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Rush University Medical Center

Present and Future Treatment Landscape for Cholestatic Liver Diseases

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Disclosures

- Consultation: AbbVie, Gilead, Arbutus, Intercept, Salix, VIR
- Research Support: AbbVie, Gilead, Salix, Eiger

Diagnosis of PBC and PSC

PBC 2 of 3

1. Unexplained Elevation of ALP > 1.5 X ULN
2. Positive anti-mitochondrial antibody or other PBC-specific antibody
3. Non-suppurative destructive cholangitis on histology

Biopsy not required for the diagnosis

- *If meets serological and biochemical criteria*
- *AND no suspicion of other liver disease (e.g. fatty liver)*

PSC

1. Cholestatic Liver Tests (elevated ALP)
2. Cholangiography with stricturing
3. Exclusion of secondary sclerosing cholangitis

(Drug-induced, ischemic, malignancy, infections)

Biopsy not required for the diagnosis

- Histology unreliable at distinguishing from other chronic liver diseases (PBC, drug injury)
- Characteristic “onion-skinning” seen in 12%

AASLD Guidelines.

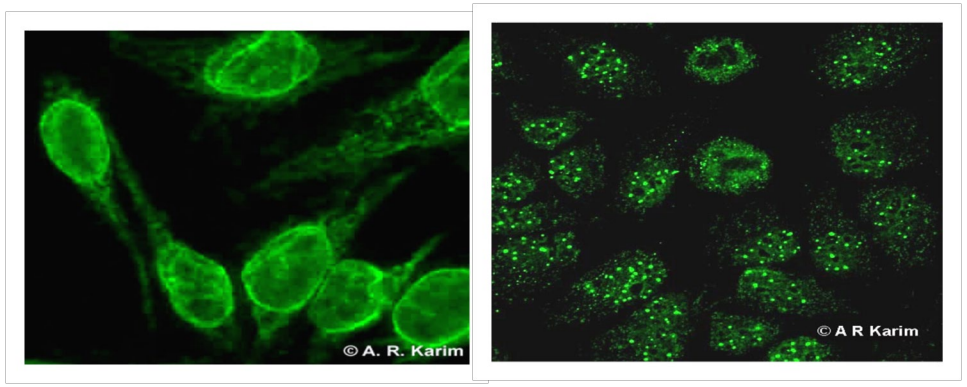
PBS vs PSC

	PBC	PSC
Population	Females (9:1)	Males (5:1)
Bile Ducts	Interlobular	Intra & Extrahepatic
ERCP	Normal	Abnormal
AMA	+	–
IBD Association	–	+
Cholangio CA Risk	–	+

PBC

PBC – Specific Antinuclear Antibodies

- 40-50% PBC is ANA positive
- PBC-specific ANAs:
  - Anti-gp210 (nuclear rim pattern)
  - Anti-sp100 (multiple nuclear dots pattern)
  - Anti Kelch like 12
  - Anti Hexokinase 1



Found in 20% of all PBC pts, and in 40-50% of AMA-neg PBC patients

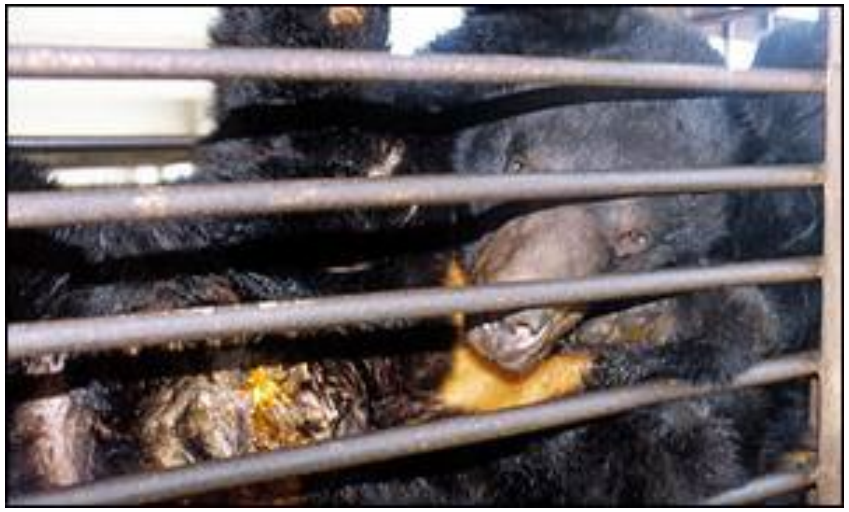
Found in 68-75% of AMA-neg PBC patients

Commercially Available In USA

Levy C, Bowlus C, et al. *Am J Gastroenterology*. 2020.

Ursodeoxycholic Acid (UDCA,Ursodiol, Urso)

- A naturally occurring Hydrophilic bile acid
- Enriches bile pool from 1% to 40% UDCA at 13-15 mg/kg.
- Decreases ability of bile to enter cell membrane and cause damage
- Increases fluidity of bile
- FDA approved for PBC



Ursus=Bear.

200mg, 250mg, 300mg, 400mg, 500mg

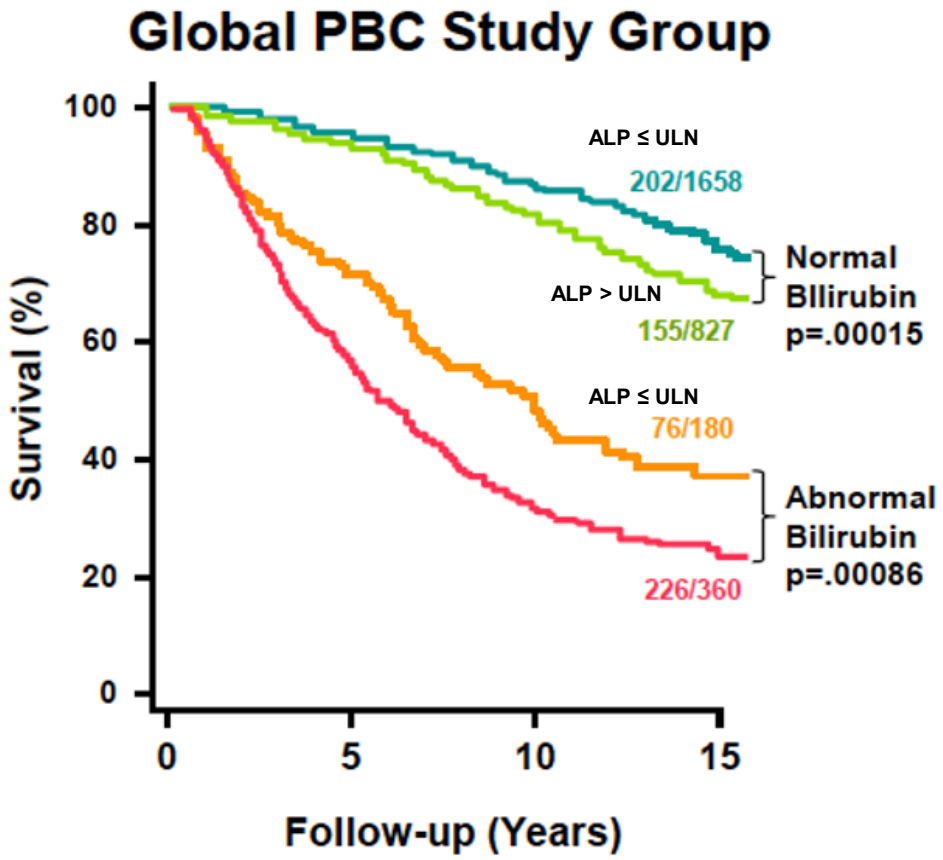
Summary of Ursodiol Benefit in PBC

- Improves biochemical liver tests
- Delays histological progression
- Prolongs expected survival without liver transplantation
- Up to 40% have suboptimal response

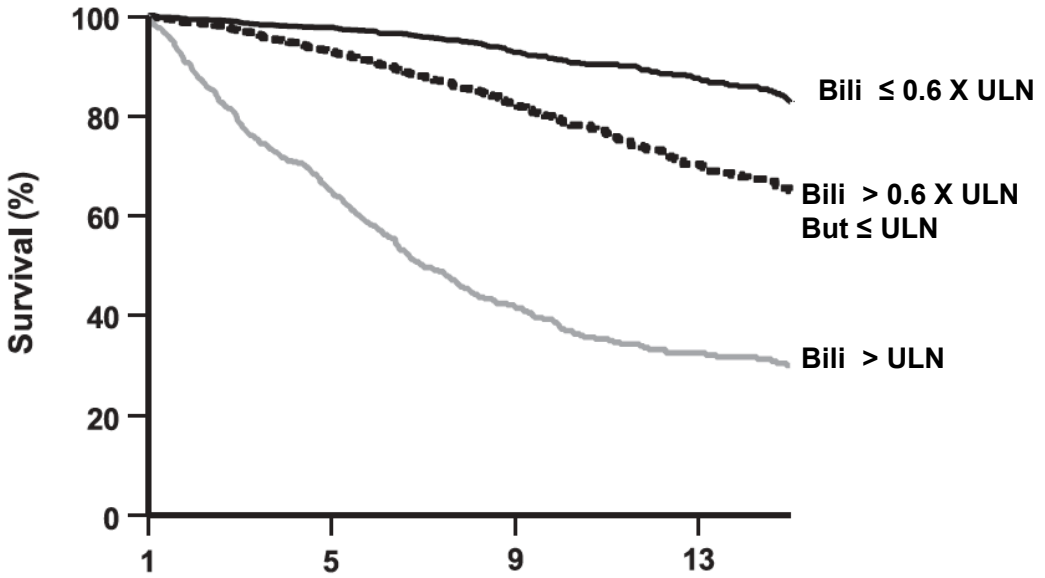
However:

Transplant-free survival of ursodiol-treated patients is significantly lower than age/sex-matched controls.

Biochemical Response to UDCA Predicts Survival



Bilirubin stratified by 0.6 x ULN

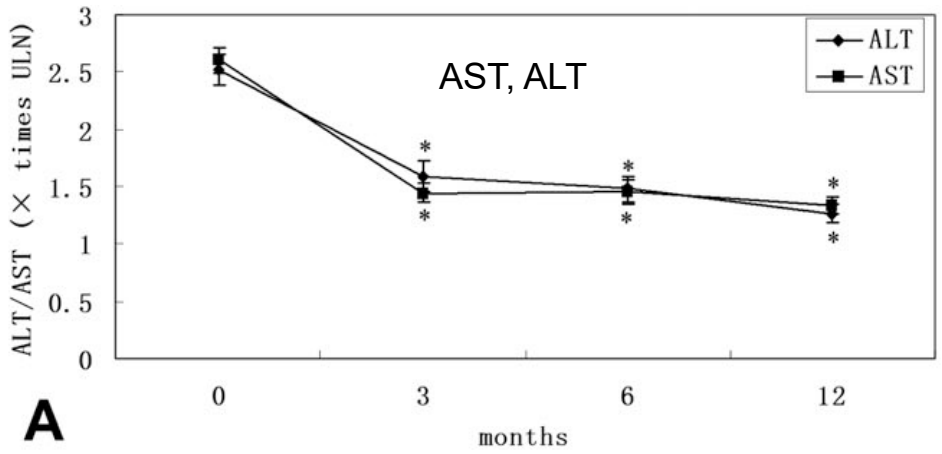


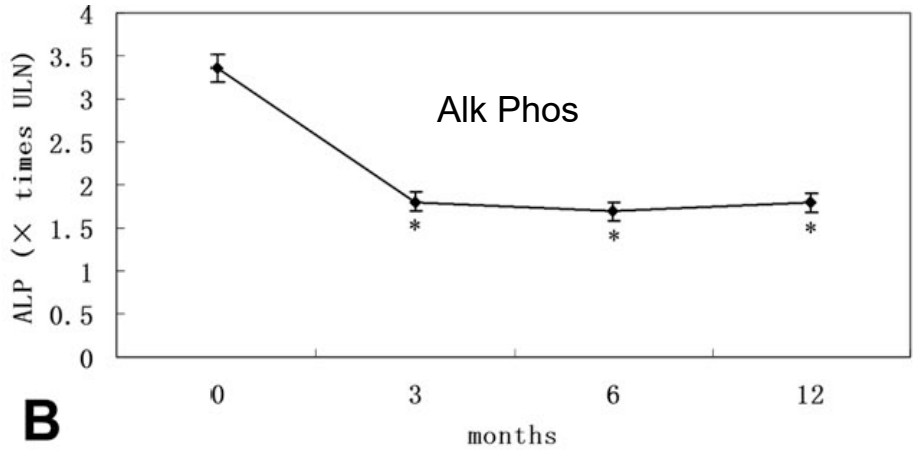
No. at risk

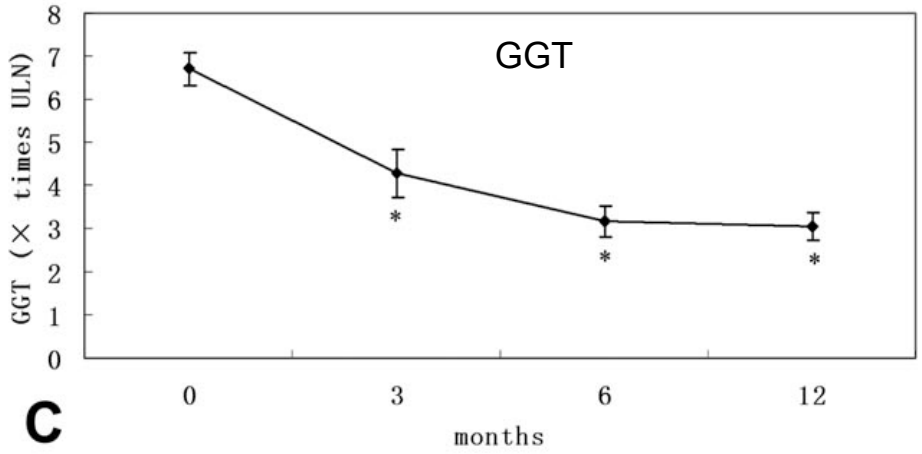
a	1718	1256	737	385
b	837	614	400	209
c	529	285	134	82

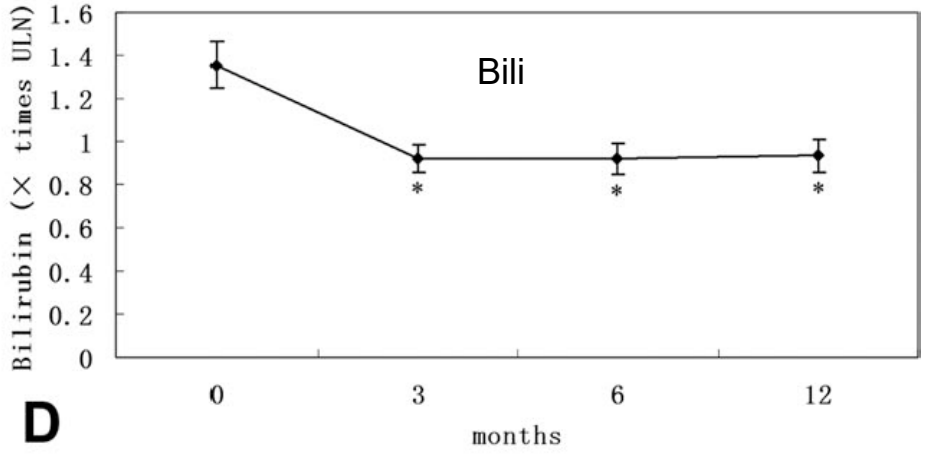
Murillo Perez et al. *Am J Gastro*. 2020.

Biochemical Response to UDCA Is Evident in 3 Mo









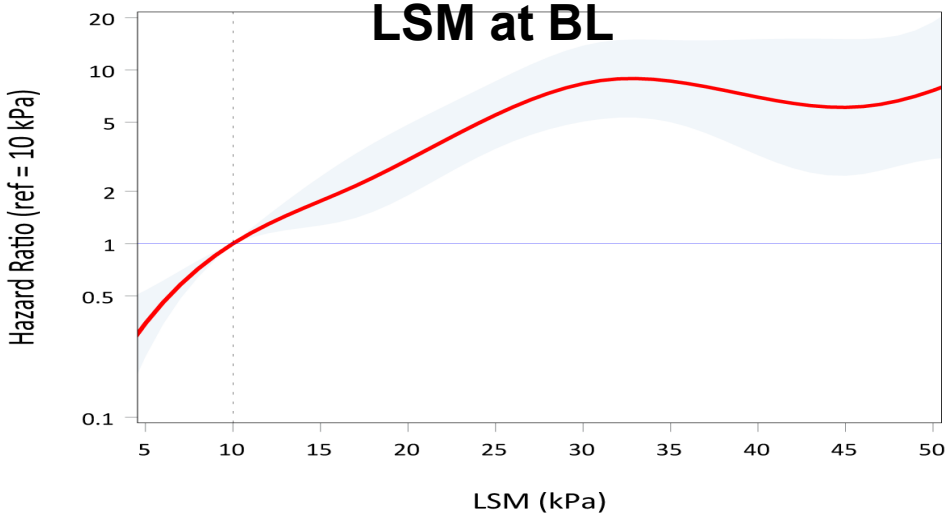
Liver stiffness assessed by FibroScan is a surrogate endpoint of outcomes of UDCA-treated patients with PBC: an international follow-up study

RESULTS

- **5324 reliable LSMs were collected in 2740 UDCA-treated patients with PBC from 18 centres across 11 countries**

Characteristics	
LSM median value at BL, kPa (IQR)	6.8 (5.3, 10.0)
Mean age of patients, years	58
% female	91
% definite/probable cirrhosis	11
Median time between UDCA start and BL LSM, years	3.0
Median follow-up from BL LSM, years (range)	4.1 (1.0−16.4)
Deaths Total Liver-related	 145 62
Liver Transplant Liver complications	56 77

Hazard of all-cause death or LT as a function of LSM at BL



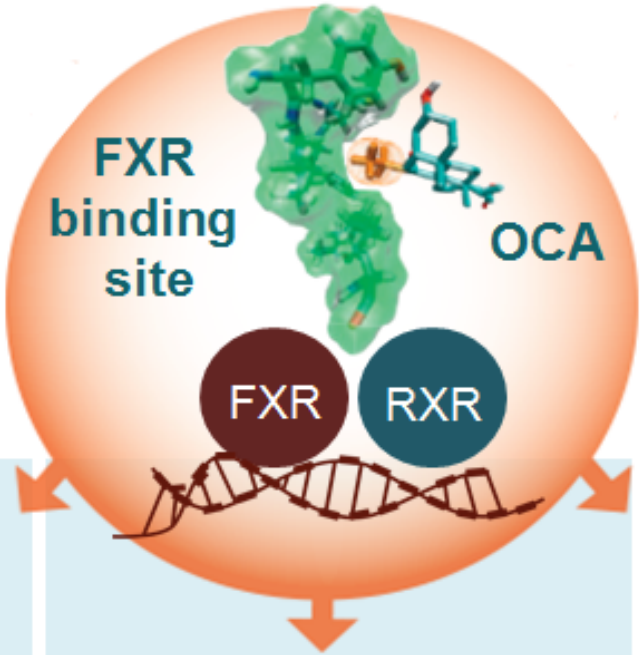
Within the 5–30 kPa range, the log-HR for all-cause death or LT increased as a linear function of LSM

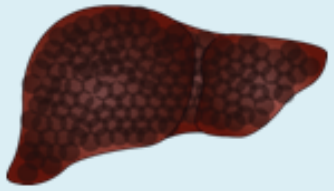
CONCLUSION

LSM assessed by FibroScan can predict clinical outcomes of patients with PBC and might be used as a surrogate endpoint in clinical trials

Corpechot C, et al. ILC 2021; OS-894

Obeticholic Acid (OCA): A Modified Bile Acid and FXR Agonist





FIBROSIS

- ↓Stellate cell activation (PDGF)
- ↓Fibrogenesis (TGF-β1)
- ↑Matrix degradation (MMP-2)

INFLAMMATION

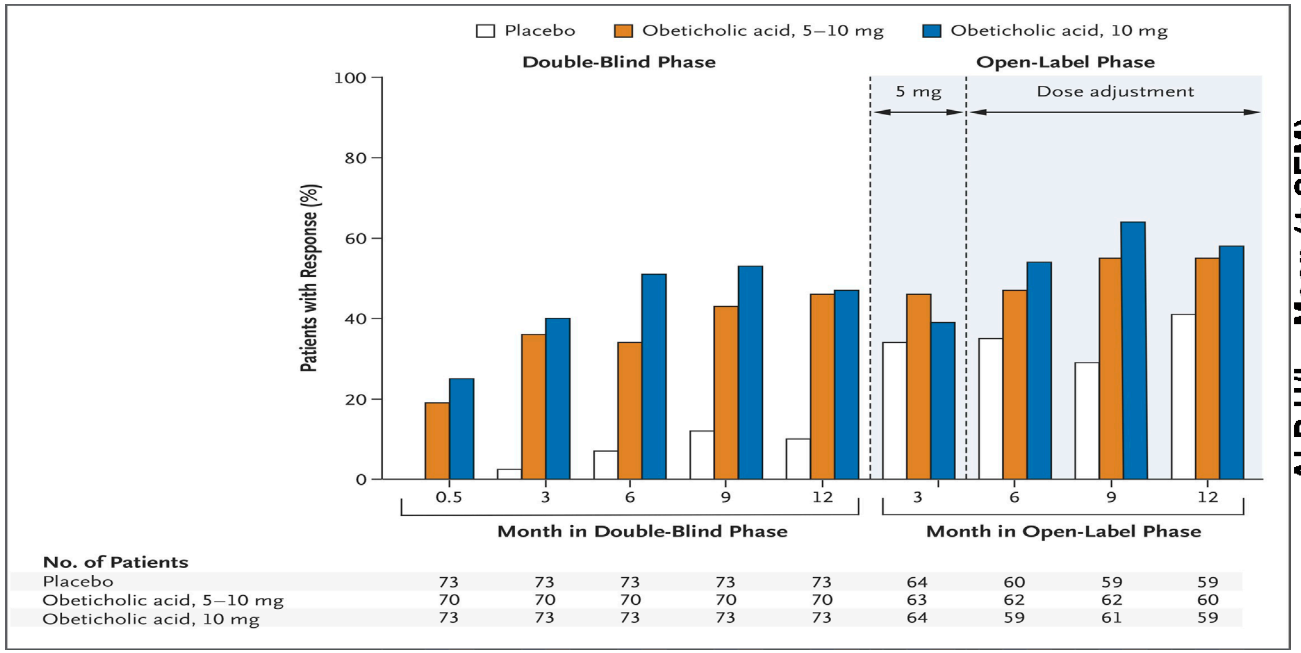
- ↓ NF-κB
- ↓ TNFα, IL-1β, IL-17, IFN-γ, etc.
- ↓ IgM
- ↓ CRP

BILE ACID HOMEOSTASIS

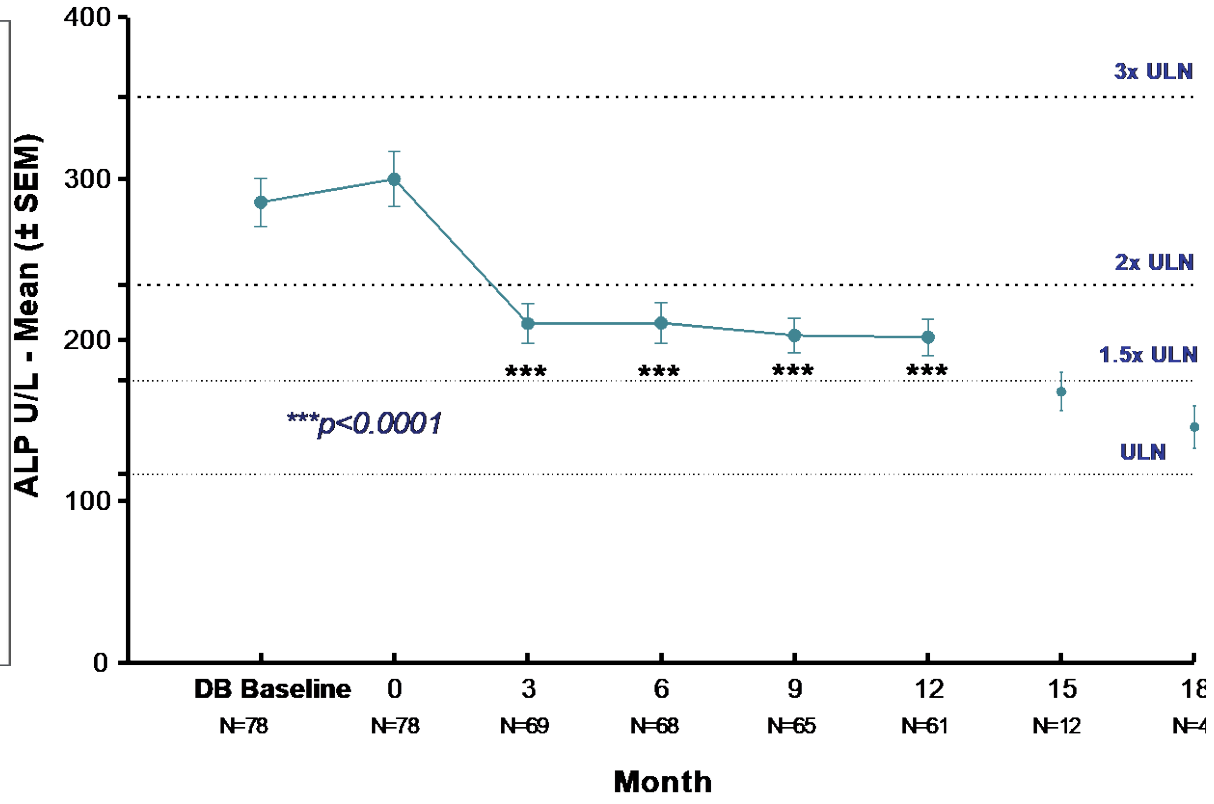
- ↓ Bile acid synthesis (CYP7A1)
- ↓ Bile acid uptake (OATP)
- ↑ Bile acid secretion (BSEP)
- ↓Bile acid absorption (ASBT)

Alk Phos Improves With Obeticholic Acid Treatment

OCA Absolute Reduction in ALP in PBC Suboptimal Ursodiol Responders



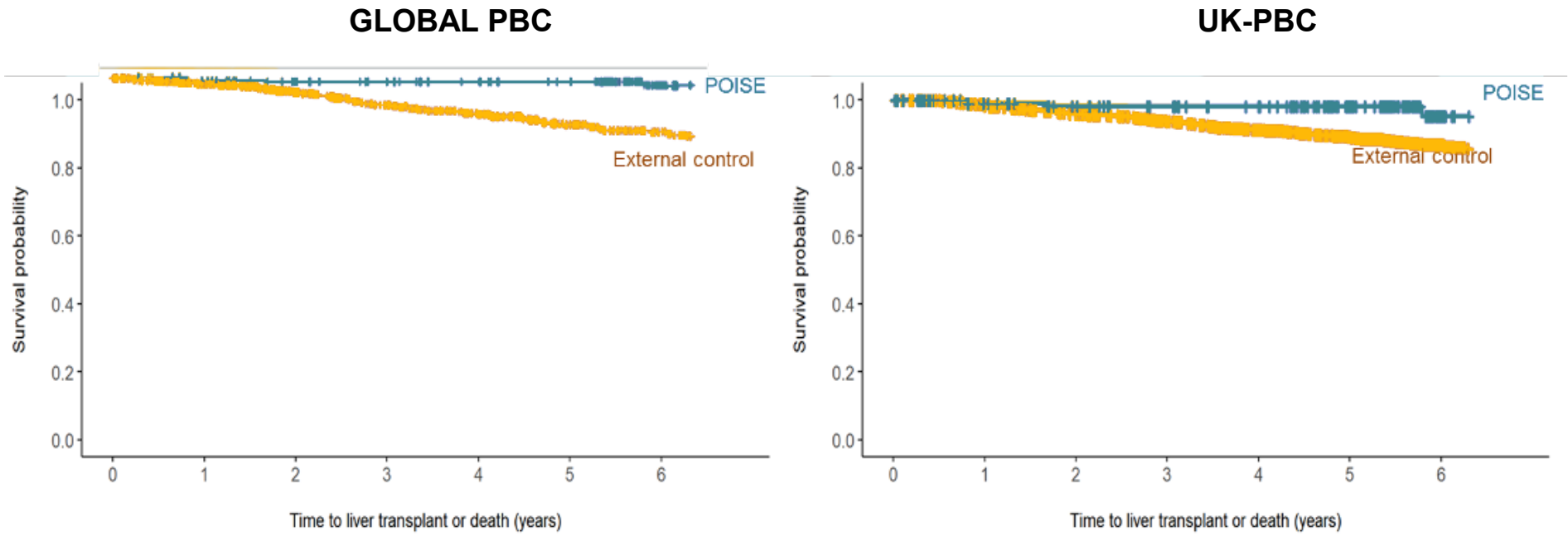
Nevens F et al. N Engl J Med 2016



- 29% reduction ALP overall. 46% pts combined endpoint
  (ALP< 1.67 X ULN +15% ALP reduction + nl Bili)
- New treatment goal ALP normalization and Bili < 0.6 X ULN (only 7% with OCA)
- Rapid (2-12 wk) and durable

Figure courtesy of D Shapiro.

Patients Treated With OCA Had Significantly Greater Transplant-free Survival Than External Controls



	POISE (n= 209)	GLOBAL PBC (n= 1,391)	UK PBC (n=2,135)
Total number of events	3	146	281
Liver transplantation	0	52	119
Death	3	94	162

AASLD: Late Breaker. 2021. Murrillo Perez CF et al. *Gastroenterology* 2022.

Potential OCA Adverse Effects: Itch, Gallstones/Cholecystitis, Hepatotoxicity

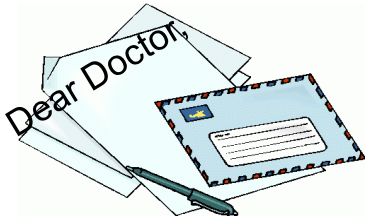
- Pruritus: Common, dose related
- Gallstones/Cholecystitis:
  - Increases [cholesterol] in gallbladder bile. Multiple post marketing reports
- Grade 3 Hepatoxicity:
  - 5.2 per 100 patient exposure years with 10 mg and 2.4 with placebo.
  - Dose related 9.8 per 100 patient years for 25 mg daily and 54.5 for 50 mg daily
  - 19 deaths and 11 cases of severe liver injury, most cirrhotic
  - No correlation with itch

Pruritus	Placebo	OCA 5->10mg	OCA 10 mg
Phase 3 trial	38%	56%	68%
4yr open label	n/a	77%	

LiverTox.Nih.gov; Nevens et al. *N Engl J Med*. 2016; Kowdley et al. *AASLD*. 2019. Late Breaker; Trauner et al. *Lancet Gastro & Hep*. 2019.

FDA Warning → Black Box → Indication Change

Sept 2017



Jan 2018

Black Box

June 2021

Indication changed in US

- Ocaliva is being incorrectly dosed in some pts with mod-severe decrease in liver function
- Resulting in increased risk of serious liver injury and death
- May be associated with liver injury in some patients with mild disease who are receiving the correct dose
- Recommended dosing:
  - Compensated Childs A: 5 mg daily
  - Childs B or C or hx decompensating event: 5mg weekly
  - May increase as tolerated after 3 months up to 10 mg daily

WARNING: HEPATIC DECOMPENSATION AND FAILURE IN INCORRECTLY DOSED PBC PATIENTS WITH CHILD-PUGH CLASS B OR C OR DECOMPENSATED CIRRHOSIS

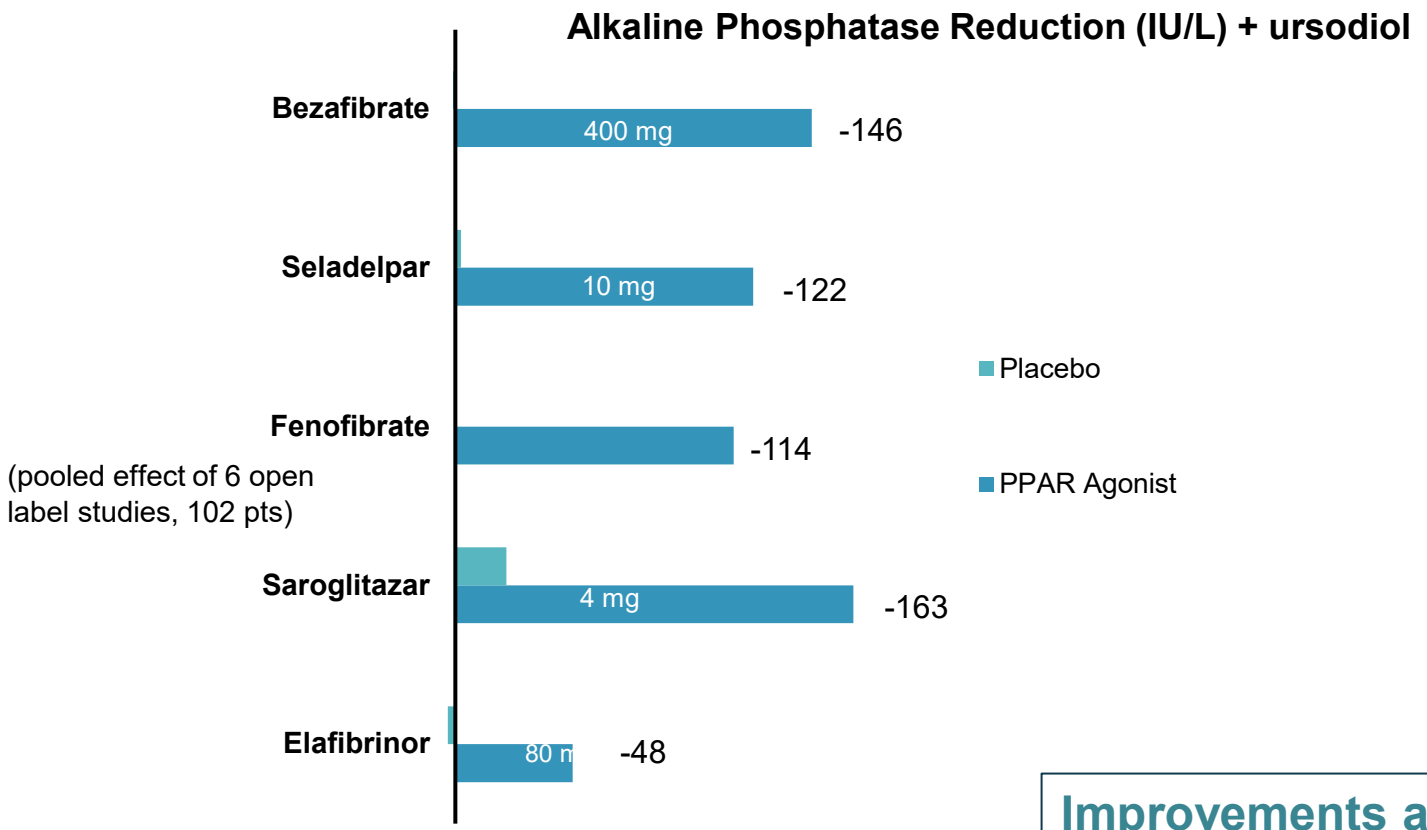
See full prescribing information for complete boxed warning

- **In postmarketing reports, hepatic decompensation and failure, in some cases fatal, have been reported in patients with primary biliary cholangitis (PBC) with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when OCALIVA was dosed more frequently than recommended. (5.1)**
- **The recommended starting dosage of OCALIVA is 5 mg once weekly for patients with Child-Pugh Class B or C hepatic impairment or a prior decompensation event. (2.2)**

Ocaliva is indicated for the treatment of adult patients with PBC who are

- *Without cirrhosis or*
- *Compensated cirrhosis who do not have evidence of portal hypertension*

PPAR Agonists (α,β/δ,γ) Improve ALP
(Peroxisome Proliferator-Activated Receptor)

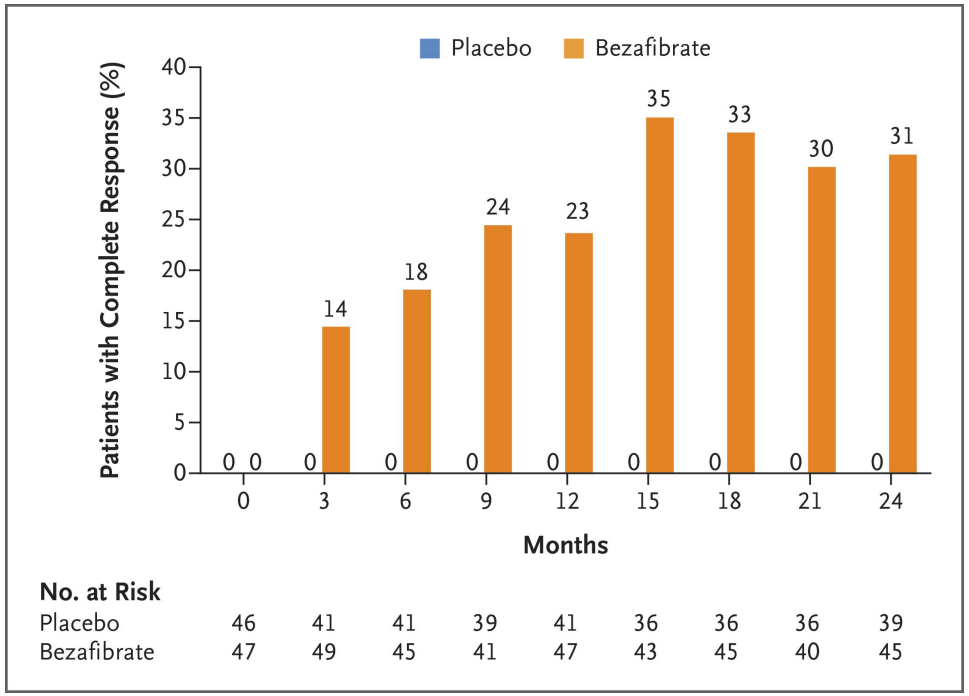


Improvements are rapid (2-12 wk) & durable (2 yrs

Corpechot et al. *NEJM*. 2018; Cymabay.com->Abstract; Grigorian et al. *Clin Res Hep.* 2015; Schattenberg et al. *J Hep.* 2021; Vupallanchi et al. *J Hep.* 2022.

Bezafibrate Improves Markers of Cholestatic Liver Injury in patients with PBC

Percentage of Patients with a Complete Biochemical Response According to Time and Trial Group

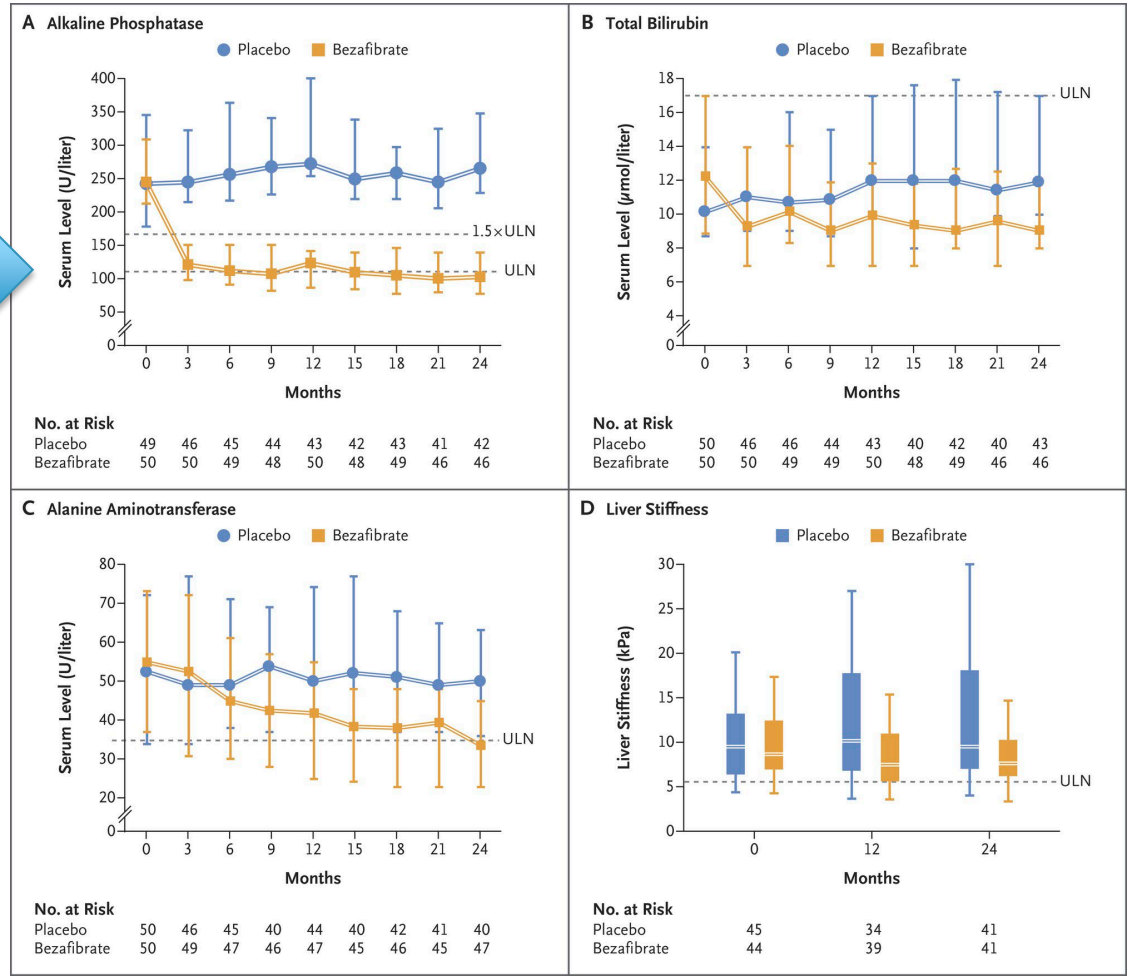


Corpechot C et al. N Engl J Med 2018

3 months

Also improved itch score

ALP, Total Bilirubin, and ALT, and Liver Stiffness According to Time and Trial Group

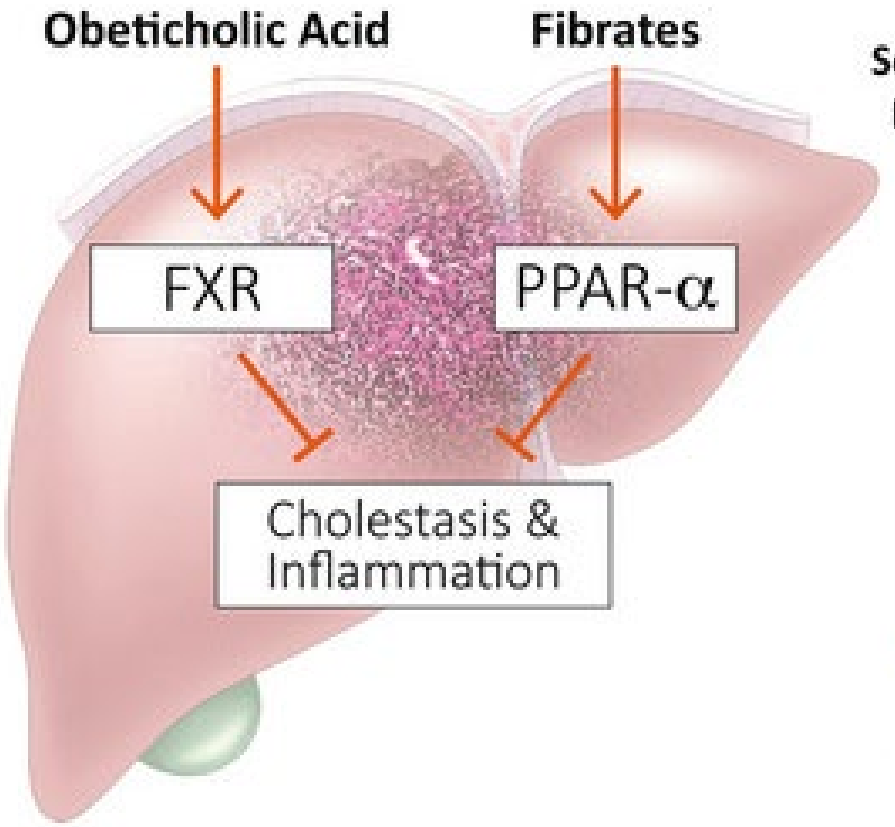


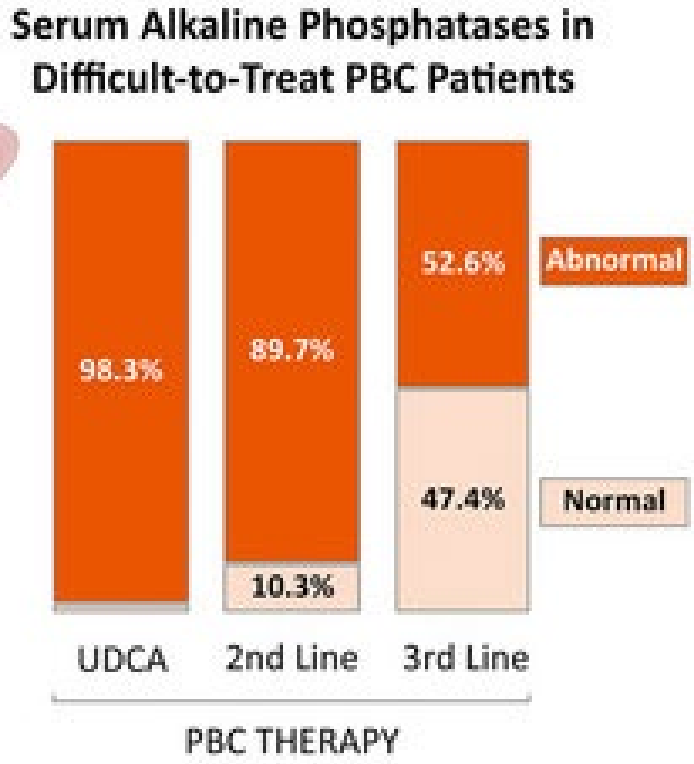
FDA Considers Fenofibrate Contraindicated in PBC

- CONTRAINDICATIONS :
  - Patients with severe renal impairment, including those receiving dialysis
  - Patients with active liver disease, **including those with primary biliary cirrhosis** and unexplained persistent liver function abnormalities
  - Patients with pre-existing gallbladder disease
  - Nursing mothers
  - Patients with known hypersensitivity to fenofibrate or fenofibric acid

- Hepatotoxicity of Fibrates
  - 20% elevated transaminases
  - 3-5% > 3X ULN
  - Rare : Acute liver failure
  - Increase in gallstones

Triple Therapy: UDCA+OCA+BZA X12 Wk





2nd line group : OCA as 2nd line + Fibrate as 3rd line; N= 29

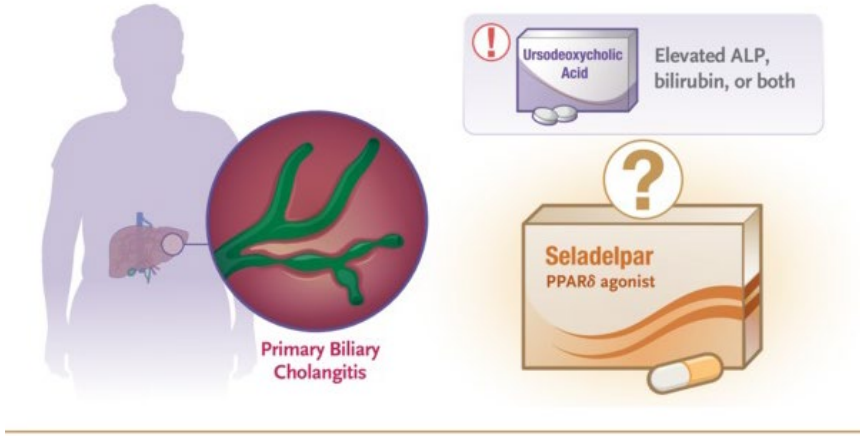
3rd line group : Fibrate as 2nd line + OCA as 3rd line; N= 29

Soret et al. *Alim Pharmacology & Therapeutics*. 2021.

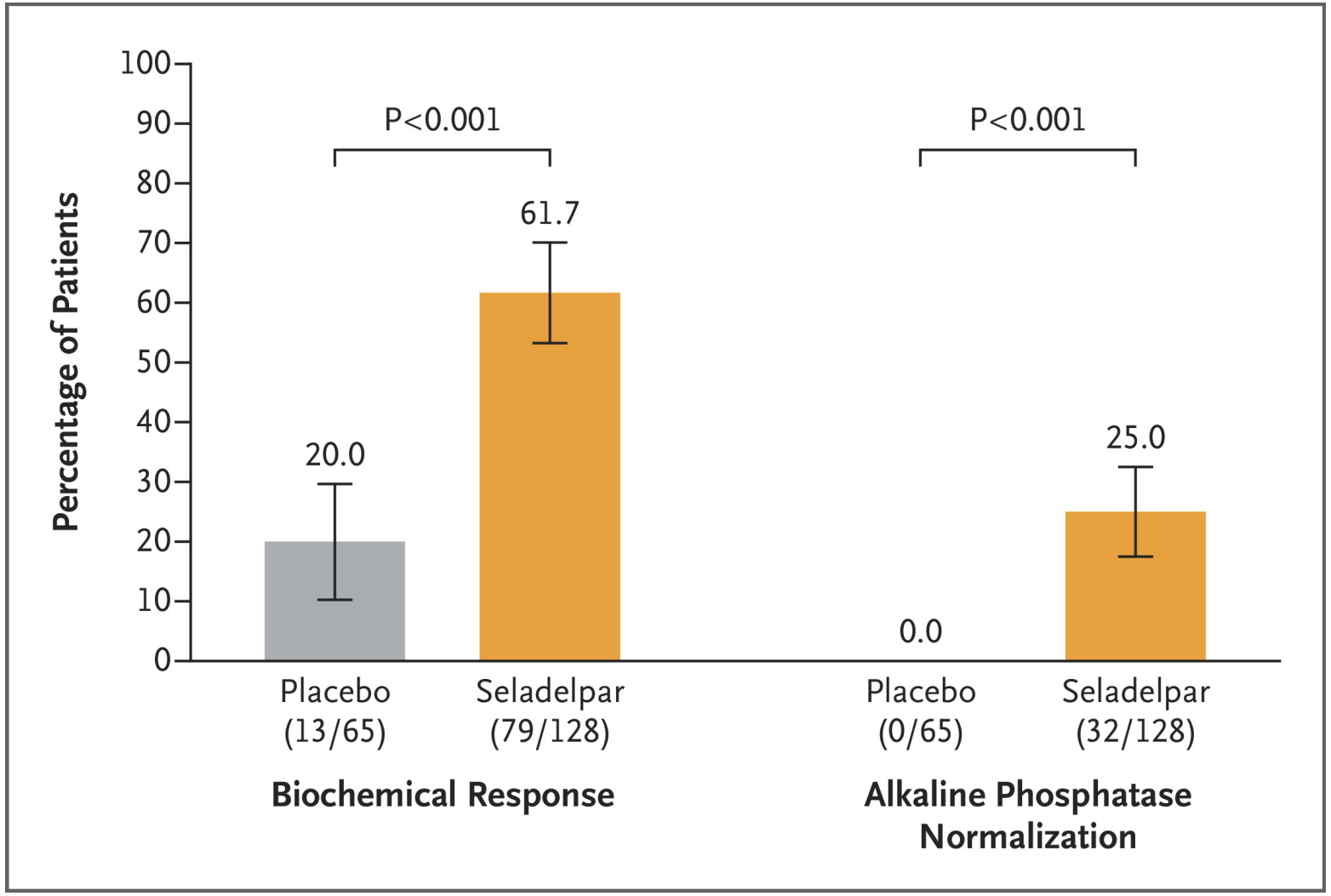
Seladelpar in Primary Biliary Cholangitis

Primary Endpoint: Month 12 Composite Biochemical Response

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

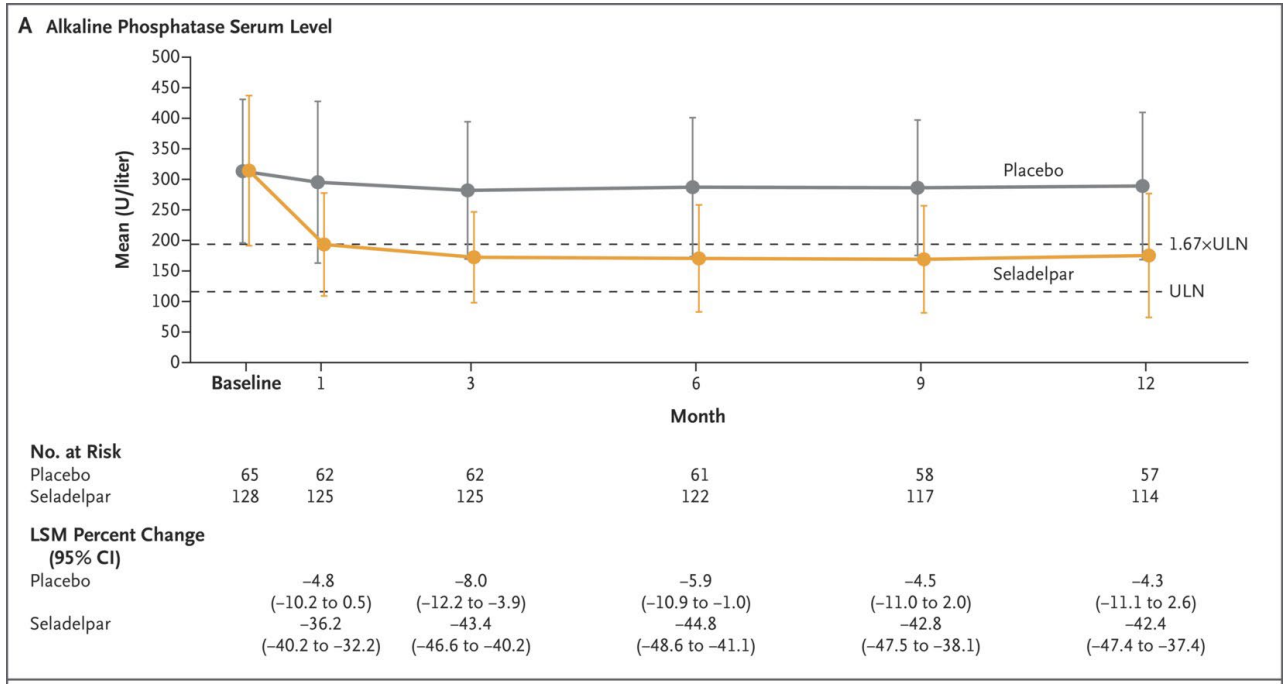


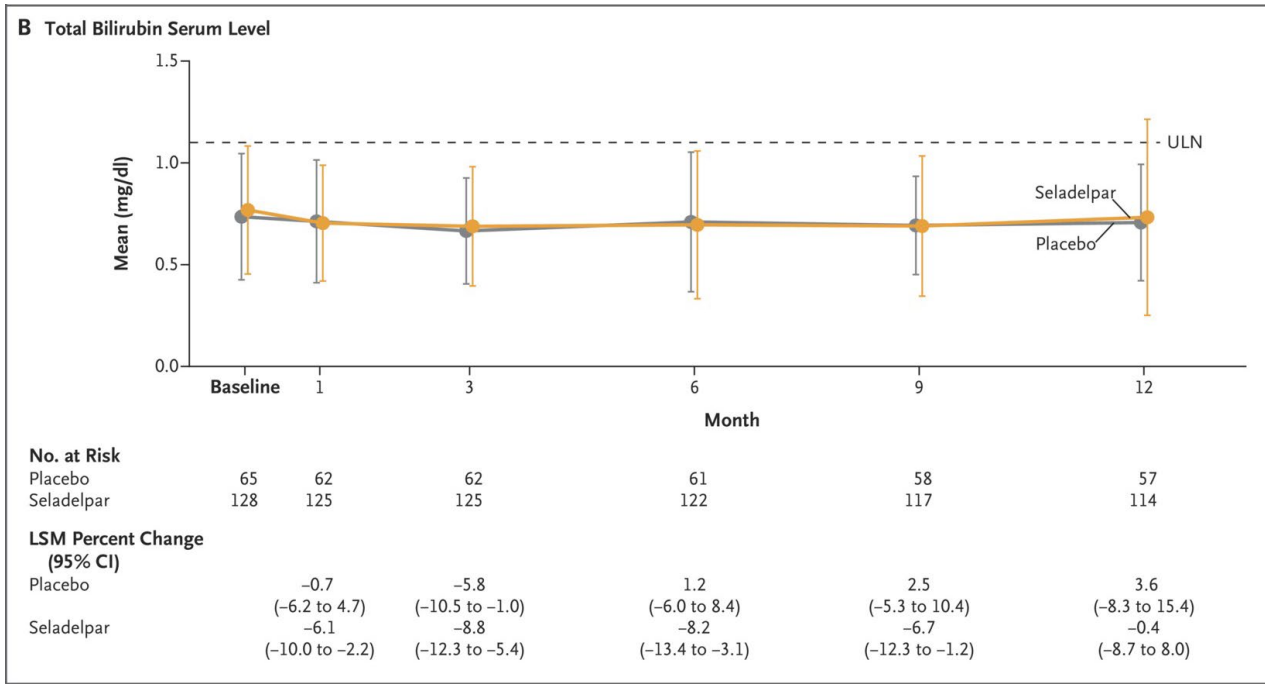
Seladelpar selectively activates PPARδ → releases fibroblast growth factor 21 (FGF21) from hepatocytes → reduces the accumulation of bile acids by inhibiting the expression of cholesterol 7α-hydroxylase, the rate-limiting enzyme for bile acid synthesis



Hirschfield GM et al. N Engl J Med2024;390:783-794

A Phase 3 Trial of Seladelpar in Primary Biliary Cholangitis

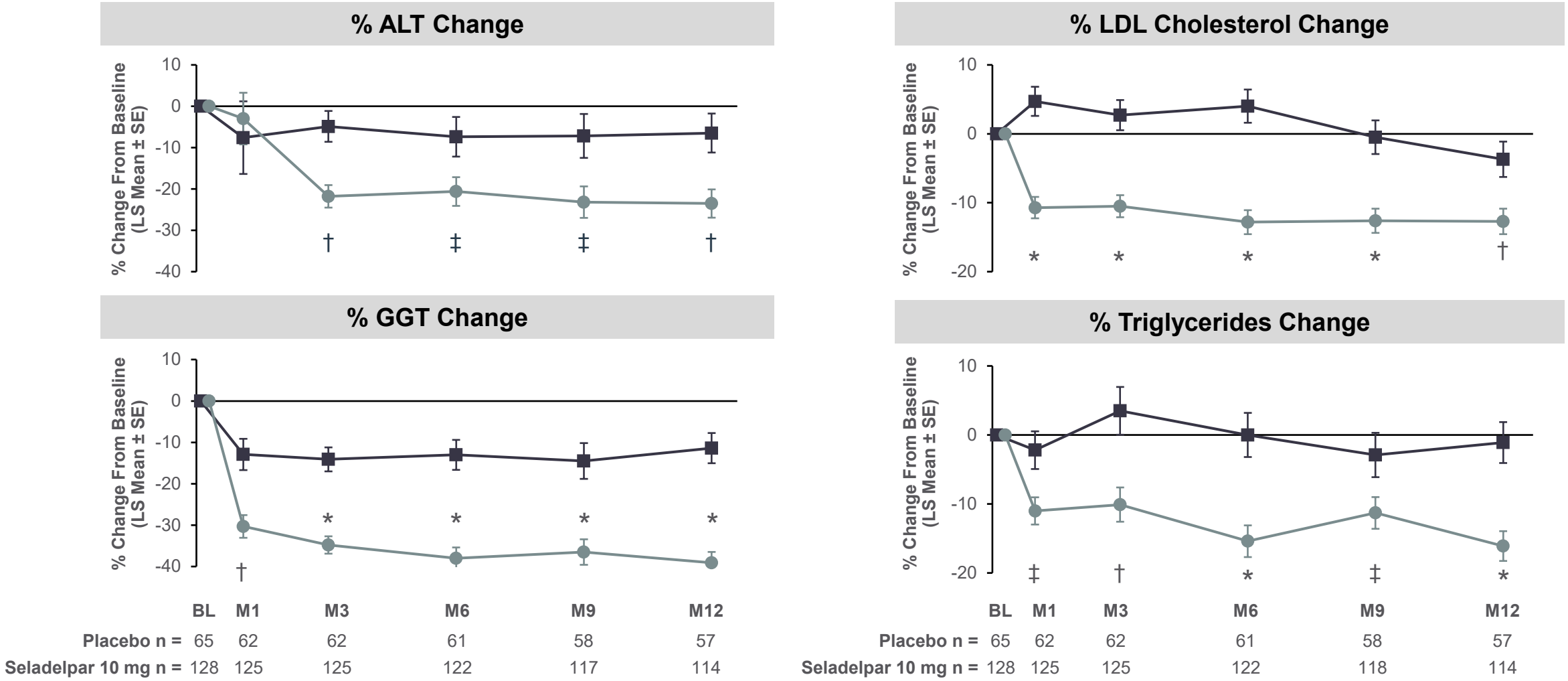




Alkaline Phosphatase and Total Bilirubin Levels through Month 12.

Hirschfield GM et al. N Engl J Med2024;390:783-794

Seladelpar Significantly Improved Serum Markers of Liver Injury and Lipid Profile

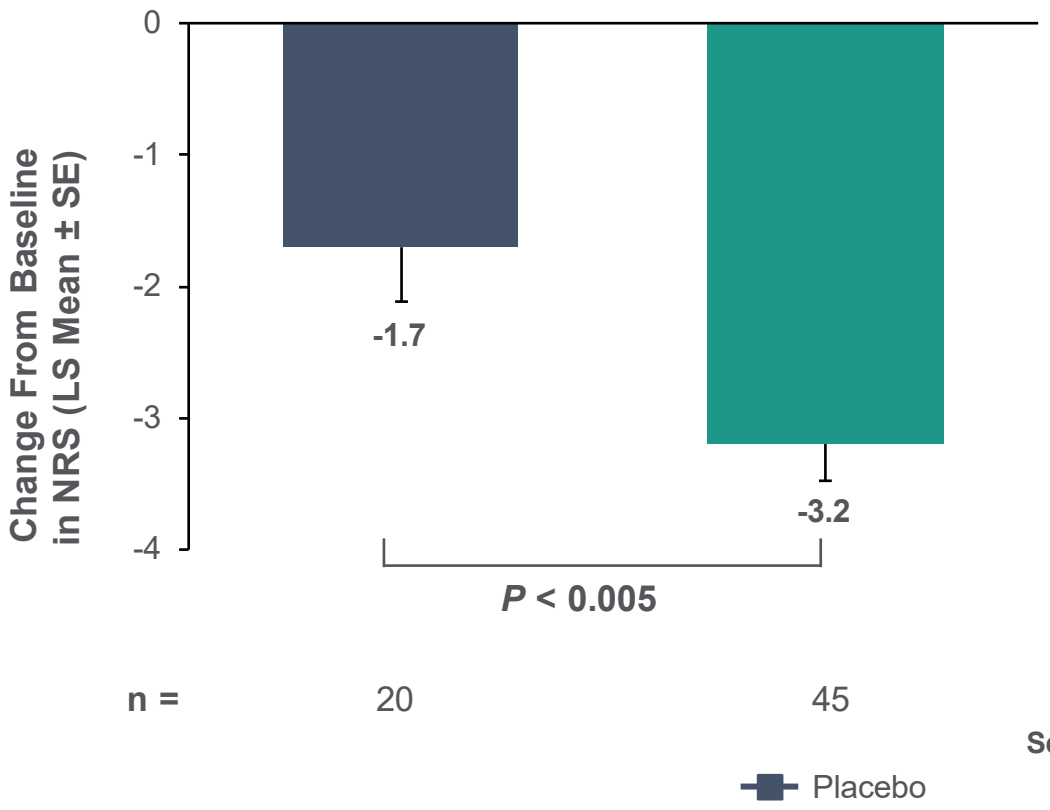


*P < 0.0001 vs placebo. †P < 0.005 vs placebo. ‡P < 0.05 vs placebo.

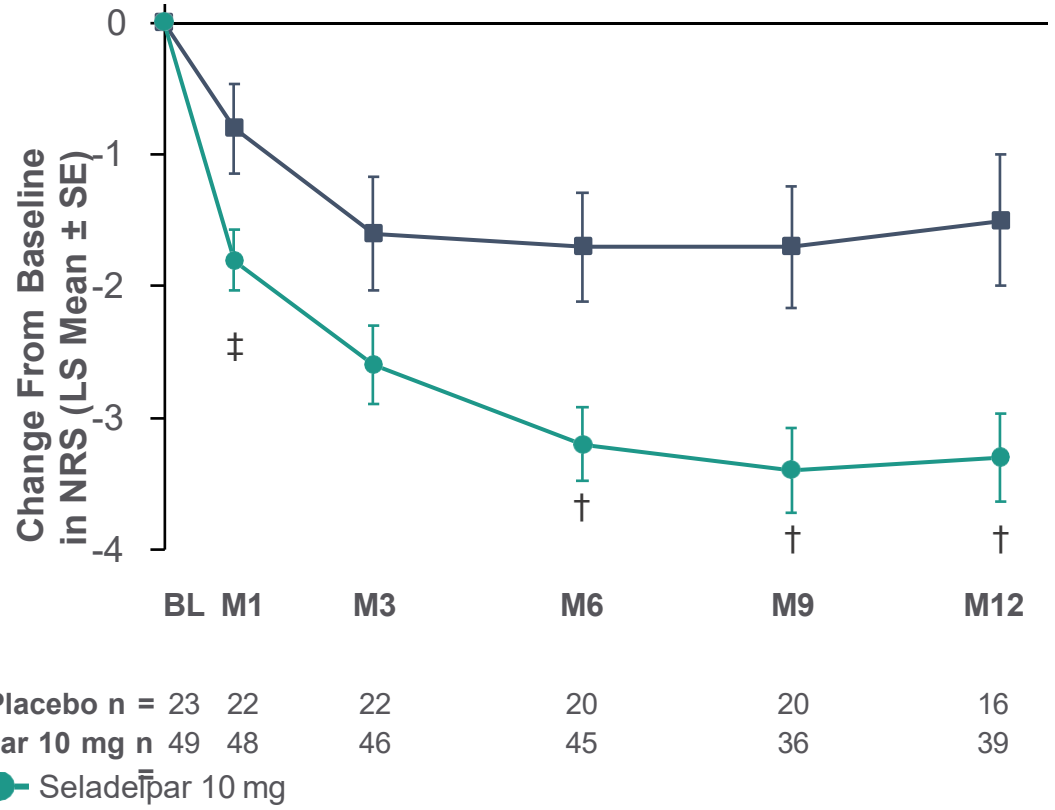
Seladelpar Significantly Improved Pruritus

Subjects With Baseline NRS ≥ 4

Key Secondary Endpoint: Change in Pruritus NRS at Month 6



Change in Pruritus NRS Over Time



MMRM analysis in subjects 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 subjects with available data at each time point.MMRM, mixed-effect model for repeated measures. †$P < 0.005$ vs placebo. ‡$P < 0.05$ vs placebo.

Phase 3 Study of Dual PPAR-α and PPAR-δ Agonist Elafibranor in PBC: Study Design

The NEW ENGLAND JOURNAL of MEDICINE

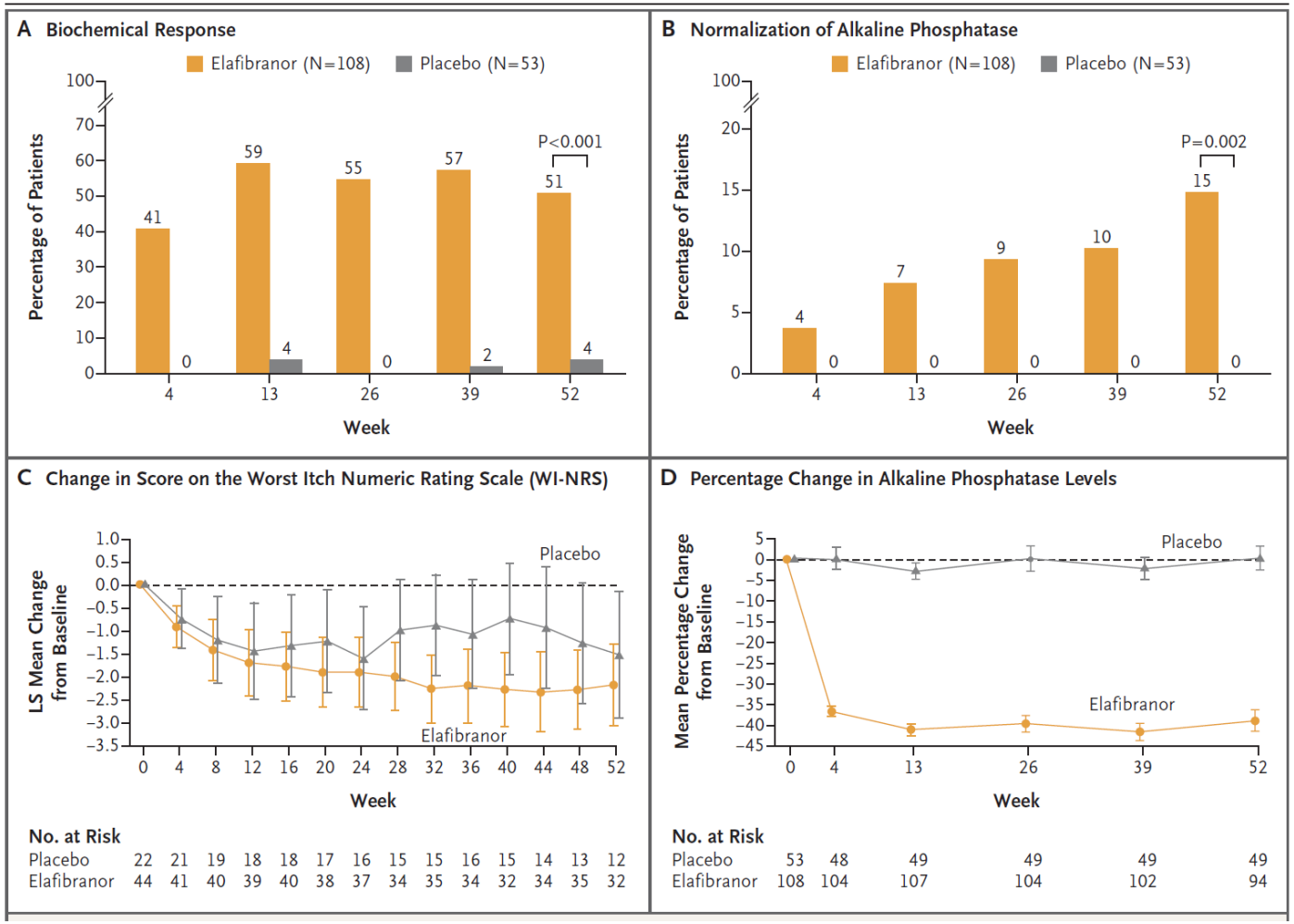
ORIGINAL ARTICLE

Efficacy and Safety of Elafibranor in Primary Biliary Cholangitis

K.V. Kowdley, C.L. Bowlus, C. Levy, U.S. Akarca, M.R. Alvares-da-Silva, P. Andreone, M. Arrese, C. Corpechot, S.M. Francque, M.A. Heneghan, P. Invernizzi, D. Jones, F.C. Kruger, E. Lawitz, M.J. Mayo, M.L. Shiffman, M.G. Swain, J.M. Valera, V. Vargas, J.M. Vierling, A. Villamil, C. Addy, J. Dietrich, J.-M. Germain, S. Mazain, D. Rafailovic, B. Taddé, B. Miller, J. Shu, C.O. Zein, and J.M. Schattenberg, for the ELATIVE Study Investigators' Group*

- **ELATIVE** trial
  - Phase 3, 12-month, placebo controlled RCT
  - Elafibranor 80mg daily (N=108)
  - Placebo (N=53)
- **Eligibility**: Inadequate response or intolerance to UDCA, ALP ≥ 1.67 x ULN, TB ≤ 2 x ULN, no AIH overlap, no decompensation
- **Participants:** N=161, 96% female, age 57 years, ALP 322 U/L, TB 9.6 mmol/L, LSM 10 kPa, WI-NRS 3.3

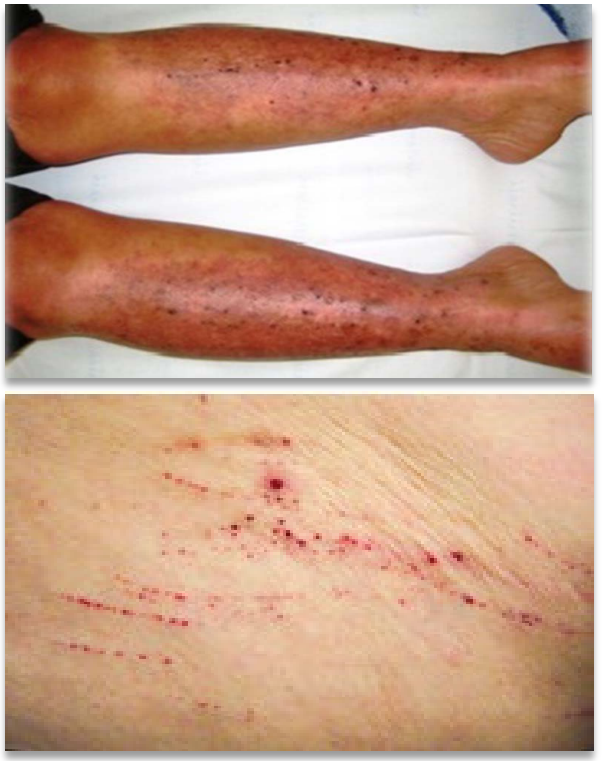
Phase 3 Study of Dual PPAR-α and PPAR-δ Agonist Elafibranor in PBC: Biochemical Response



LS, least square; PBC, primary biliary cholangitis; PPAR, peroxisome proliferator-activated receptor; WI-NRS, Worst Itch Numeric Rating Scale. **Kowdley KV, et al. NEJM. 2023. DOI: 10.1056/NEJMoa2306185**

Pruritus Is Common Among Patient with Primary Biliary Cholangitis

- Prevalence reported as high as 69%
- Unknown etiology
- Diurnal variation – most intense itch in the late evening
- Localization reported at limbs – soles of feet, palms of hands
- Exacerbated by contact with wool, heat, or pregnancy



Pinheiro NC, et al. *BMJ Case Rep.* 2013. https://thebileflow.wordpress.com/2011/10 /19/ pathology-pruritus/.

Imam MH, et al. *J Gastroenterol Hepatol.* 2012; Beuers U, et al. *Hepatology.* 2014; Lindor KD, et al. *Hepatology.* 2009.

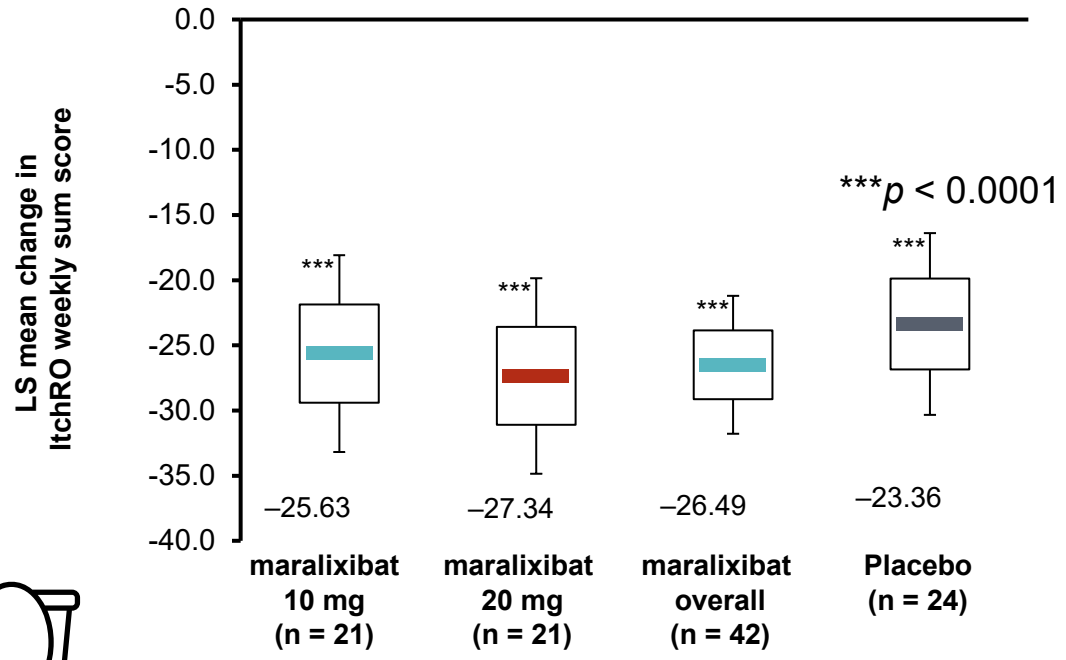
Numerous Treatment Options to Help Patients Manage Their Pruritus

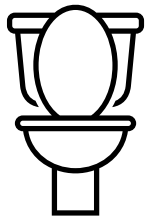
General Recommendations[1]	• Skin moisturizer • Wet, cooling, or moist wraps • Topical agents with symptomatic relief (eg, camphor, menthol) • Relaxation techniques • Training to stop the cycle of itch, scratch, itch
First-line[2-4]	Bile acid sequestrants: • Cholestyramine • Colestipol, colesevelam
The following agents may be used for pruritus that is refractory to bile acid sequestrants:	
Second-line[2-4]	Rifampicin
Third-line[2-4]	Oral opioid antagonists: • Naltrexone • Nalmefene
Fourth-line[2-4]	Selective serotonin reuptake inhibitors: • Sertraline

Weisshaar E, et al. *Acta Derm Venereol*. 2012: EASL. *J Hepatol*. 2009; Lindor KD, et al. *Hepatology*. 2009; Hohenester S, et al. *Semin Immunopathol*. 2009.

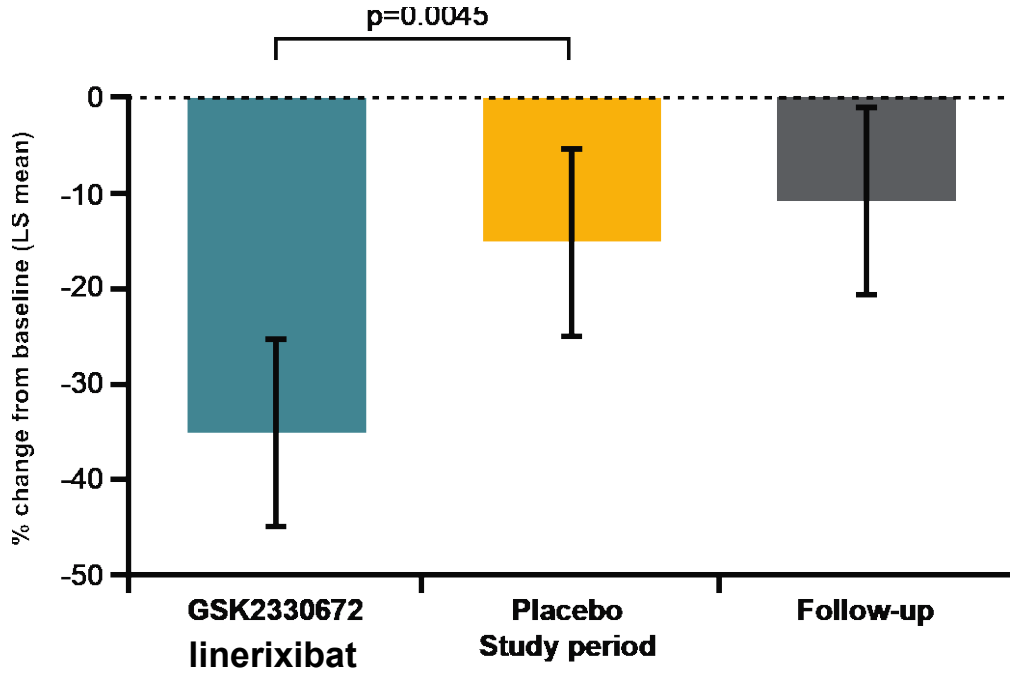
ASBT/IBAT Inhibitors May Improve Pruritus

- Apical Sodium-Dependent Bile Acid Transporter/
- Ileal Bile Acid Transporter





Side effect: diarrhea, abdominal discomfort



June 2021- Odevixibat FDA approved to treat itch in PFIC
Aug 2021- Maralixibat FDA approved to treat itch in Alagille's ongoing trial in PSC

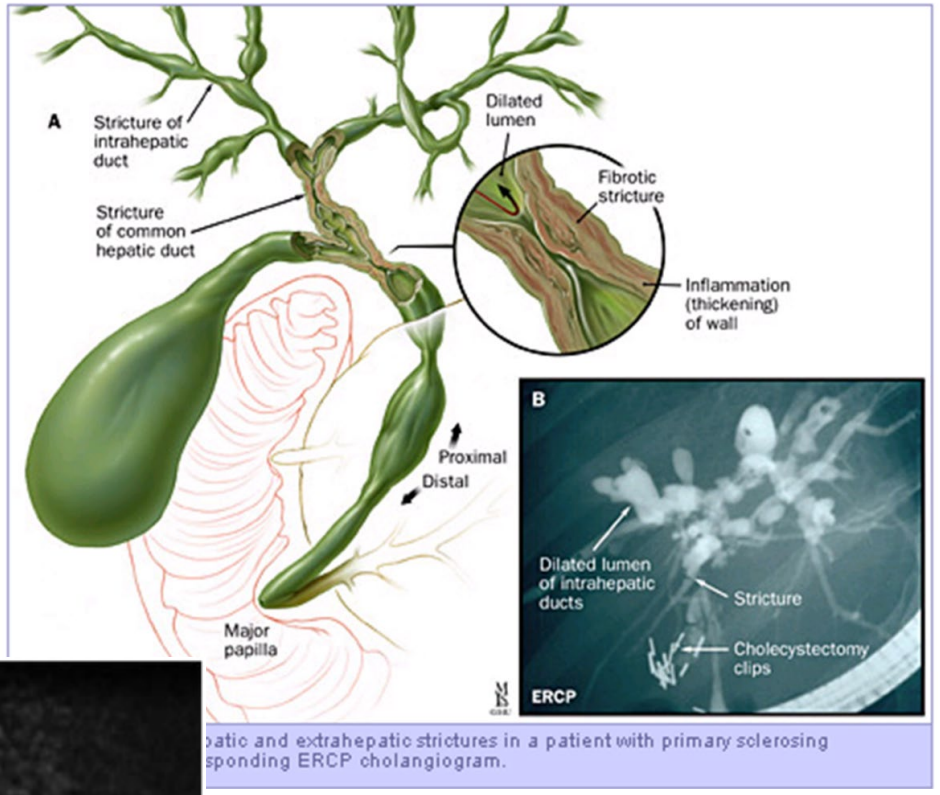
Heagadi et al. *Lancet*. 2017; Mayo et al. *J Hep*. 2017.

PSC

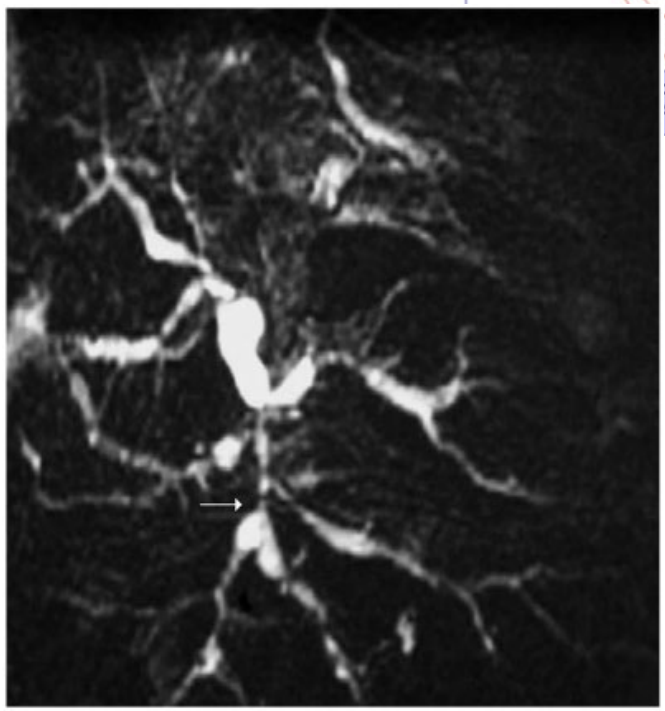
Diagnosis

- MRI/MRCP
  - 75% intra and extrahepatic strictures

- Liver Biopsy
  - Normal cholangiogram: Small-duct PSC
  - Features of AIH (esp children)
    - AST, ALT 5x ULN
  - High IGG4 → IGG4 sclerosing cholangitis



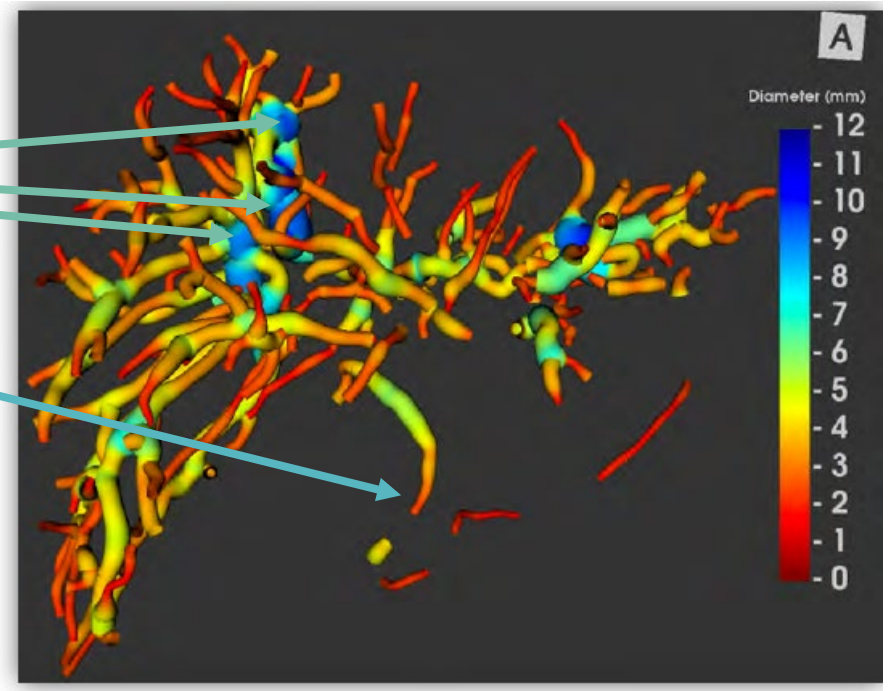
patic and extrahepatic strictures in a patient with primary sclerosing
sponding ERCP cholangiogram.



Quantitative Magnetic Cholangiography

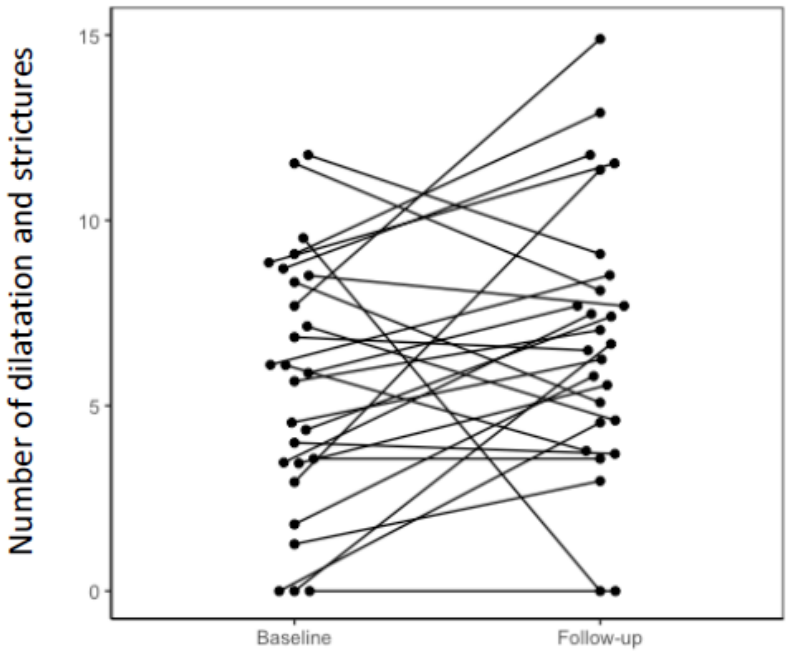
Dilation

Stricture



	Measured value
Biliary tree volume:[2]	33.2ml
Gallbladder volume:[2]	39.5ml
Percent of ducts with median width less than 3mm:	58%
Percent of ducts with median width greater than 3mm up to 5mm:	39%
Percent of ducts with median width greater than 5mm up to 7mm:	2%
Percent of ducts with median width greater than 7mm:	1%

Changes over 1 year in PSC patients in number of stricture/dilatations



p<0.01

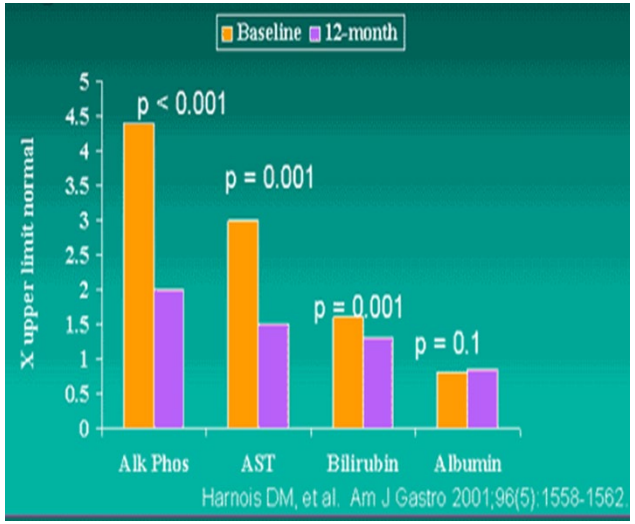
Image courtesy of Perspectum Diagnostics.
2019. *EASL Abstract* # 3815 .

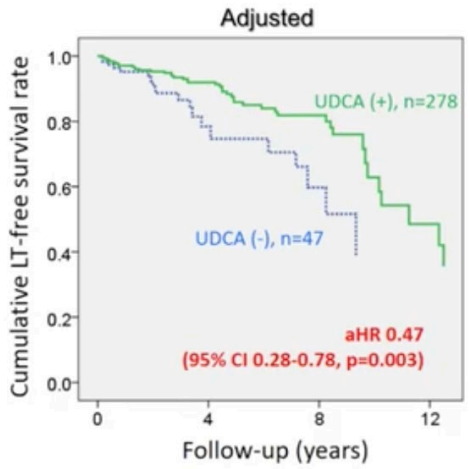
PSC: Medical Therapy
No approved medication for PSC

Tried and failed

Prednisone
Azathioprine
Penicillamine
Pentoxifylline
Colchicine
Nicotine
Metronidazole
Vancomycin
Tetracycline
Azithromycin
Silymarin
Pifenidone
Mycophenolate mofetil
Tacrolimus
Budesonide
Rapamycin
Methotrexate
Etanercept

URSO





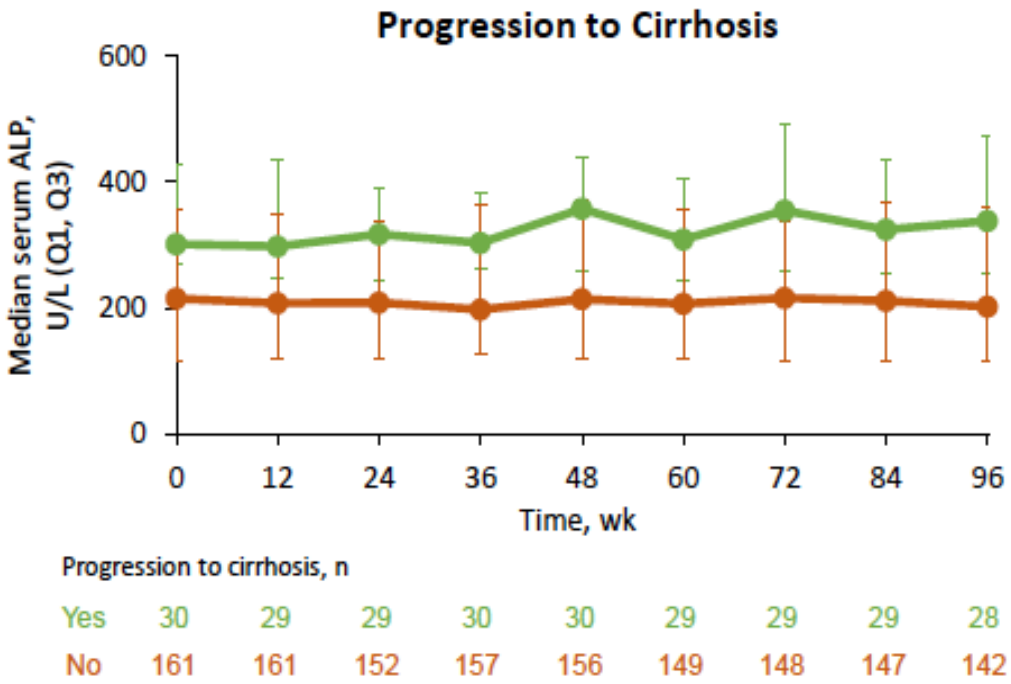
Conclusion: Long-term, high-dose UDCA improves serum liver tests but not survival; higher rates of serious adverse events (inc CRC).
HEPATOLOGY 2009;50:808-814

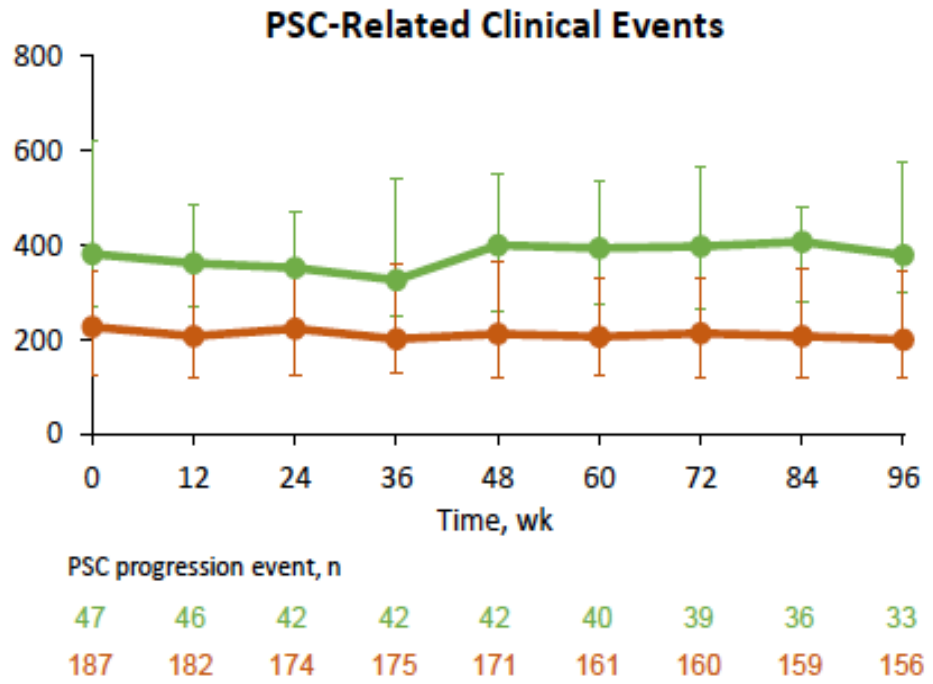
***Conclusion*:** Neither standard nor high-dose UDCA influence favorably the progression of PSC.
Aliment Pharmacol Ther 2011; 34: 901-910

Conclusion: No difference in long-term survival between patients with PSC given UDCA (17-23 mg/kg/day) or placebo for 5 years. Reduced or normal levels of ALP have longer survival times, regardless of whether they receive UDCA or placebo.
Clin Gastroenterol Hepatol. 2013 Jul;11(7):841-6

THE ASSOCIATION OF UDCA TREATMENT WITH LONG-TERM OUTCOME AND BILIARY TRACT CANCER IN PATIENTS WITH PRIMARY SCLEROSING CHOLANGITIS Oral AASLD 2020 Toshihiko Arizumi
Japanese PSC project

Prognostic Utility of Serum ALP





- **Baseline serum ALP was associated with:**
  - **Progression to cirrhosis (OR per 10-U/L: 1.02; 95% CI 1.00, 1.03)**
  - **PSC-related clinical events (HR per 10-U/L: 1.02; 95% CI 1.01, 1.02)**
- **Changes in serum ALP from baseline to Wk 12, 24, and 48 were not prognostic**

CGH 2020:S1542-3565

CI, confidence interval; OR, odds ratio; HR, hazard ratio.

The role of URSO is evolving

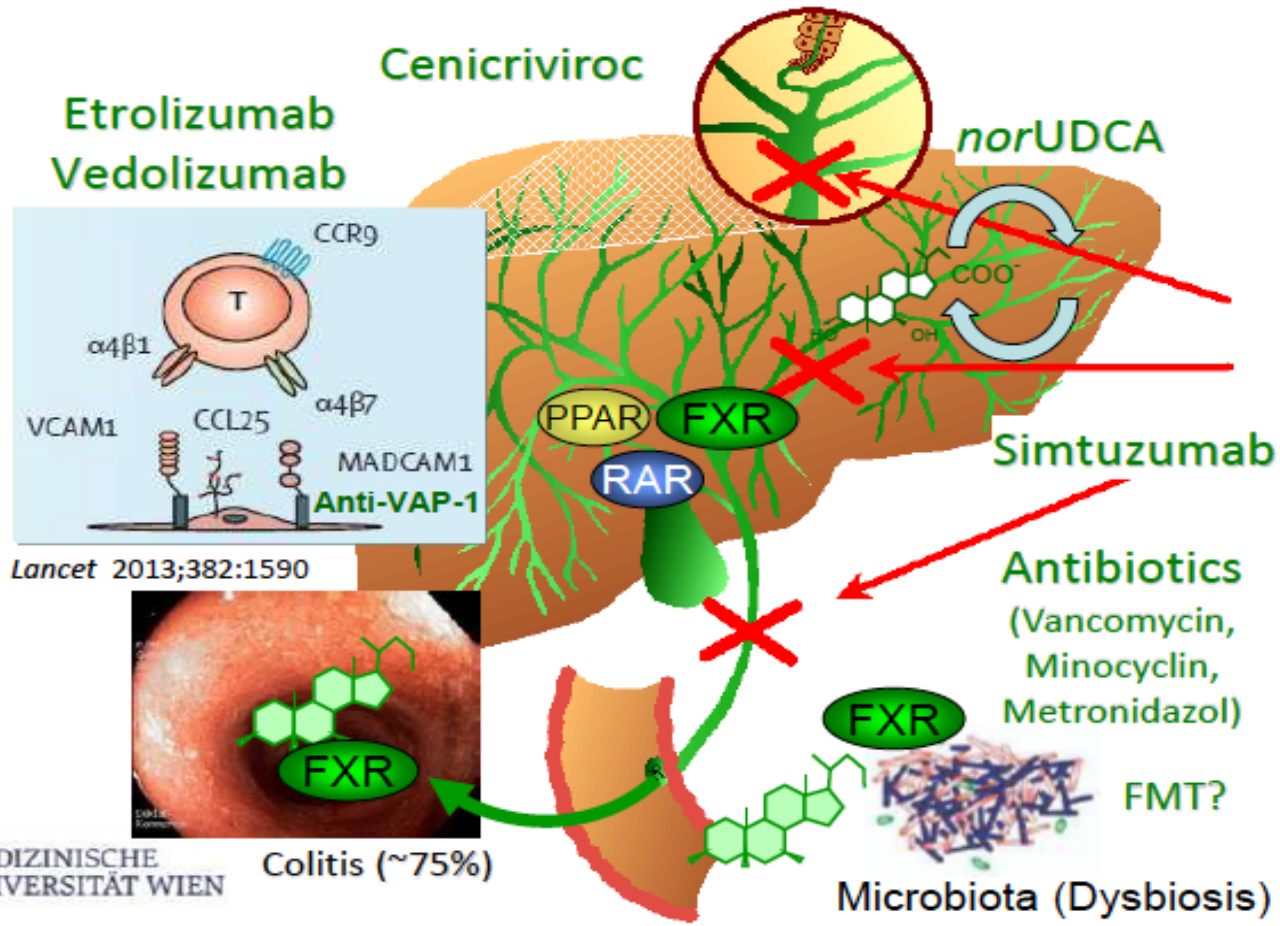
- ALP < 1.5 x ULN and GGT <50 U/L associated with better prognosis

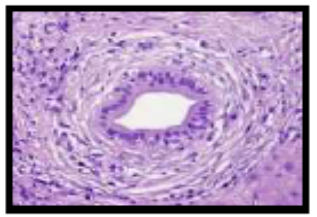
12. In patients not eligible or interested in clinical trials with persistently elevated alkaline phosphatase (ALP) or γ-glutamyl transferase (GGT), ursodeoxycholic acid 13–23 mg/kg/day can be considered for treatment and continued if there is a meaningful reduction or normalization in ALP (GGT in children) and/or symptoms improve with 12 months of treatment.

AASLD 2022

Drugs in Development for PSC

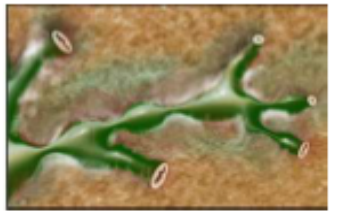
Novel Therapeutic Strategies in PSC Currently Tested in Clinical Trials - Overview





Small Duct PSC

Obliterative fibrosis of bile ducts



Large Duct PSC

www.mayoclinic.org

Courtesy of Dr. Michael Trauner

Reviews: Hirschfield et al., *Lancet* 2013
Halilbasic et al., *Dig Dis* 2015
Ali et al., *Intract Rare Dis Res* 2015
Karlsen et al., *J Hepatol* 2017

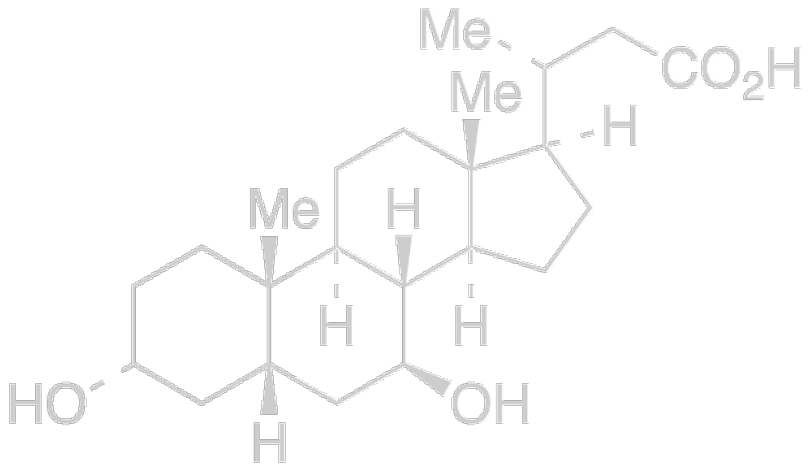
MEDIZINISCHE UNIVERSITÄT WIEN

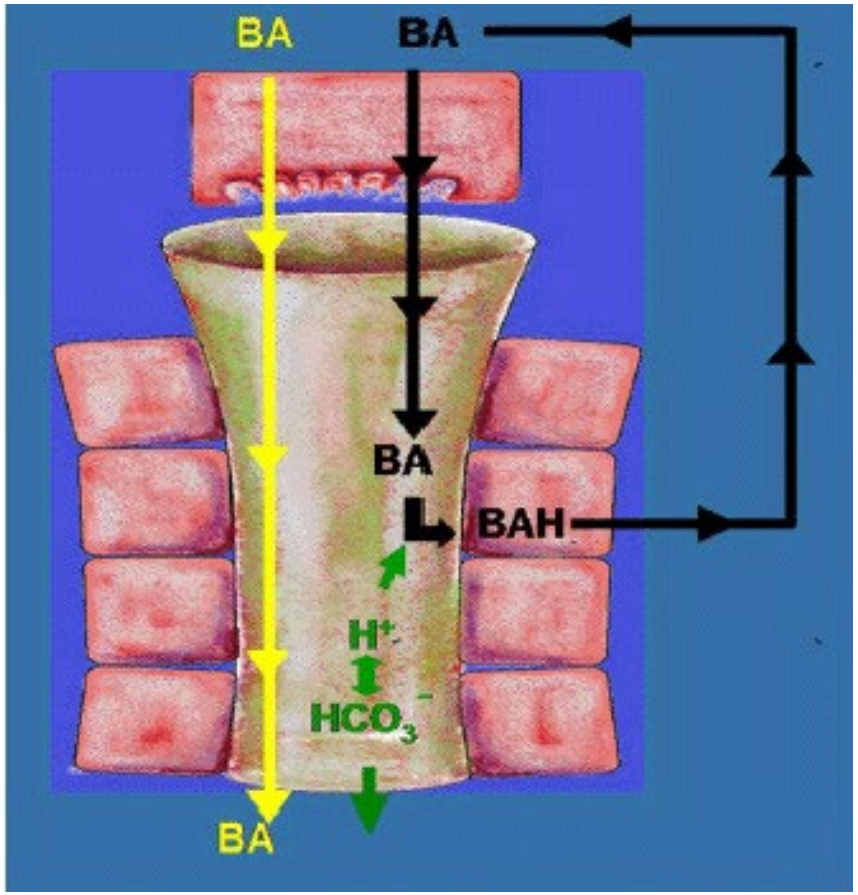
Therapy in evaluation

- Enroll your patient in a clinical trial
- ~~Obeticholic acid (OCA)~~
- Cilofexor (FXR agonist)
- Fibrates
- *nor*-ursodeoxycholic acid
- Statins
  - Nationwide case control study in Sweden showed reduced risk of all-cause mortality, death and LT

Nor-Ursodeoxycholic Acid (24-nor-UDCA)

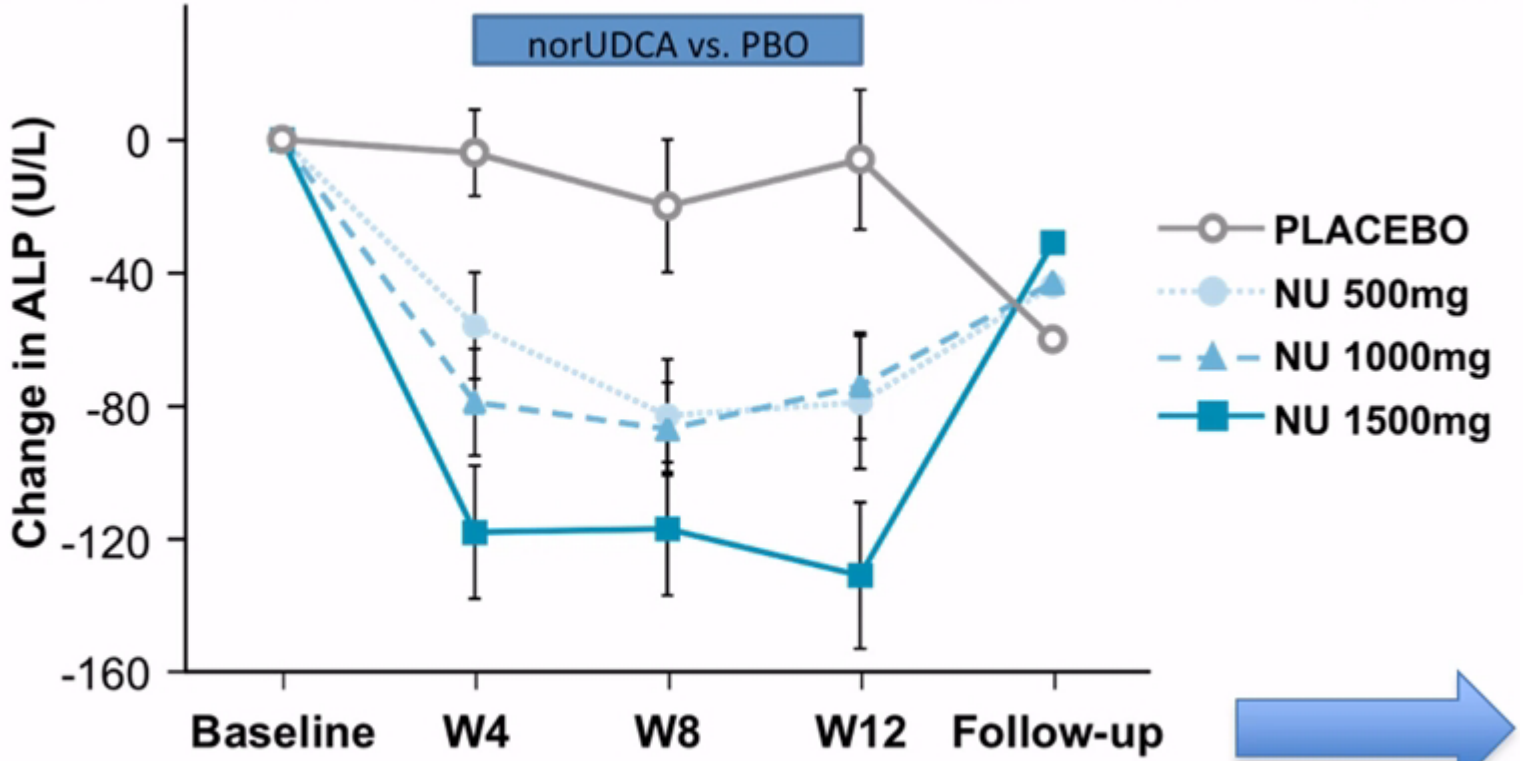
- Side chain shortened homologue of UDCA.
- More hydrophilic and conjugation resistant
- →Increases cholehepatic shunting
- → Fortifies the bicarbonate umbrella





norUDCA Improves Cholestasis in PSC

Double-blind, randomized, placebo-controlled Phase II dose-finding study



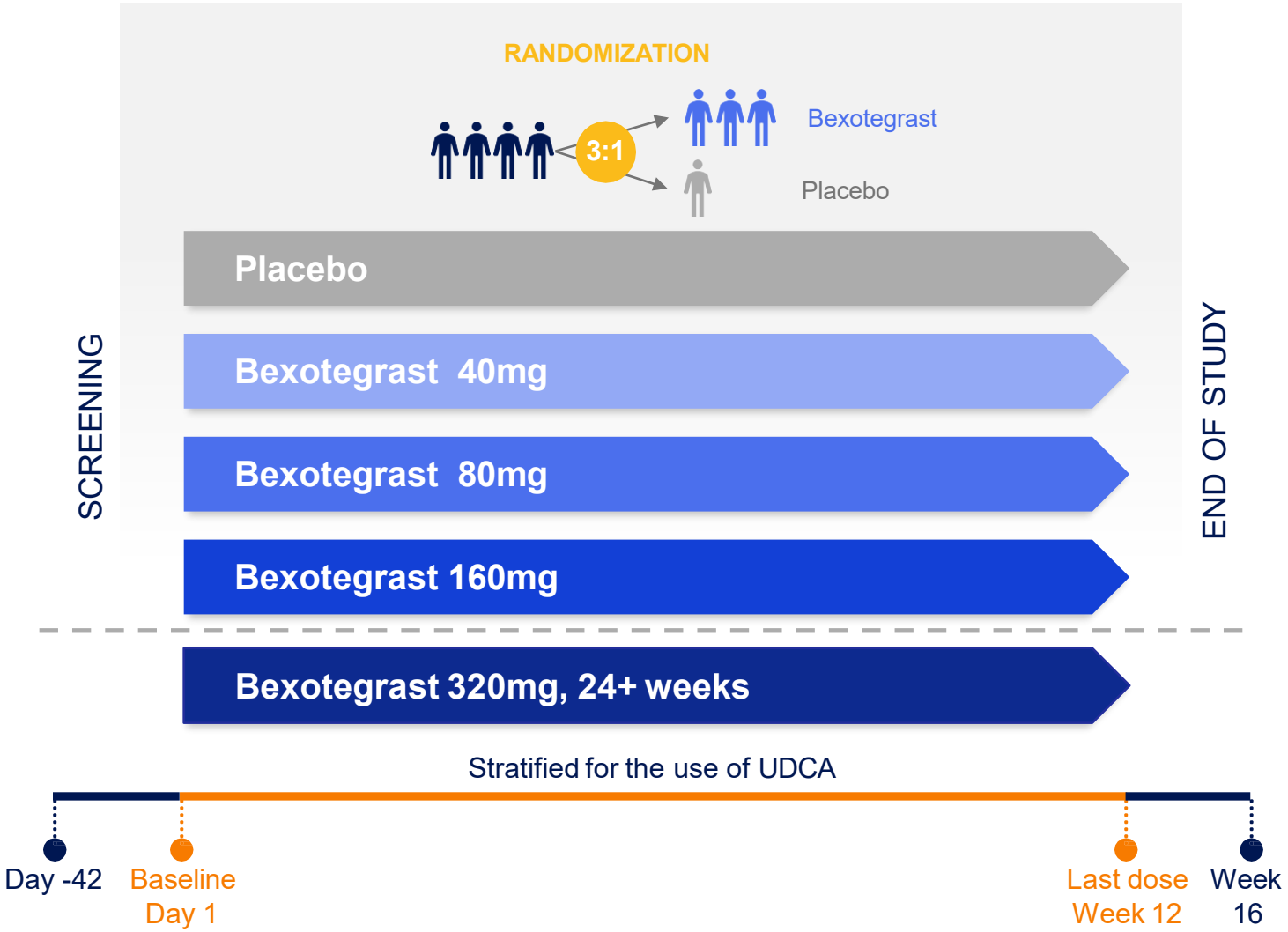
- Mean values (SE)
- Follow-up: ALP absolute change compared to week 12

Phase 3 Results
→2024

Fickert et al. *J Hep*. 2017.

INTEGRIS-PSC: Study Design and Objectives

Oral $\alpha_v\beta_6/\alpha_v\beta_1$ Integrin Inhibition



PRIMARY AND SECONDARY ENDPOINTS

- Safety and tolerability
- Pharmacokinetics[a]

EXPLORATORY ENDPOINTS

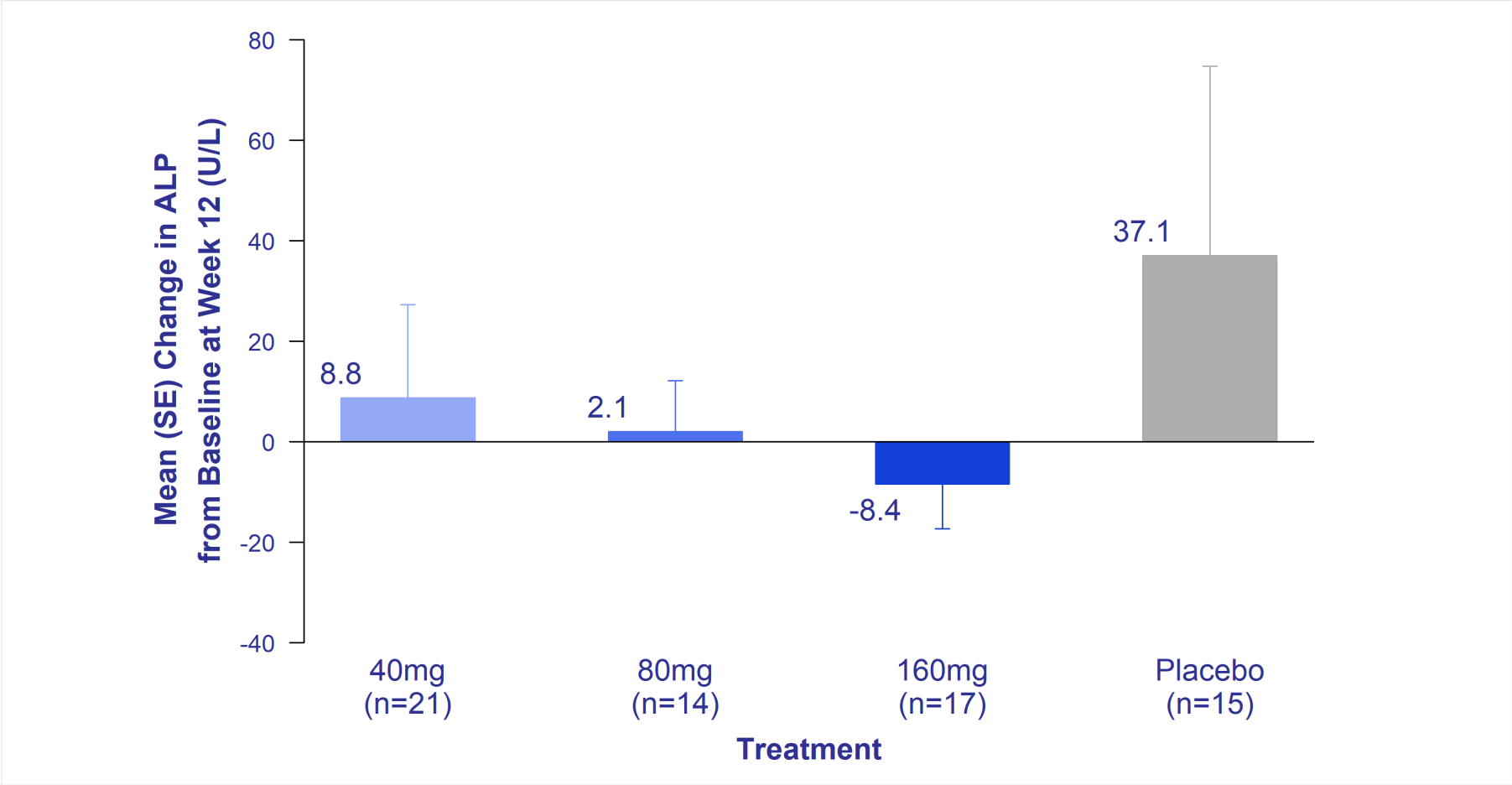
- Change in liver fibrosis markers: ELF score and PRO-C3
- Change in gadoxetate-enhanced MR parameters (voluntary sub-study)
- Change in ALP
- Change in Itch NRS

[a]Pharmacokinetics results are not presented but are available in the ePoster

ALP, alkaline phosphatase; ELF, enhanced liver fibrosis; MR, magnetic resonance; NRS, numerical rating scale; PRO-C3, neo-epitope pro-peptide of type III collagen formation

Alkaline Phosphatase
Participants with Baseline ALP > ULN

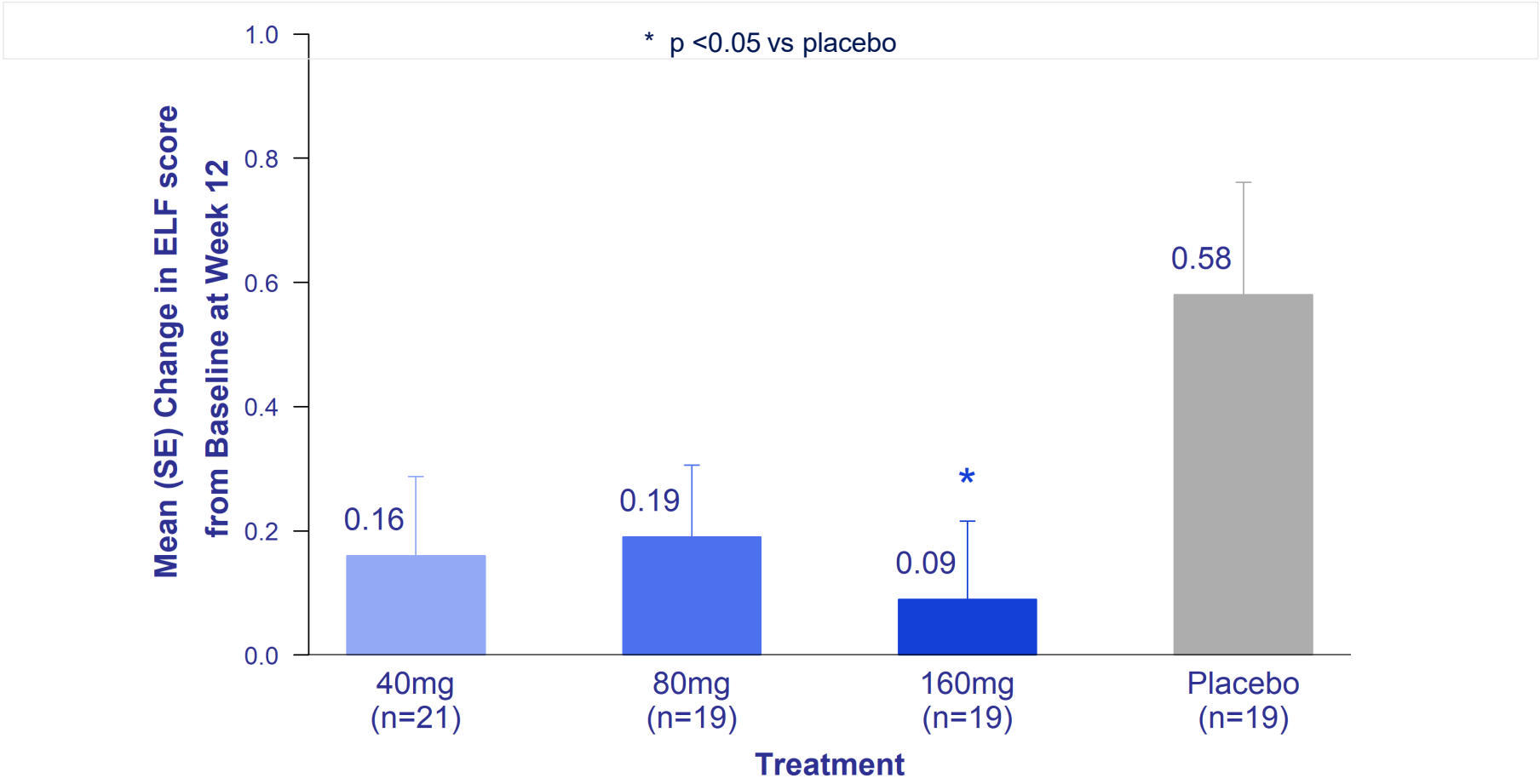
ALP (U/L) Change from Baseline at Week 12



ALP, alkaline phosphatase; EOT, end of treatment; SE, standard error; ULN, upper limit of normal

ELF Score

Lower Mean Change in ELF with Bexotegrast vs Placebo



All participants had baseline ELF ≥ 7.7 (moderate to severe liver fibrosis)[1]

1. Vesterhus M et al. *Hepatology* 2015 62(1):188-197

ELF, enhanced liver fibrosis; SE, standard error

Liver Transplantation for PBC, PSC

- Definitive treatment, but not a cure
- Recurrence 20% – 40%
- Txp for PBC dropped in millenium (“urso effect”) and has remained stable for last decade
- PSC rapidly increasing indication for living donor

Summary: PBC

- New Treatment goal is Bili < 0.6 X ULN and normal ALP @ 3mo
- UDCA alone: 50%
- UDCA+ OCA: 50% +7% = 57%
- PPAR agonists: 50% + 30% = 80%
- Triple therapy? UDCA+FXR agonist + PPAR

Summary: PSC

- UDCA for PSC benefit/risk is poorly understood
- Nor UDCA may offer a solution?
- Living Donor txp becoming a safety net for cholestatic patients who are MELD-disadvantaged
- IBAT inhibitors may become an addition to itch therapies (with a therapeutic window)

Thank you.

RUSH
Rush University Medical Center

Excellence is just the beginning.