

The background is a light blue gradient with various medical and technology icons. At the top, there are icons for a heart, a globe, a building, a water drop, a pill, a hospital bed, a stethoscope, and a virus. Below these are more icons, including a heart with a pulse line, a globe, and a globe with a network overlay. The overall theme is healthcare and modern medicine.

Primary Biliary Cholangitis: New Treatment Options

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University of Texas Southwestern

Disclosures

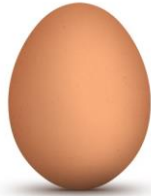
- Intercept: Clinical Trial Agreement (PBC)
- Cymabay: Clinical Trial Agreement, Consulting (PBC)
- Glaxo Smith Kline: Clinical Trial Agreement, Consulting (PBC)
- Target: Clinical Trial Agreement, Consulting (PBC)
- Mallinckrodt: Clinical Trial Agreement (Hepatorenal Syndrome)
- Mirum: Clinical Trial Agreement, Consulting (PBC)
- Salix: Clinical Trial Agreement (Hepatic Encephalopathy)

Primary Biliary Cholangitis/Cirrhosis

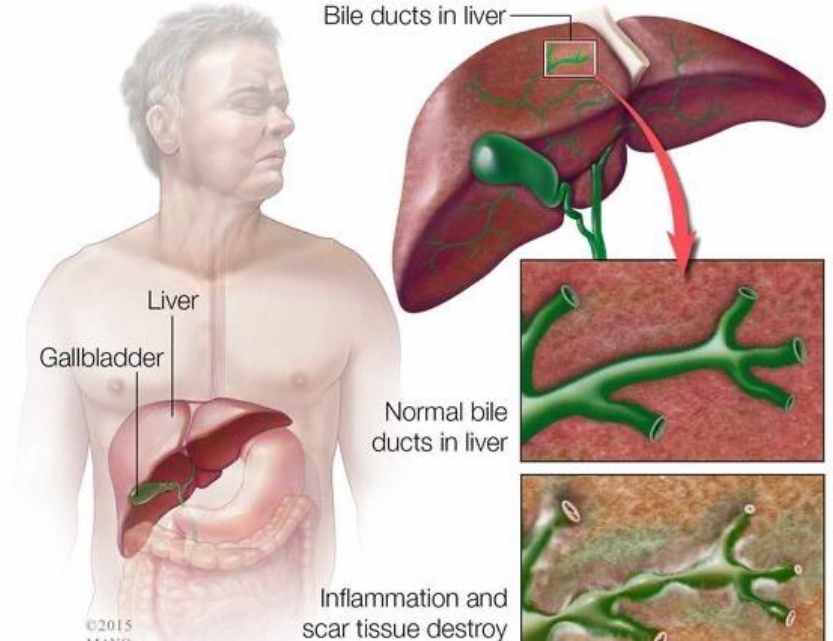
Chronic cholestatic liver disease characterized by inflammatory destruction of small/medium sized bile ducts



Cholestasis



**Immune-mediated
Destruction of Bile Ducts**



Liver Biopsy Is Not Required for Diagnosis of PBC if...

- **AMA positive**
- **Elevated Alkaline Phosphatase > 6mo**
- **AST/ALT <500**
- **No suspicion of other liver disease (e.g., NASH)**

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
- Increases AE2 expression
- Restores HCO_3^- umbrella
- FDA approved for PBC



Summary of Ursodiol Benefit in PBC

- Improves biochemical liver tests
- Delays histological progression
- Prolongs *expected* survival without liver transplantation

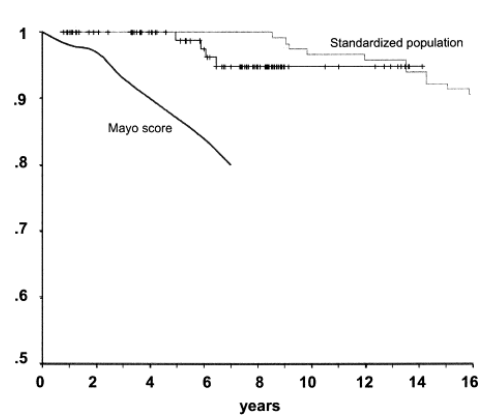
However:

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

Suboptimal Ursodiol Responders

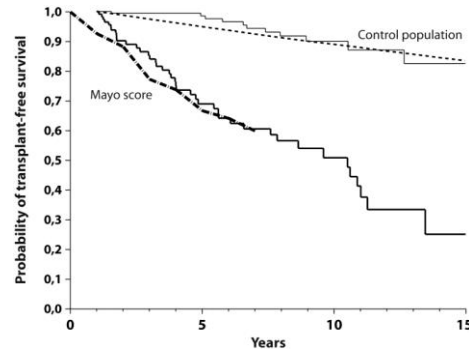


Survival



ALP < 40%
Baseline
Or
Normal

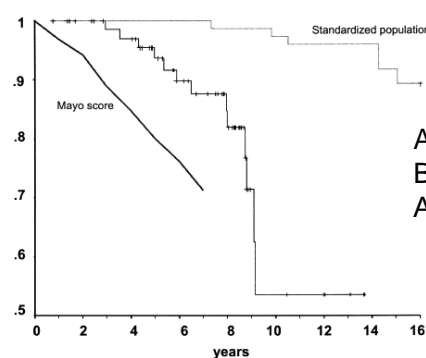
**20-40% of PBC Patients are
Suboptimal Responders**



AP \leq 3 X ULN
Bilirubin \leq 1 mg/dL
AST \leq 2X ULN

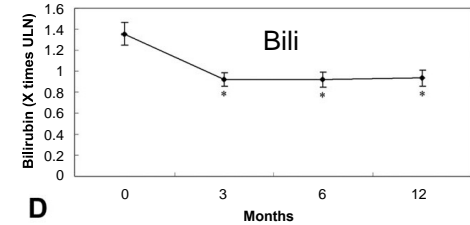
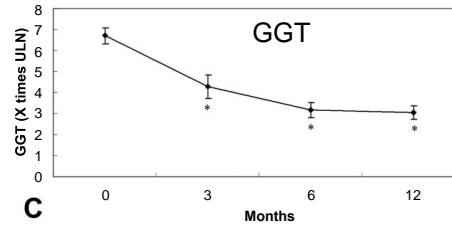
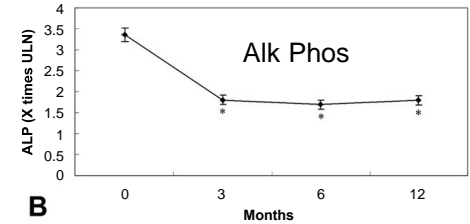
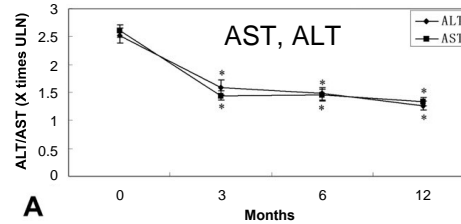


Survival



AP > 3 X ULN
Bilirubin > 1 mg/dL
AST \geq 2X ULN

How Is My PBC Patient Doing?

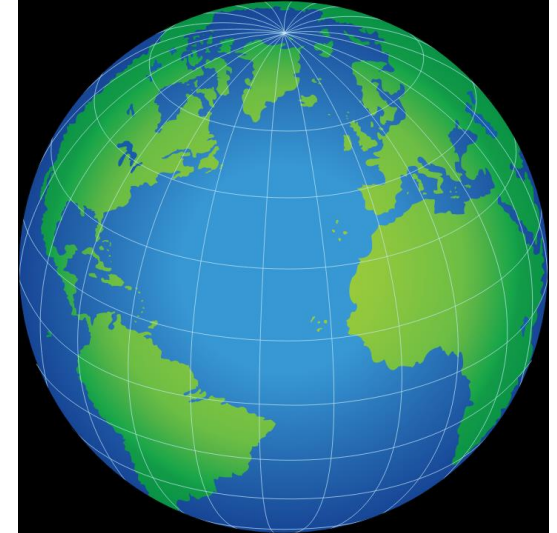


* If uncertain about possible overlap, treat with urso first and then biopsy if transaminases still high.

The PBC-GLOBE SCORE

VARIABLE	
Age at initiation of UDCA	53
Total Bilirubin after 1 year	1.3
Alkaline Phos after 1 year	323
Albumin	3.9
Platelets	256

SURVIVAL	Tracey	Matched Peers
3 year (57)	93.8%	98.0
5 year (59)	89.1%	96.6
10 year (64)	73.2%	92.1
15 year (69)	57.2%	85.2

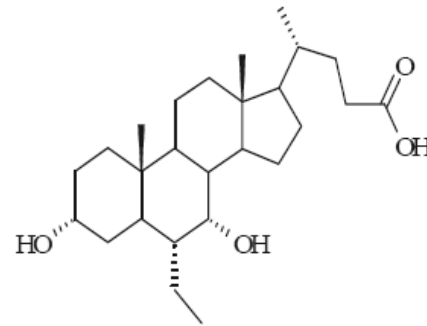


FXR Agonists: Obeticholic Acid (OCA)

6-Ethyl-Chenodeoxycholic Acid



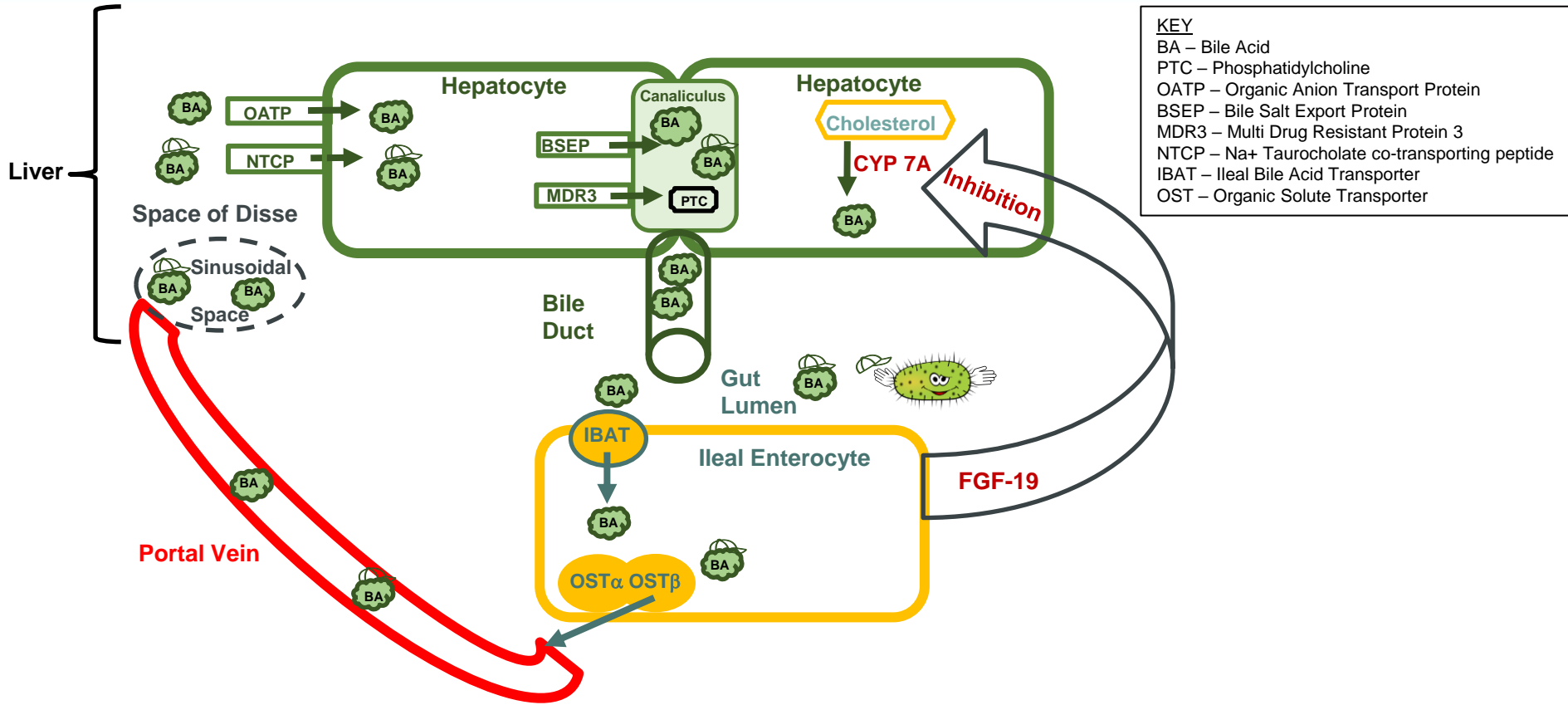
Chemical Structure of INT-747 (6-ECDCDA)



100X more potent stimulation of farnesoid X receptor (FXR) than CDCA

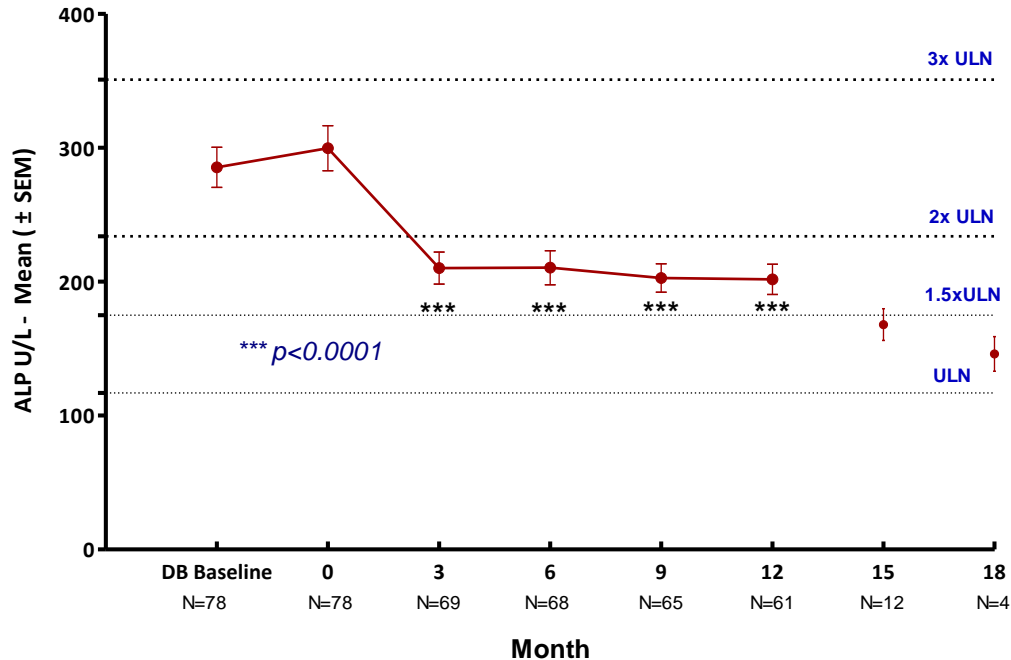
Ursodiol has negligible FXR activity

Enterohepatic Circulation



Alkaline Phosphatase Improves With Obeticholic Acid Treatment

OCA Absolute Reduction in ALP in PBC Suboptimal Ursodiol Responders



Wilcoxon signed rank test (p-value)

29% reduction
Rapid (2-12 wk)
Durable up to 5 yr

Can OCA Do More Than Just Improve ALP?

1. A placebo-controlled trial with clinical outcomes was mandated by FDA upon conditional approval and is ongoing. Recruitment is slow

2. OCA has a positive effect on GLOBE score, predicting improved survival

3. OCA has a positive effect on APRI score

4. OCA, 10mg, is associated with reduced liver stiffness, although not statistically significant after 1 or 2 yrs

APRI Improvement Baseline APRI > 0.54 → Month 12 APRI ≤ 0.54		
Placebo n (%)	OCA 5 -> 10 mg n (%)	OCA 10 mg n (%)
6 (9)	16 (27)	15 (25)

Liver Stiffness (Fibroscan)		
	Placebo mean kPa (SD)	OCA 10mg mean kPa (SD)
Baseline	12.7 (10.7)	11.4 (8.2)
12 mo	+ 0.5 (3.0)	-0.3 (6.9)
24 mo	+ 0.9 (4.4)	-0.9 (7.4)

Potential Adverse Effects: Itch, Gallstones/Cholecystitis Hepatotoxicity

Pruritus: Common, dose related

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

Gallstones/Cholecystitis: Increases [cholesterol] in gallbladder bile. Multiple post marketing reports

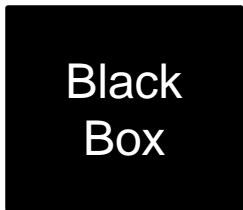
Grade 3 Hepatotoxicity: 5.2 per 100 patient exposure years with 10 mg and 2.4 with placebo.
Dose related 9.8 per 100 patient years for 25 mg daily and 54.5 for 50 mg daily

19 deaths and 11 cases of severe liver injury, most cirrhotic
No correlation with itch

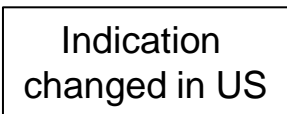
Sept 2017



Jan 2018



June 2021



FDA WARNING:

- 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

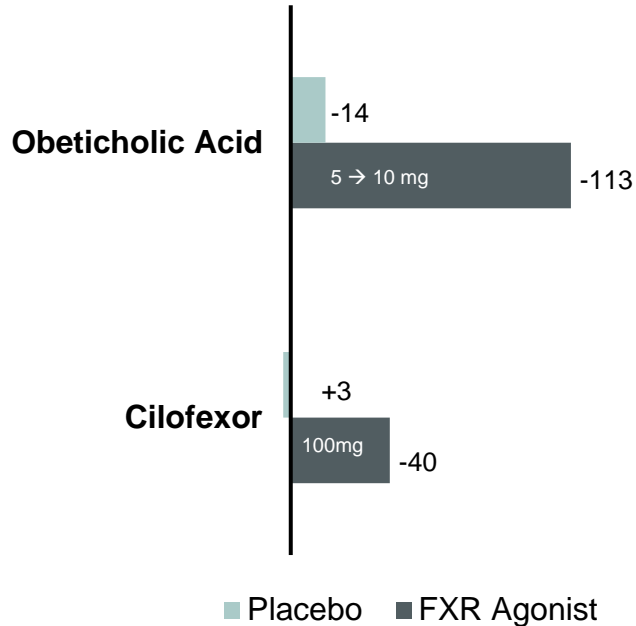
- In postmarketing reports, hepatic decompensation and failure, in some cases fatal, have been reported in patients with primary biliary cholangitis (PBC) with decompensated cirrhosis or Child-Pugh Class B or C hepatic impairment when OCALIVA was dosed more frequently than recommended. (5.1)
- The recommended 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*

Alternative Farnesiod X Receptor (FXR) Agonists (Cilofexor, EDP-305, tropifexor)

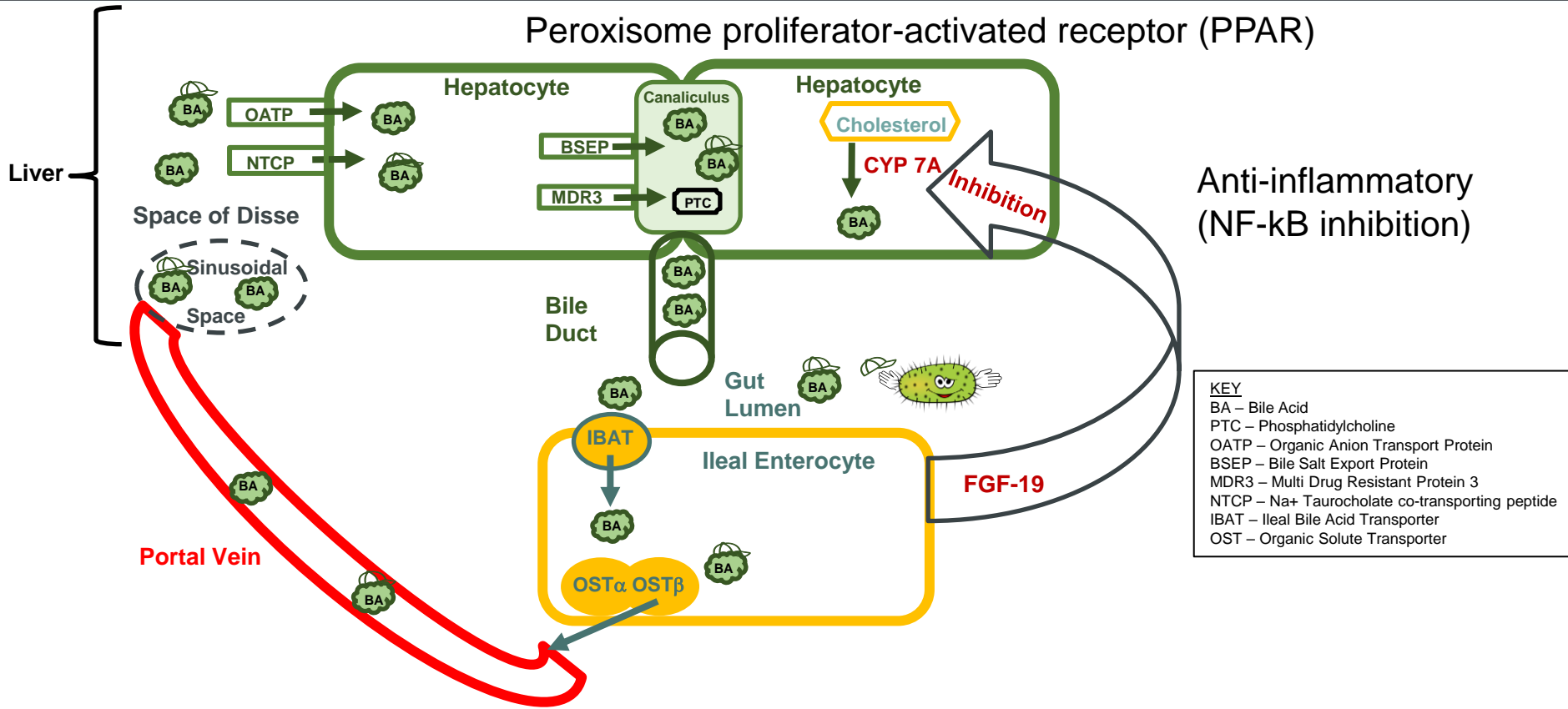
Alkaline Phosphatase Reduction (IU/L)
in in suboptimal ursodiol responders/ intolerant



Itching even in non-steroidal FXR agonists

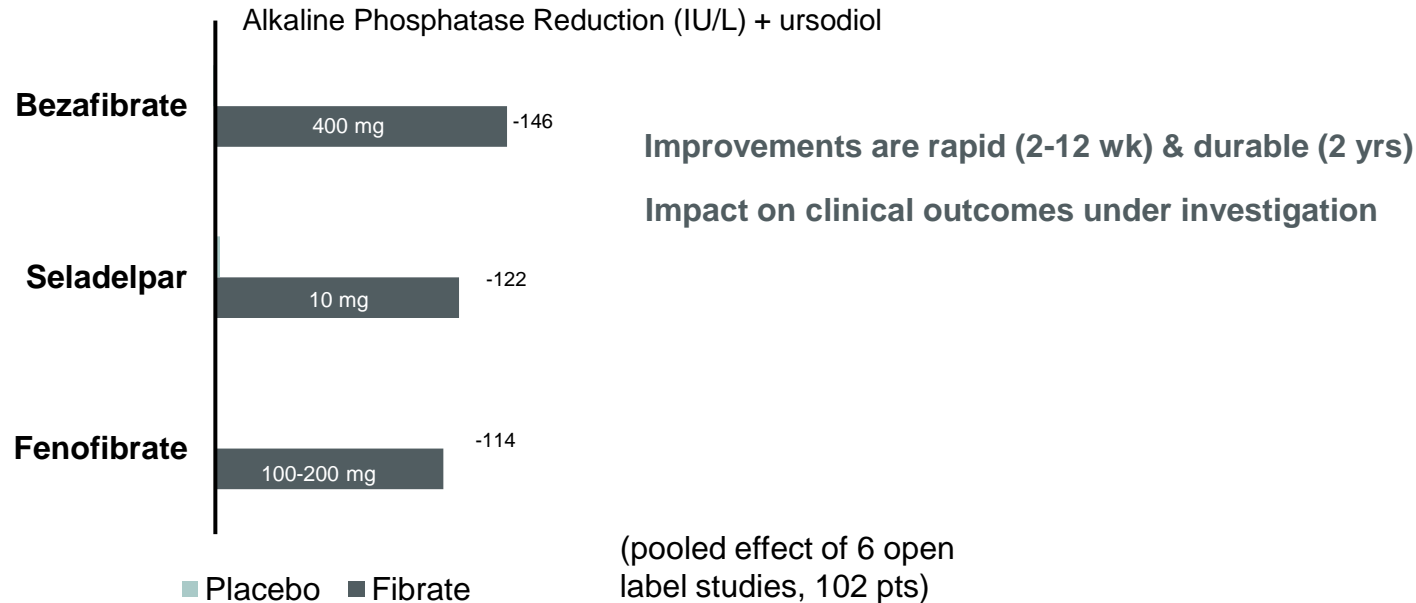
	Placebo	Cilofexor 100mg
Pruritus	10%	39%

Enterohepatic Circulation:

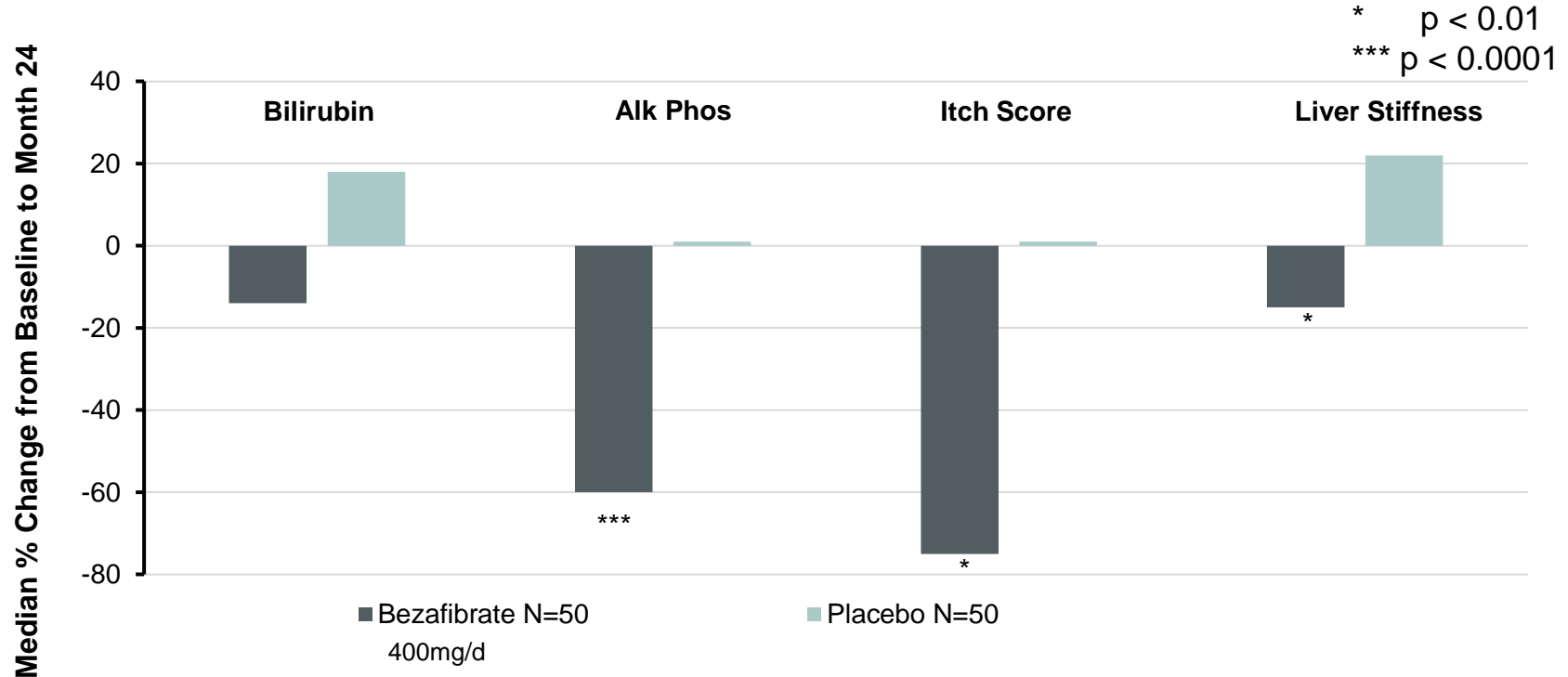


PPAR Agonists ($\alpha, \beta/\delta, \gamma$) Improve ALP

Improve biochemistries \rightarrow predicted survival



Bezafibrate Also Improves Itch and Liver Stiffness



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

PBC Therapeutic CLINICAL TRIALS IN USA

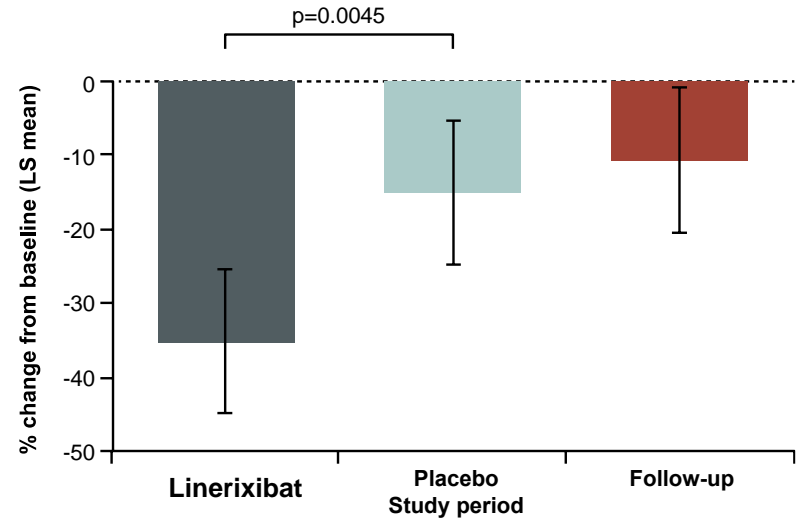
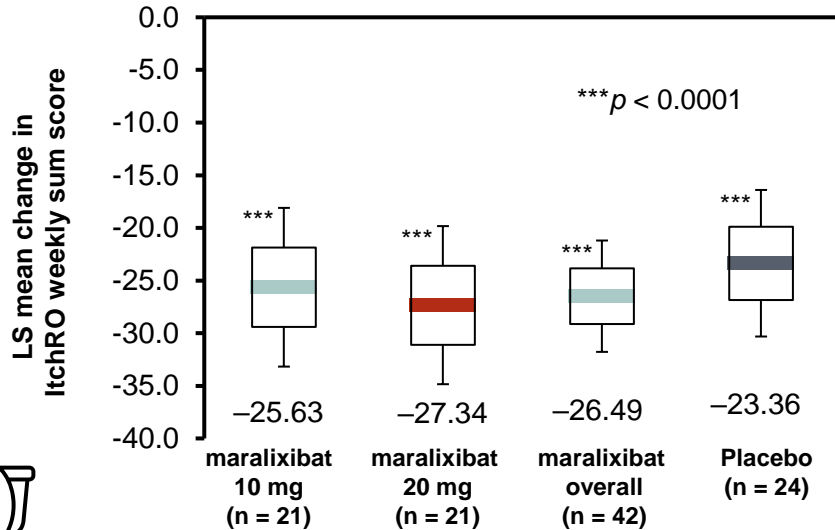
Patient	Drug	Status	Near You
Suboptimal UDCA Responder ALP > 1.67 X ULN or intolerant	Seladelpar	Enrolling	Pittsburgh, PA New York, NY Richmond, VA
Suboptimal UDCA Responder ALP > 1.67 X ULN or intolerant	Elafibranor	Enrolling	New York NY x3 Hershey, Philadelphia, PA Charlottesville, Richmond, Newport News, VA
Compensated Cirrhosis (Bili 1-3XULN or ALP > 5X ULN)	Obeticholic Acid	Enrolling	Worcester, MA Baltimore, MD Paterson, NJ New York, Rochester, NY Philadelphia, PA Richmond, VA

Liver Transplantation for PBC

- Definitive treatment, but not a cure
- Recurrent PBC 20% – 40%, rarely progresses to cirrhosis
- 3% of all LT
- New additions to waitlist decreasing each year

ASBT/IBAT Inhibitors May Improve Pruritus

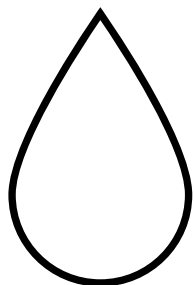
- Apical Sodium-Dependent Bile Acid Transporter/
- Ileal Bile Acid Transporter



June 2021 – odevixibat FDA approved to treat itch in PFIC

Side effect: diarrhea, abdominal discomfort

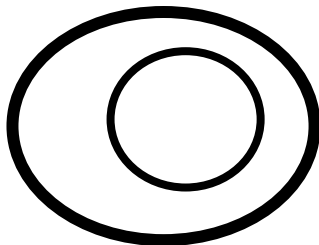
Potential Targets for New Therapies



Bile

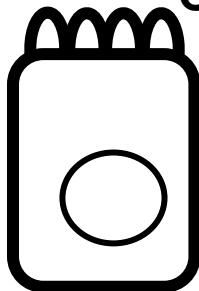
- ↓ Bile Acid Concentration
- ↑ Bile Acid Hydrophilicity
- ↑ Phosphatidylcholine

Inflammation



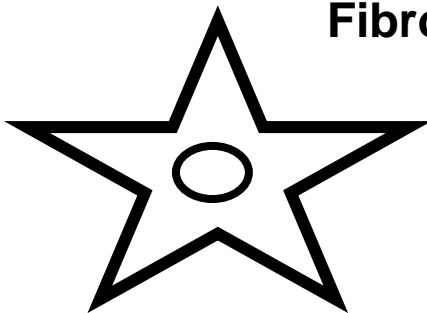
- ↓ Lymphocyte Activation, Proliferation, Trafficking
- ↓ Cytokine Signaling

Cell Survival



- ↑ HCO₃ umbrella
- ↓ Apoptosis
- ↑ Regeneration

Fibrosis



- ↓ Stellate Cell Activation
- ↑ Collagen Breakdown