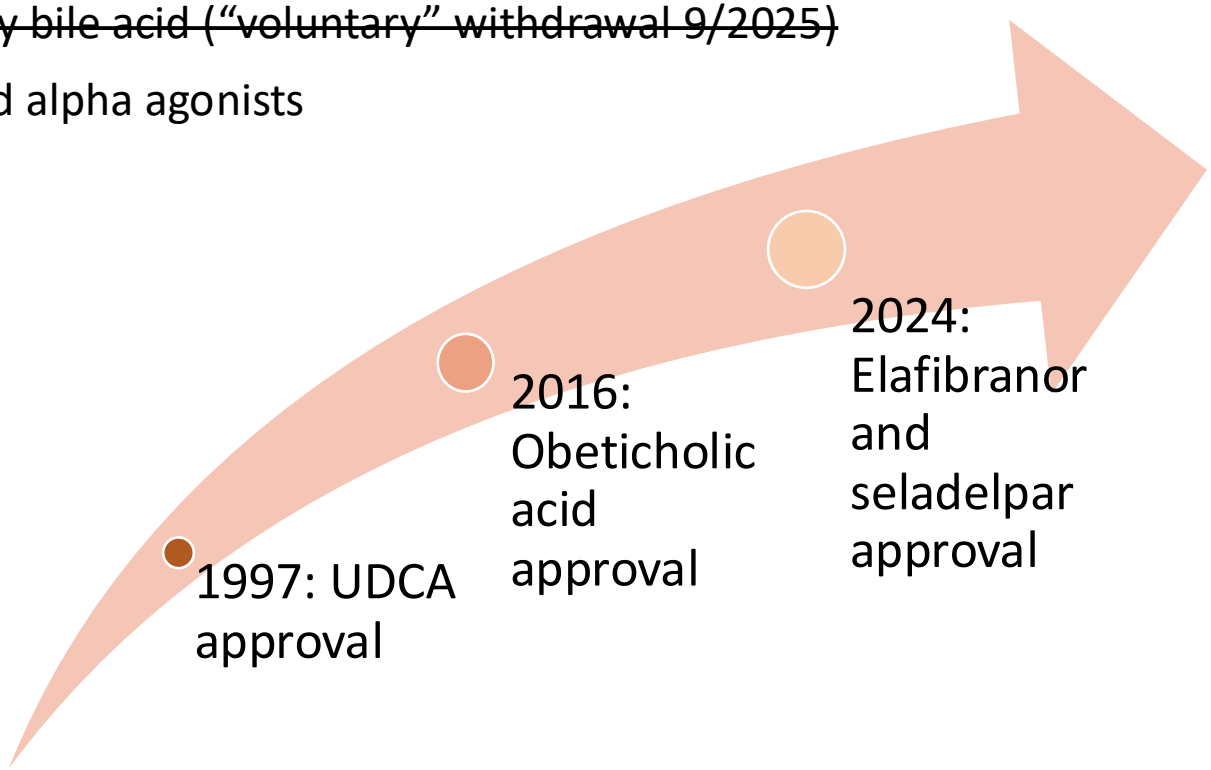
- Individual risk assessed at baseline
- Earlier initiation of second-line therapy for high-risk individuals
- Normalize liver chemistry
- Prioritize patient QOL

Levy C et al. *Clin Gastroenterol Hepatol*. 2023; 21:2076-2087.

FDA-Approved Treatments for PBC

- Four treatment options are approved and indicated for the treatment of PBC, having demonstrated efficacy in improving liver biochemistry indicators (e.g., ALP)
  - **UDCA**: naturally-occurring secondary bile acid (gold standard and only approved 1st line treatment)
  - ~~**Obeticholic acid**: synthetic derivative of a primary bile acid ("voluntary" withdrawal 9/2025)~~
  - **Elafibranor** and **seladelpar**: PPAR alpha/delta and alpha agonists

- These agents vary in their efficacy for managing the symptoms of PBC
  - **Currently, no FDA-approved options are indicated specifically for the treatment of itching and fatigue in patients with PBC.**

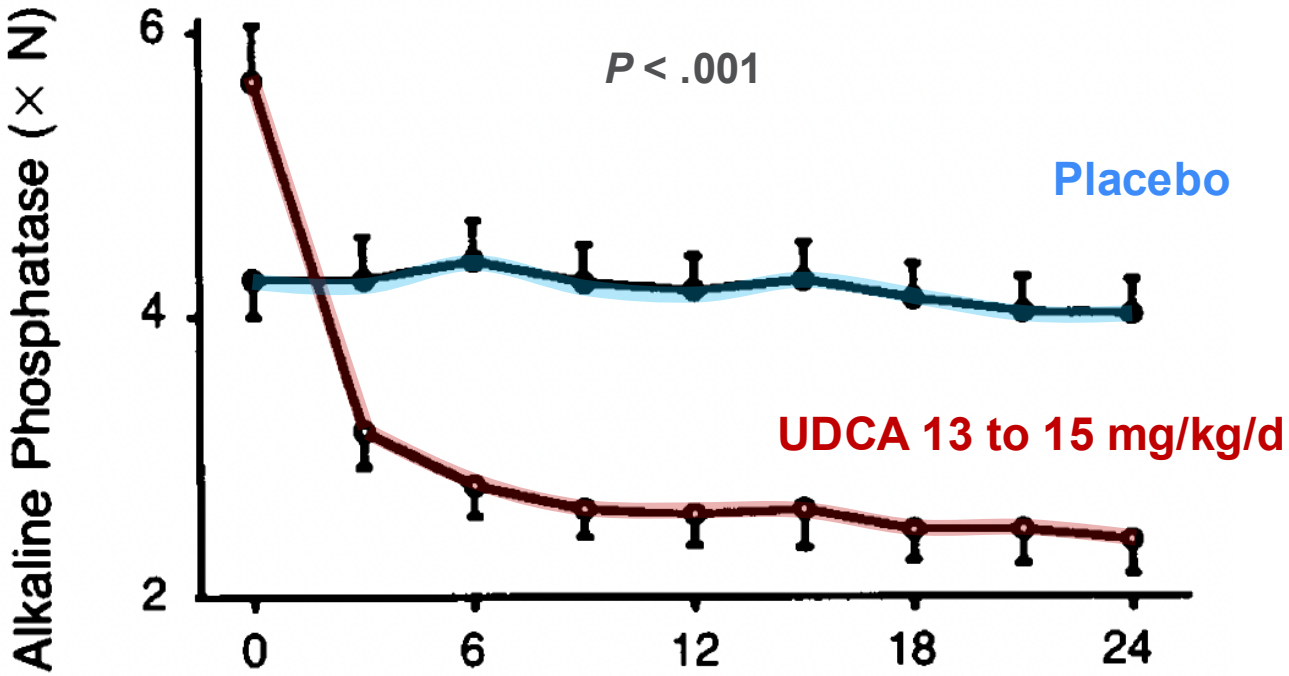


PPAR = peroxisome proliferator-activated receptor; UDCA = ursodeoxycholic acid.

Smith HT et al. *Dig Dis Sci.* 2023; 68:2710-2730; Levy C et al. *Clin Gastro Hep.* 2023; 21(8):2076-2087.

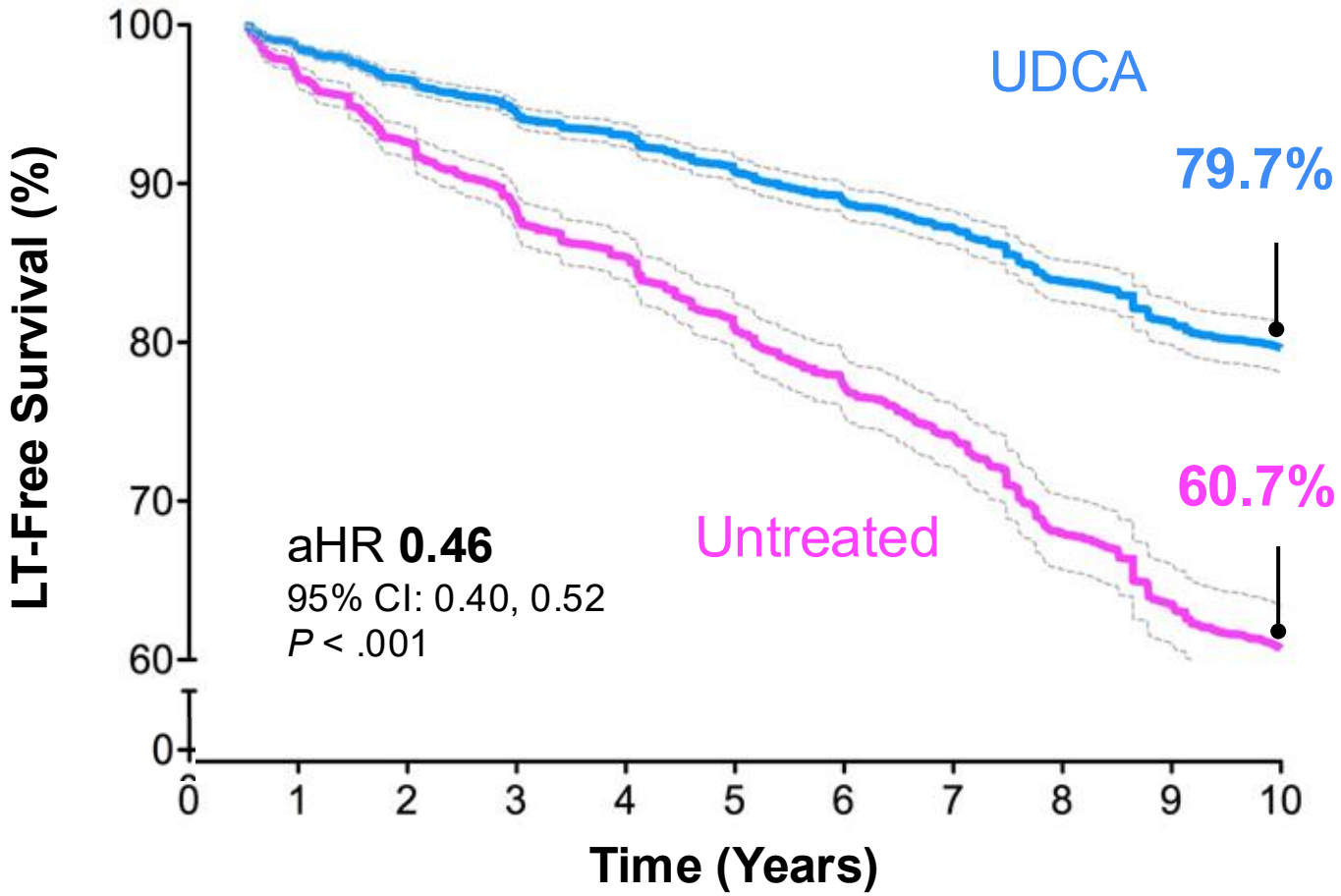
UDCA as First-Line Treatment

A 2-year double-blind trial: patients randomized to **placebo (n = 73)** or **UDCA (n = 73)**



Poupon RE et al. *N Engl J Med*. 1991; 324:1548-1554; Lindor KD et al. *Hepatology*. 2022; 75:1012-1013.

UDCA Improves LT-Free Survival



- Largest real-world international PBC cohort
  - UDCA treated: 3529
  - Untreated: 373
- Median follow-up: 7.8 years
- LT or death: **866**
- Dose-effect relationship[a]
  - **< 13** mg/kg/d: **aHR 0.50**
  - **≥ 13** mg/kg/d: **aHR 0.29**

[a]Data on UDCA dosage available in 1958 (50%).
aHR, adjusted HR; LT, liver transplantation.
Harms MH et al. *J Hepatol.* 2019; 71:357-365.

PPAR Agonists in PBC: Second Line Therapy

Elafibranor

- Dual PPARα and PPARδ agonist[1]
- 80 mg daily tablet[2]
- **Phase 3:** RCT (ELATIVE)[3]
- Approval
  - FDA: June 2024

Seladelpar

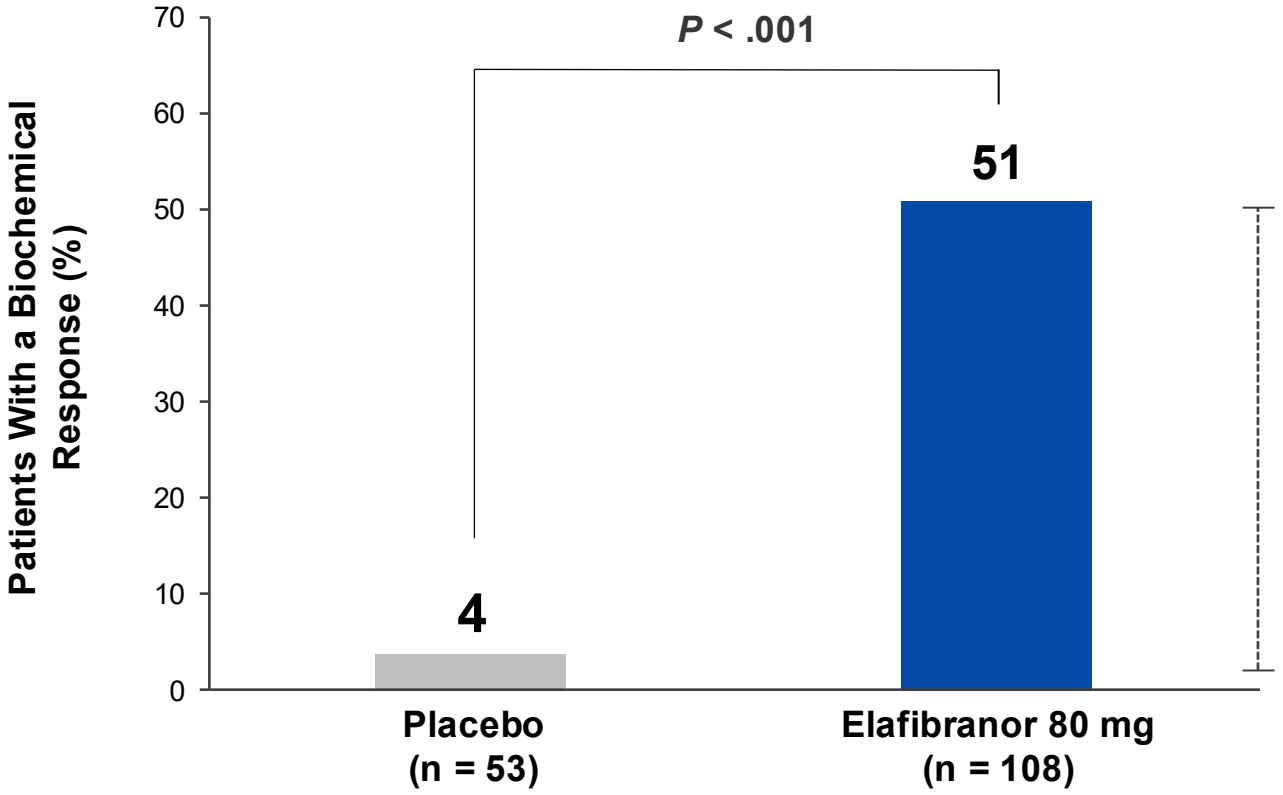
- Selective PPARδ agonist[4]
- 10 mg daily capsule[5]
- **Phase 3:** RCT (RESPONSE)[6]
- Approval
  - FDA: August 2024

1. Schattenberg JM et al. *J Hepatol.* 2021; 74:1344-1354; 2. Elafibranor [PI]. EMA. Published September 20, 2024. Updated July 28, 2025; 3. Kowdley KV et al. *N Engl J Med*. 2024; 390:795-805; 4. Jones D et al. *Lancet Gastroenterol Hepatol.* 2017; 2:716-726; 5. Seladelpar [PI]. EMA. Published February 25, 2025. Updated April 14, 2025; 6. Hirschfield GM et al. *N Engl J Med.* 2024; 390:783-794; 7. Vuppalachanchi R et al. *J Hepatol*. 2022; 76:75-85; 8. ClinicalTrials.gov. NCT05133336. Accessed April 30, 2025.

ELATIVE: Phase 3 Study of Elafibranor in PBC

Primary Endpoint Result

Biochemical response was defined as a composite of ALP < 1.67 × ULN, with a reduction of ≥ 15% from baseline, and TB at or below the ULN



Treatment difference: 47%

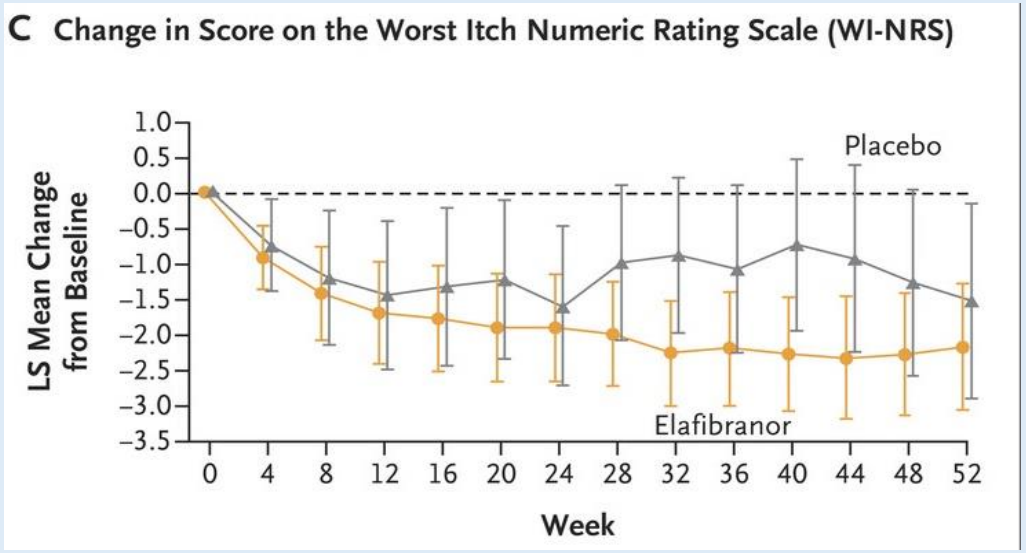
95% CI: 32, 57

Treatment with elafibranor led to a significant improvement in biochemical response at week 52

Kowdley KV et al. ELATIVE Study Investigators' Group. *N Engl J Med.* 2024; 390:795-805.

Elafibranor: Phase 3 ELATIVE Pruritus and QoL Outcomes

No significant difference in key secondary endpoints of mean change in pruritus NRS score among patients with moderate to severe pruritus at baseline (n = 66)



Outcomes for Itch-Related Items in PBC-40 Among Patients With Moderate to Severe Pruritus at Baseline

	Elafibranor (n = 42)	Placebo (n = 18)
Itching disturbed my sleep		
Improved	50.0%	33.3%
No change	33.3%	38.9%
Worsened	16.7%	27.8%
I scratched so much I made my skin raw		
Improved	61.9%	22.2%
No change	31.0%	55.6%
Worsened	7.1%	22.2%
I felt embarrassed because of the itching		
Improved	35.7%	27.8%
No change	61.9%	38.9%
Worsened	2.4%	33.3%

Kowdley KV et al. *N Engl J Med.* 2024; 390(9):795-805; Kremer AE et al. *EASL.* 2024; Abstract LBP-028.

ELATIVE Phase 3 Study of Elafibranor in PBC

Safety

Events, n (%)[a]	Elafibranor (N = 108)	Placebo (N = 53)
Any adverse event[b]	**104 (96)**	**48 (91)**
COVID-19	31 (29)	20 (38)
Pruritus	22 (20)	14 (26)
Abdominal weight gain	21 (19)	10 (19)
Abdominal pain, including upper and lower abdomen	12 (11)	3 (6)
Diarrhea	12 (11)	5 (9)
Nausea	12 (11)	3 (6)
Urinary tract infection	12 (11)	10 (19)
Vomiting	12 (11)	1 (2)
Fatigue	10 (9)	7 (13)
Headache	9 (8)	6 (11)
Back pain	4 (4)	6(11)

[a]Incidence of AEs occurring in ≥10% of patients.

AE, adverse event; TRAE, treatment-related adverse event.

Kowdley KV et al. ELATIVE Study Investigators' Group. *N Engl J Med.* 2024; 390:795-805.

Any AE that emerged during treatment period:

- Elafibranor: 96%
- Placebo: 91%

Any severe AE:

- Elafibranor: 11%
- Placebo: 11%

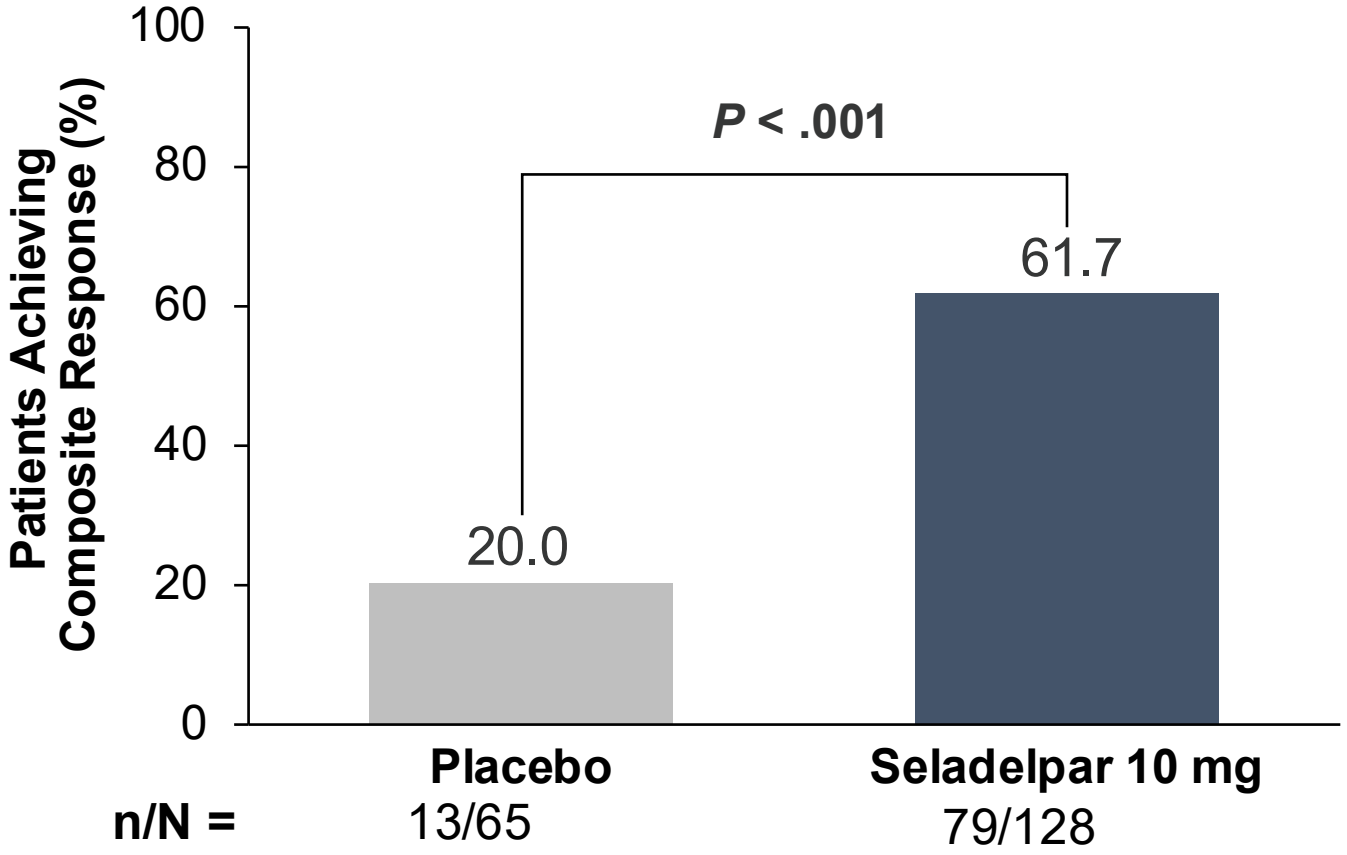
Discontinuation due AE during treatment period:

- Elafibranor: 10%
- Placebo: 9%

RESPONSE: Phase 3 Trial of Seladelpar in PBC

Primary Endpoint: Month 12 Composite Biochemical Response

ALP < 1.67 × ULN, ≥ 15% Decrease in ALP, TB ≤ ULN



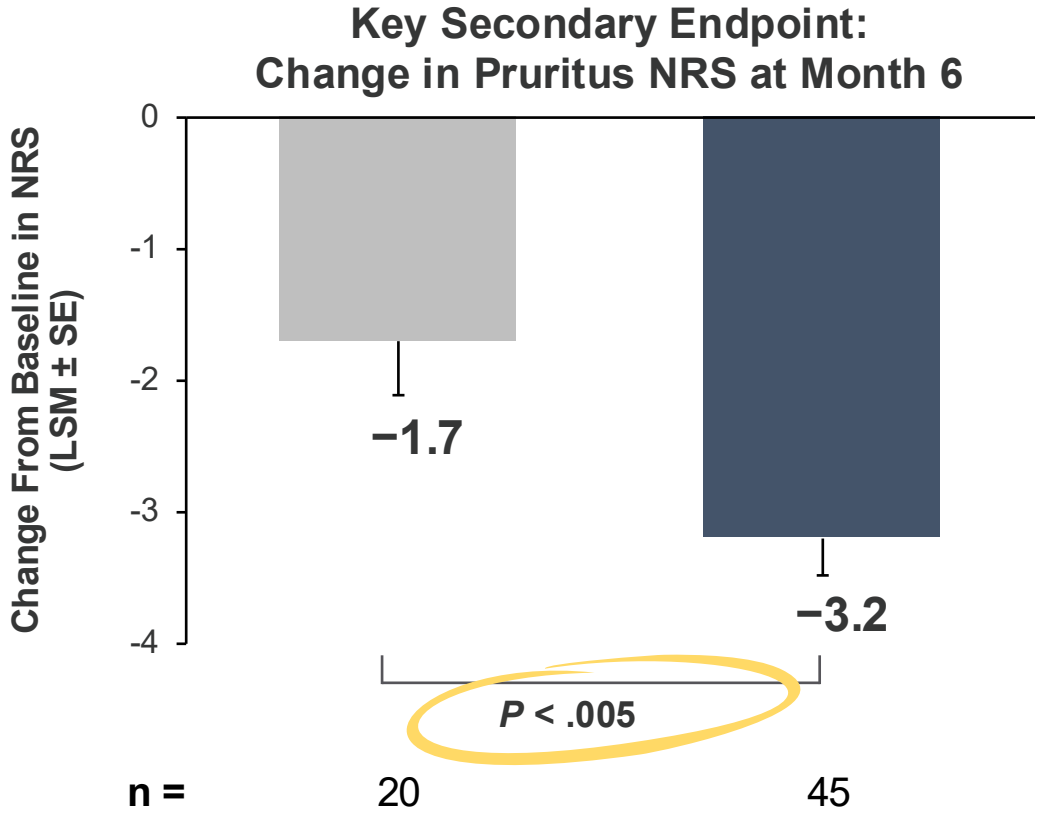
Treatment difference: 41.7%
95% CI: 27.7, 53.4

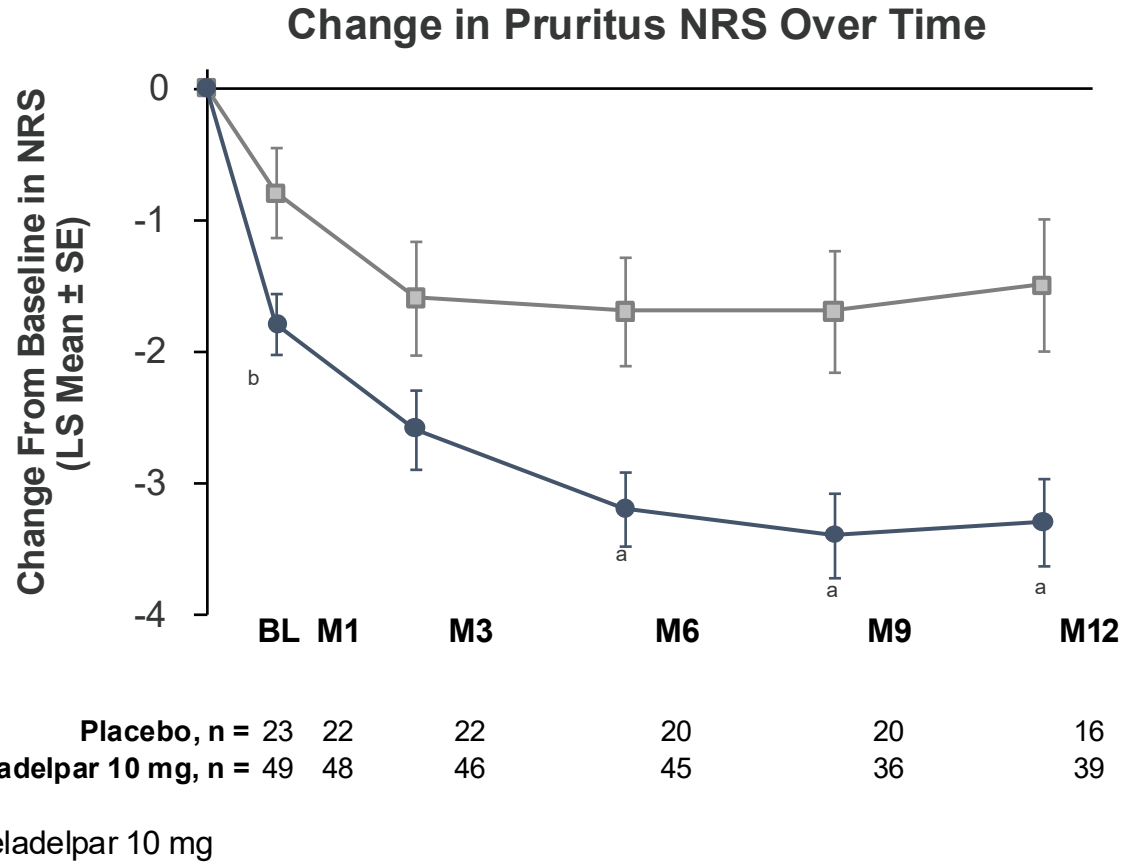
P value by Cochran–Mantel–Haenszel test.

Hirschfield GM et al. RESPONSE Study Group. *N Engl J Med.* 2024; 390:783-794.

RESPONSE: Phase 3 Trial of Seladelpar in PBC

Change in Pruritus NRS in Participants With Baseline NRS ≥ 4





MMRM analysis in patients with baseline NRS ≥ 4 using weekly averages. Baseline pruritus NRS is defined as the mean of all daily recorded scores during the run-in period and on day 1. The n values represent the number of patients with available data at each time point.

[a]*P* < .005 vs placebo; [b]*P* < .05 vs placebo.

MMRM, mixed-effect model for repeated measures.

Hirschfield GM et al. RESPONSE Study Group. *N Engl J Med*. 2024; 390:783-794.

RESPONSE: Phase 3 Trial of Seladelpar in PBC

AEs Occurring in ≥ 5% of Patients in Either Arm

Event, n (%)	Placebo (N = 65)	Seladelpar 10 mg (N = 128)
COVID-19	10 (15.4)	23 (18.0)
Pruritus	10 (15.4)	6 (4.7)
Upper respiratory tract infection	6 (9.2)	1 (0.8)
Headache	2 (3.1)	10 (7.8)
Nasopharyngitis	5 (7.7)	7 (5.5)
Pharyngitis	5 (7.7)	4 (3.1)
Abdominal pain	1 (1.5)	9 (7.0)
Arthralgia	4 (6.2)	8 (6.2)
Fatigue	4 (6.2)	8 (6.2)
Nausea	3 (4.6)	8 (6.2)
Abdominal distension	2 (3.1)	8 (6.2)
Asthenia	4 (6.2)	5 (3.9)
Urinary tract infection	4 (6.2)	4 (3.1)
Hypertension	4 (6.2)	4 (3.1)
Vertigo positional	4 (6.2)	1 (0.8)

All AEs were treatment emergent.
SAE, serious adverse event.
Hirschfield GM et al. RESPONSE Study Group. *N Engl J Med.* 2024; 390:783-794.

Any AE:

- Seladelpar: 86.7%
- Placebo: 84.6%

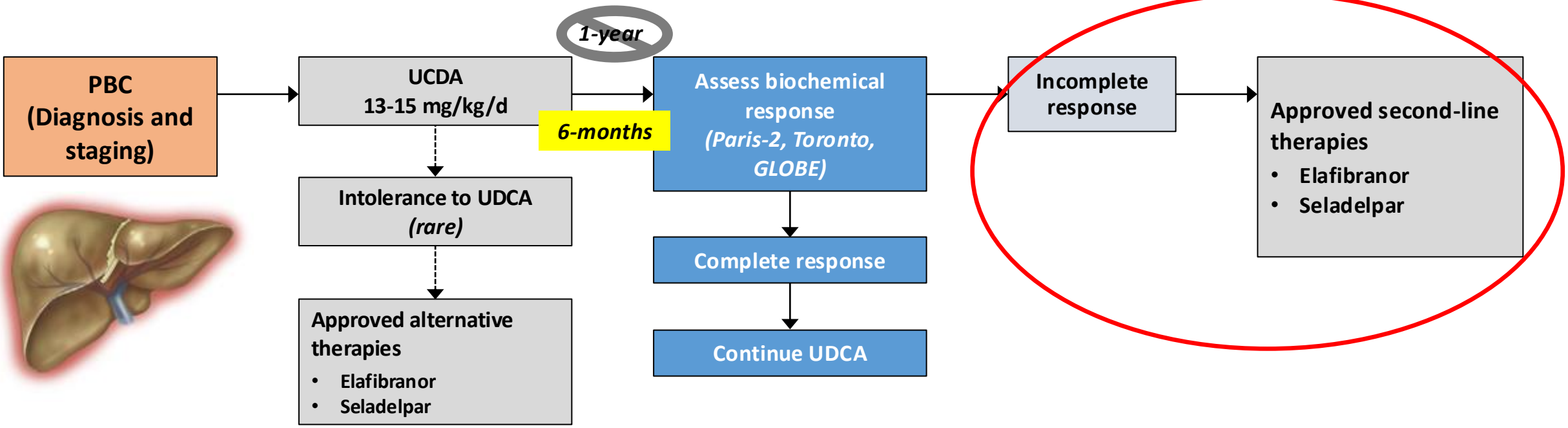
Any serious AE:

- Seladelpar: 7%
- Placebo: 6.2%

AEs resulting in treatment discontinuation:

- Seladelpar: 3.1%
- Placebo: 4.6%

PBC Treatment Algorithm



Modified from Montano-Loza AJ et al. *Clin Gastroenterol Hepatol*. 2021; 19:2241-2251.e1.

PBC: Key Takeaways

- Chronic autoimmune disorder affecting small bile ducts, leading to cholestasis and progressive liver damage.
- Key features include elevated alkaline phosphatase (ALP) and positive antimitochondrial antibodies (AMA).
- Ursodeoxycholic acid (UDCA) is the first line treatment to slow progression.
- 2nd line therapies for PBC
  - Elafibranor
  - Seladelpar

Summary

- Early diagnosis and treatment are essential to prevent progression to cirrhosis.
- Regular monitoring for liver function, complications, and liver transplantation when indicated.