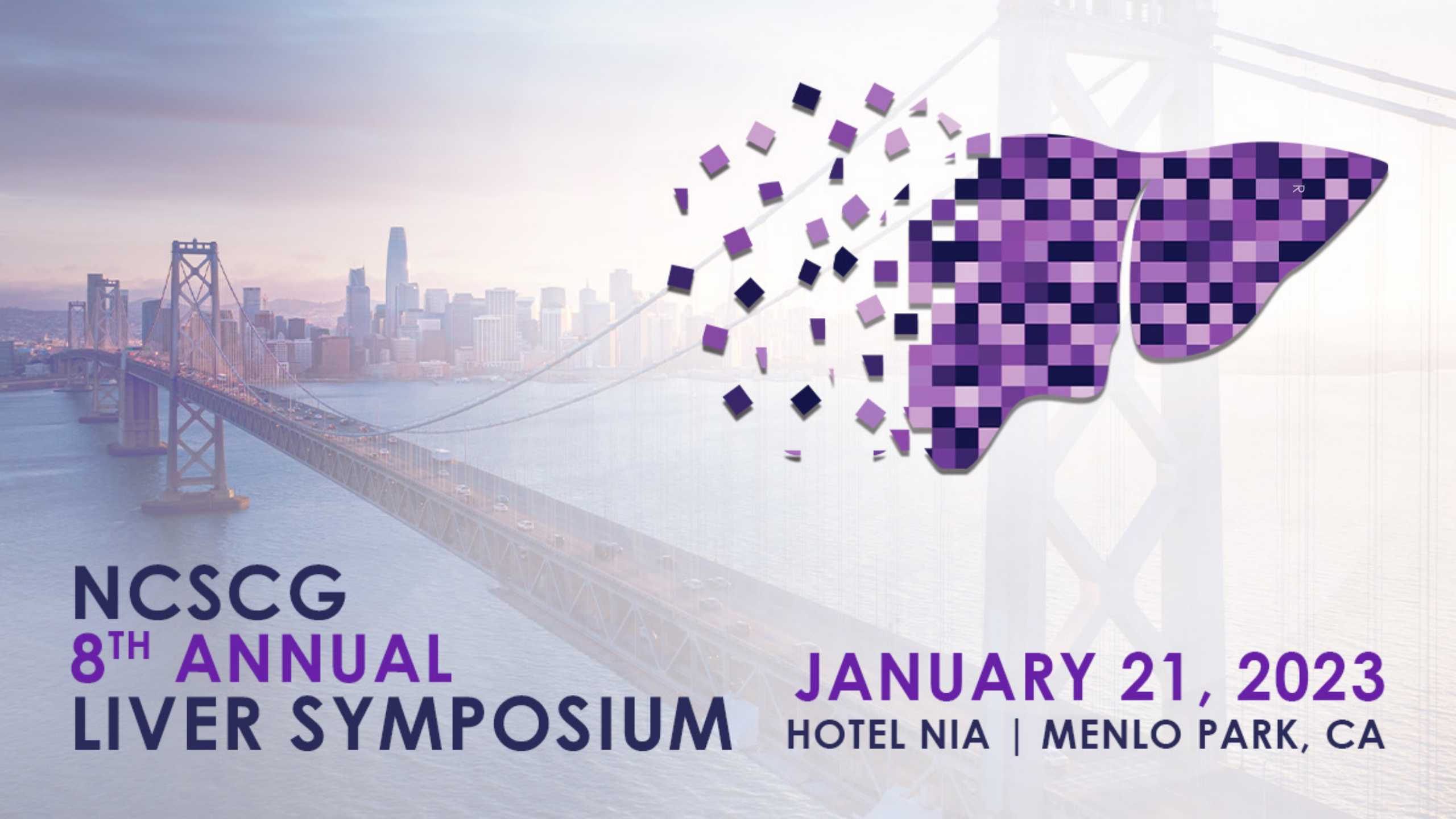

NCSCG
8TH ANNUAL LIVER SYMPOSIUM

JANUARY 21, 2023
HOTEL NIA | MENLO PARK, CA

Updates in Cholestatic Liver Diseases

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JANUARY 21, 2022

Emerging Therapies

PRIMARY BILIARY CHOLANGITIS (PBC)

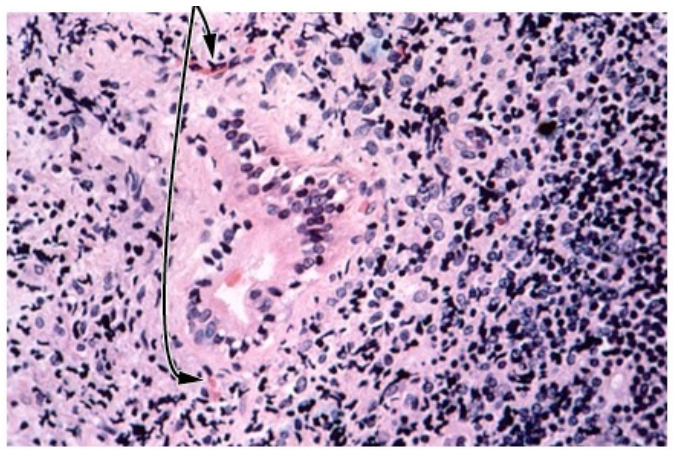
PRIMARY SCLEROSING CHOLANGITIS (PSC)

Objectives

- PBC and PSC
  - Current treatment
  - Emerging therapies
    - Disease specific
    - Symptoms related

Primary biliary cholangitis (PBC)

- Previously referred to as primary biliary cirrhosis, is characterized by a T-lymphocyte-mediated attack on small intralobular bile ducts
- A continuous assault on the bile duct epithelial cells leads to their gradual destruction and eventual disappearance (ductopenia)
- Causes the signs and symptoms of cholestasis and eventually cirrhosis and liver failure



florid bile duct lesion

Beuers U, Gershwin ME, Gish RG, Invernizzi P, Jones DE, Lindor K, Ma X, Mackay IR, Parés A, Tanaka A, Vierling JM, Poupon R Changing nomenclature for PBC: From 'cirrhosis' to 'cholangitis'. Hepatology. 2015;62(5):1620.
Kaplan MM. Primary biliary cirrhosis. N Engl J Med. 1996;335(21):1570.

PBC: treatment

- Goals
  - Suppression of the underlying pathogenic process: the destruction of small intralobular hepatic bile ducts
  - Treatment of the symptoms and complications that result from chronic cholestasis

PBC: treatment 1st line agent

- Suppression of the underlying pathogenic process: the destruction of small intralobular hepatic bile ducts
  - **Ursodeoxycholic acid (UDCA): (13 to 15 mg/kg per day)** delays the progression to end-stage liver disease, enhances survival, and is well tolerated
  - The extent of the biochemical response to UDCA during the first year of therapy is a simple and useful marker of long-term prognosis
  - ~ 35 percent of patients have a suboptimal response to UDCA

Lindor KD, Gershwin ME, Poupon R, Kaplan M, Bergasa NV, Heathcote EJ, American Association for Study of Liver Diseases Primary biliary cirrhosis.Hepatology. 2009;50(1):291

PBC: treatment
2nd line agent

- **Obeticholic acid (OCA)**: ligand for the farnesoid X receptor, which plays a role in bile acid homeostasis
  - FDA approved (May 29, 2016)
  - To be used in combination with UDCA in patients with PBC who have inadequate response to at least 1 year of treatment with UDCA, or as monotherapy for those patients who are intolerant to UDCA
  - Recent FDA warning

Corpechot C, Abenavoli L, Rabahi N, Chrétien Y, Andréani T, Johanet C, Chazouillères O, Poupon R Biochemical response to ursodeoxycholic acid and long-term prognosis in primary biliary cirrhosis. Hepatology. 2008;48(3):871.
Yimam KK; Bowlus C. Obeticholic acid for the treatment of primary biliary cirrhosis. Expert Opinion on Orphan Drugs, 2014; 2(12);1351-1358.

Key Obeticholic Acid Label Change Boxed Warning

Previous Label (2018)

OCALIVA® (obeticholic acid) tablets, for oral use
Initial U.S. Approval: 2016

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)**

Updated Label (2021)

OCALIVA® (obeticholic acid) tablets, for oral use
Initial U.S. Approval: 2016

WARNING: HEPATIC DECOMPENSATION AND FAILURE IN PRIMARY BILIARY CHOLANGITIS PATIENTS WITH CIRRHOSIS
See full prescribing information for complete boxed warning

- **Hepatic decompensation and failure, sometimes fatal or resulting in liver transplant, have been reported with OCALIVA treatment in primary biliary cholangitis (PBC) patients with either compensated or decompensated cirrhosis. (5.1)**
- **OCALIVA is contraindicated in PBC patients with decompensated cirrhosis, a prior decompensation event, or with compensated cirrhosis who have evidence of portal hypertension. (4)**
- **Permanently discontinue OCALIVA in patients who develop laboratory or clinical evidence of hepatic decompensation, have compensated cirrhosis and develop evidence of portal hypertension, or experience clinically significant hepatic adverse reactions while on treatment. (2.3, 5.1)**

US Food and rug Administration
https://www.accessdata.fda.gov

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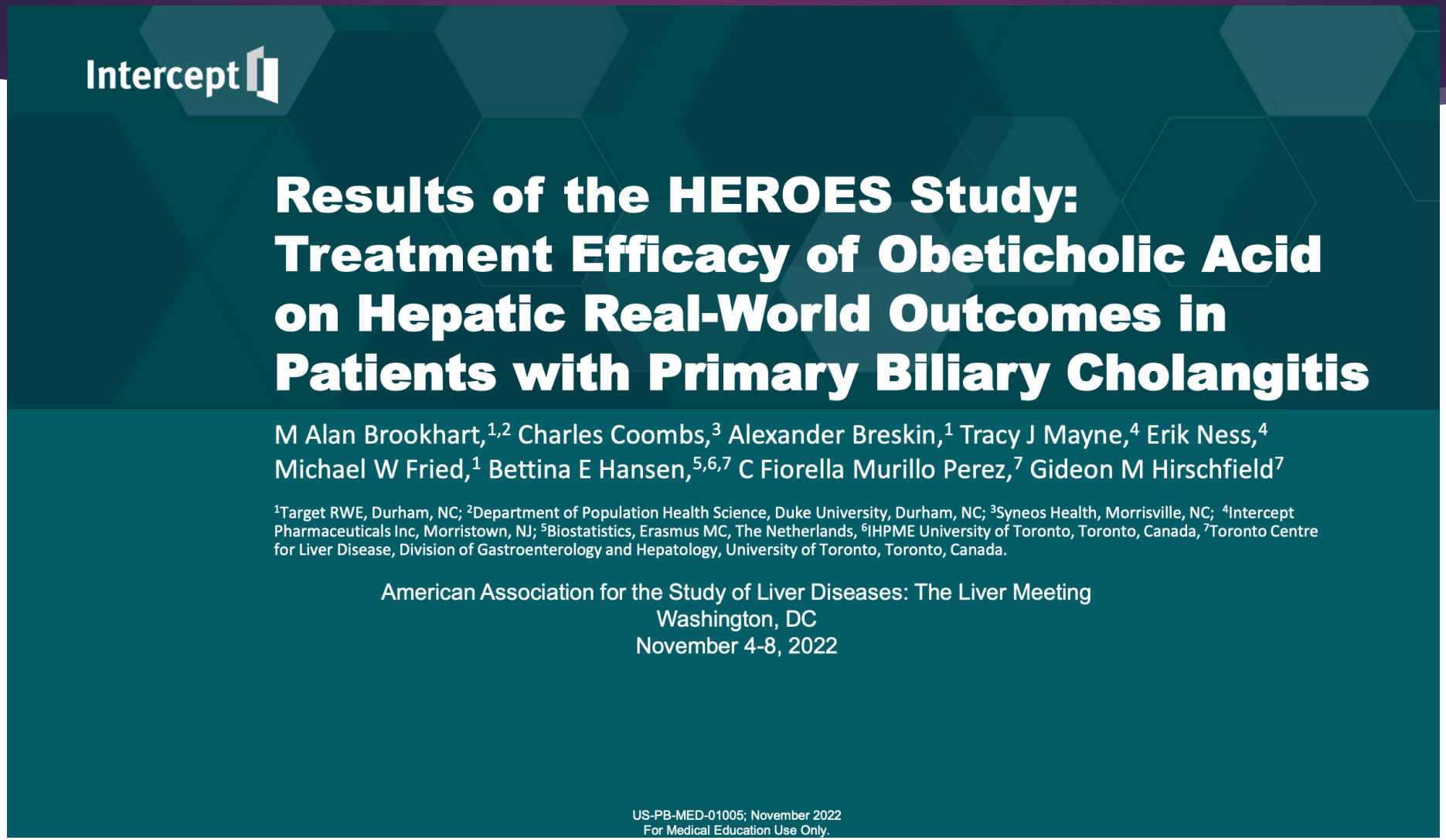
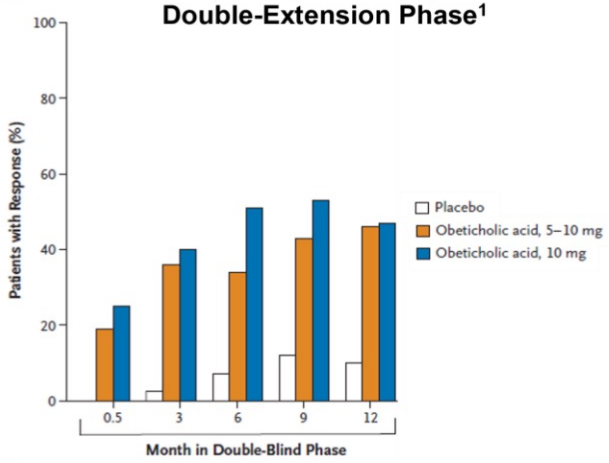
OCA in PBC


Intercept
Results of the HEROES Study: Treatment Efficacy of Obeticholic Acid on Hepatic Real-World Outcomes in Patients with Primary Biliary Cholangitis
M Alan Brookhart,[1,2] Charles Coombs,[3] Alexander Breskin,[1] Tracy J Mayne,[4] Erik Ness,[4] Michael W Fried,[1] Bettina E Hansen,[5,6,7] C Fiorella Murillo Perez,[7] Gideon M Hirschfield[7]
[1]Target RWE, Durham, NC; [2]Department of Population Health Science, Duke University, Durham, NC; [3]Syneos Health, Morrisville, NC; [4]Intercept Pharmaceuticals Inc, Morristown, NJ; [5]Biostatistics, Erasmus MC, The Netherlands, [6]IHPME University of Toronto, Toronto, Canada, [7]Toronto Centre for Liver Disease, Division of Gastroenterology and Hepatology, University of Toronto, Toronto, Canada.
American Association for the Study of Liver Diseases: The Liver Meeting
Washington, DC
November 4-8, 2022
US-PB-MED-01005; November 2022
For Medical Education Use Only.

OCA: Lasting Improvements in ALP and Improved Transplant-Free Survival Compared With Matched External Controls

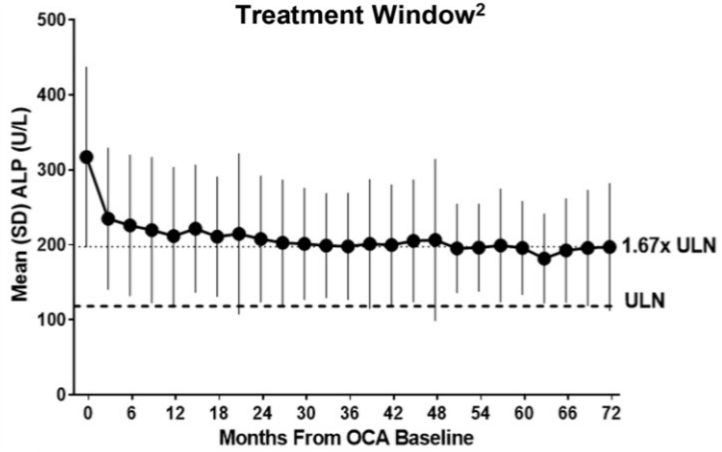
A

Primary Composite Endpoint in Double-Extension Phase[1]



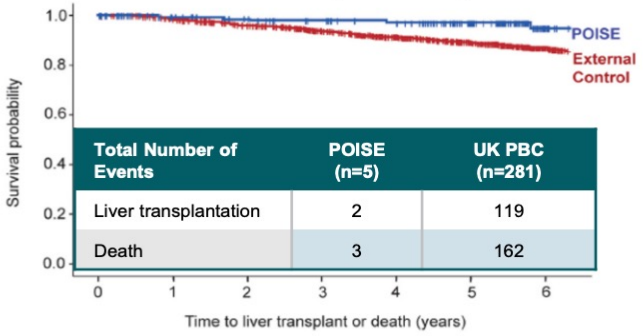
B

ALP Levels Over a 6-Year OCA Treatment Window[2]



C

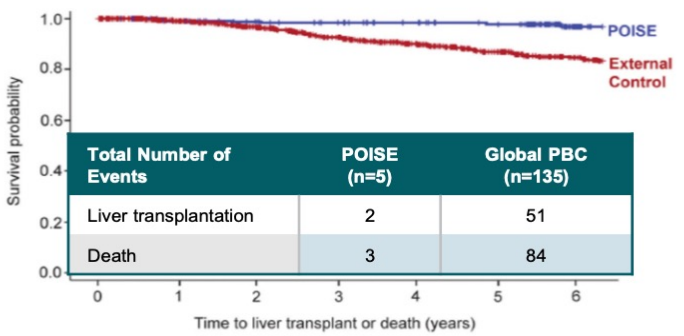
Transplant-Free Survival of POISE and UK PBC (Censored)[3]



Total Number of Events	POISE (n=5)	UK PBC (n=281)
Liver transplantation	2	119
Death	3	162

D

Transplant-Free Survival of POISE and GLOBAL PBC[3]



Total Number of Events	POISE (n=5)	Global PBC (n=135)
Liver transplantation	2	51
Death	3	84

ALP, alkaline phosphatase; OCA, obeticholic acid; PBC, primary biliary cholangitis; ULN, upper limit of normal.

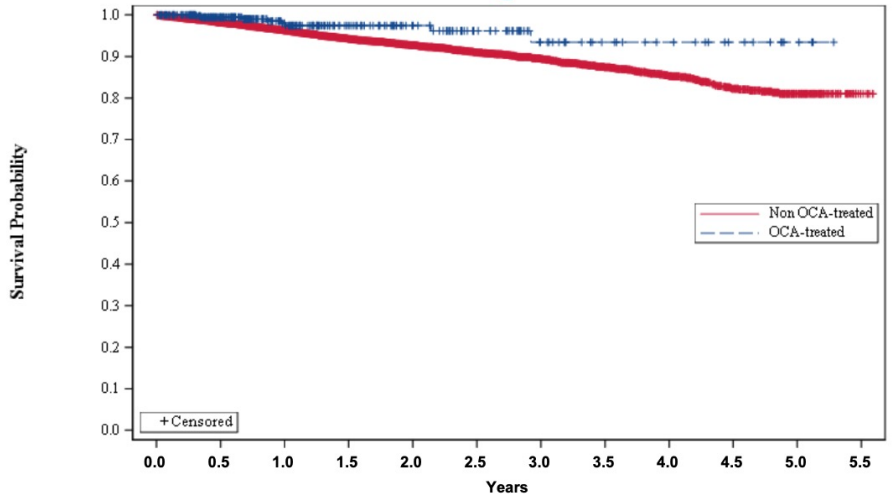
1. Nevens F et al. *New Engl J Med*. 2016;375:631-643. 2. Nevens F. *AASLD*. 2019, Boston, MA. 3. Murillo Perez CF et al. *Gastroenterology*. 2022;S0016-5085(22)0160-5. doi:10.1053/j.gastro.2022.08.054

Intercept

Hero Study

OCA Treatment Resulted in 63% Reduction in Relative Risk for Death, Liver Transplant, and Hepatic Decompensation

Unweighted

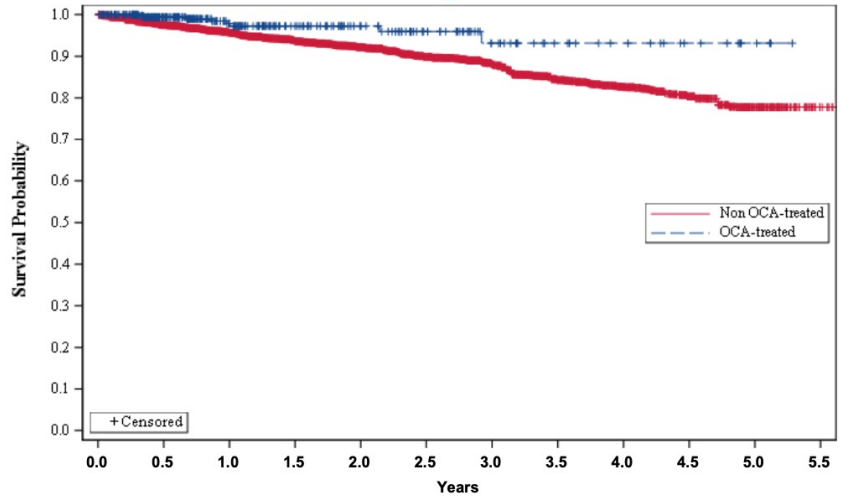


Number of index at risk

OCA-treated	432	288	176	115	83	55	32	21	16	10	4	0
Non-OCA–treated	12399	9109	6842	5079	3836	2785	1973	1304	817	468	174	9

HR	95% CI	*P value*
0.407	0.148, 0.736	<0.001

Weighted



Number of index at risk

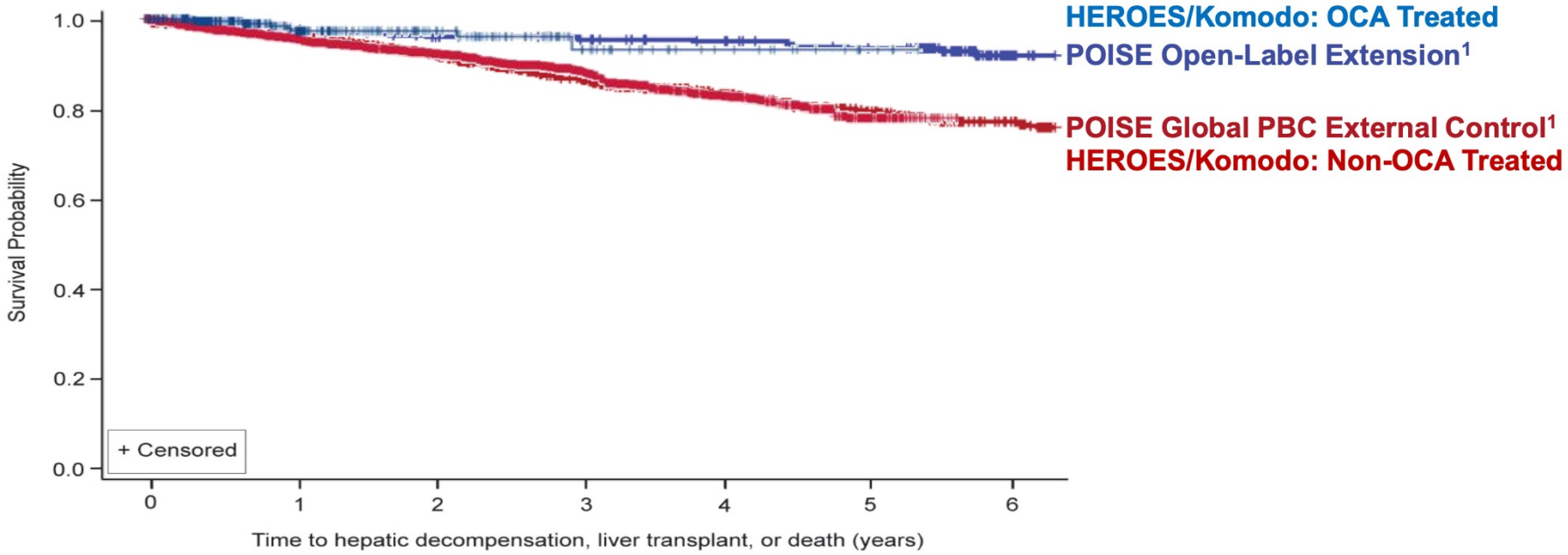
OCA-treated	403	269	165	108	78	52	31	20	15	9	4	0
Non-OCA–treated	405	300	226	187	149	113	86	62	39	23	10	1

HR	95% CI	*P value*
0.370	0.143, 0.752	<0.001

Similar effect size in unweighted and weighted analyses

HR, hazard ratio; OCA, obeticholic acid.

HEROES Replicates POISE External Control Results: Time to Death, Liver Transplant, and Hepatic Decompensation



Study	HR	95% CI	*P value*
POISE Global PBC External Control	0.42	0.21, 0.85	0.02
HEROES	0.37	0.14, 0.75	<0.001

HR, hazard ratio; OCA, obeticholic acid; PBC, primary biliary cholangitis.

1. Murillo Perez CF et al. *Gastroenterology*. 2022;S0016-5085(22)0160-5. doi:10.1053/j.gastro.2022.08.054

US-PB-MED-01005; November 2022
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Intercept

Efficacy of Obeticholic Acid (OCA) vs Placebo and External Controls on Clinical Outcomes in Primary Biliary Cholangitis (PBC)

Poster #5032

Kris V. Kowdley[1]; M. Alan Brookhart[2]; Gideon M. Hirschfield[3]; Charles Coombs[4]; Elizabeth Malecha[5]; Tracy Mayne[5]; Erik Ness[5]; Jing Li[5]; Alexander Breskin[2]; Nuvan Rathnayaka[2]; George Mells[6]; David Jones[7]; Palak J. Trivedi[8]; Bettina E. Hansen[9]; Rachel Smith[10]; James Wason[7]; Shaun Hiu[7]; Dorcas N. Kareithi[7]; Andrew L. Mason[11]; Christopher L. Bowlus[12]; Kate Muller[13]; Marco Carbone[14]; Marina Berenguer[15]; Piotr Milkiewicz[16]; Femi Adekunle[17]; Alejandra Villamil[18]

[1]Liver Institute Northwest; [2]Target RWE; [3]Toronto Centre for Liver Disease, University of Toronto; [4]Syneos Health; [5]Intercept Pharmaceuticals, US; [6]Cambridge University Hospitals NHS Foundation Trust MRC Clinical Academic Research Partner, Academic Department of Medical Genetics, University of Cambridge; [7]Population Health Sciences Institute, Newcastle University; [8]National Institute for Health and Care Research Birmingham Biomedical Research Centre, Centre for Liver and Gastroenterology Research, University of Birmingham. Liver Unit, University Hospitals Birmingham Queen Elizabeth. Institute of Immunology and Immunotherapy, University of Birmingham; [9]Toronto Centre for Liver Disease, Toronto General Hospital; [10]Cambridge Liver Unit, Cambridge University Hospitals NHS Foundation Trust; [11]The Applied Genomic Core, Center of Excellence for Gastrointestinal Inflammation and Immunity Research, University of Alberta; [12]University of California Davis; [13]Flinders Medical Centre; [14]University of Milano-Bicocca; [15]La Fe University Hospital; [16]Medical University of Warsaw; [17]Intercept Pharmaceuticals, UK (at the time the study was conducted); [18]Hospital Italiano de Buenos Aires.

Introduction

- PBC is a rare, progressive, autoimmune disease affecting an estimated 100 to 200 thousand people in the United States (US), predominately women over the age of 50
- OCA received accelerated Food and Drug Administration (FDA) approval in 2016 for the treatment of PBC patients who failed ursodeoxycholic acid (UDCA) treatment, based on its effect on surrogate endpoints as evaluated in the POISE trial
- COBALT was a Phase 3b/4 randomized, double-blind, placebo-controlled confirmatory trial aimed to assess efficacy and safety of OCA in patients with advanced PBC
- COBALT included an external control group as a second comparator arm to address challenges maintaining patients on placebo following OCA commercial availability

Objective

Assess the effect of OCA treatment on time to first occurrence of PBC disease progression, liver transplant or death versus placebo (COBALT) and versus Komodo Health external control

Methods

COBALT

- From February 2015 to December 2020, eligible patients were randomized 1:1 to once-daily oral placebo or OCA 5mg, titrated to 10mg if tolerated
- Inclusion criteria:
  - Alkaline phosphatase (ALP) >3x ULN and/or total bilirubin >ULN and ≤5x ULN
  - Discontinued UDCA ≥3 months; or taking UDCA ≥12 months with an approved, stable dose for ≥3 months prior to enrollment
- Exclusion criteria:
  - Significant hepatic and non-hepatic comorbidities
  - Hepatic decompensating events in 12 months before enrollment

Primary Endpoints

Analyses were conducted separately for FDA- and EMA-specified primary endpoints.

- **Primary EMA composite endpoint:** time to first occurrence of
  - Death (all-cause)
  - Liver transplant
  - Hospitalization for new onset or recurrence of:
    - Variceal bleed
    - Hepatic encephalopathy
    - Spontaneous bacterial peritonitis
  - Uncontrolled ascites
  - Model of end stage liver disease (MELD) score ≥15
- **FDA expanded composite endpoint:** time to first occurrence of
  - Death (all-cause)
  - Liver transplant
  - Hospitalization for new onset or recurrence of:
    - Variceal bleed
    - Hepatic encephalopathy
    - Spontaneous bacterial peritonitis
    - Bacterial empyema
  - Uncontrolled or refractory ascites requiring large volume paracentesis
  - Portal hypertension syndromes
    - Hepatorenal syndrome
    - Portopulmonary hypertension
    - Hepatopulmonary syndrome
  - MELD-Na score ≥15 if MELD-Na <12 at baseline; MELD score ≥15 if MELD-Na ≥12 at baseline

If without decompensation at baseline, also:

- New onset hepatic hydrothorax, variceal bleeding, or ascites requiring treatment
- Hepatic encephalopathy requiring treatment
- New onset Child-Pugh ≥7 or TB >3 mg/dL

If without decompensation or portal hypertension at baseline, also:

- Endoscopic evidence of portal hypertension without bleeding
- Platelets <150x10^9/L with splenomegaly and/or transient elastography >15 kPa

External Controls

- Non-OCA treated External Controls were created from Komodo Health US claims database
- An OCA-treated group was created from Komodo Health database for additional comparison
- Komodo data were merged with lab data from LabCorp and Quest Diagnostics, liver transplant data from Organ Procurement and Transplantation Network, and death data from US Social Security Death Index + obituary search
- External controls had to meet COBALT inclusion/exclusion criteria, and were weighted using propensity score-derived standardized morbidity ratios (SMRs)
- EMA endpoint excluded MELD; FDA endpoint excluded MELD, Child-Pugh, bacterial empyema

Results

PATIENT CHARACTERISTICS

- COBALT randomized 168 patients to OCA and 166 to placebo (planned ~214 per arm)
- The study was terminated in December 2021 due to recruitment and retention challenges
- The external control included 1050 non-OCA patients with a SMR-weighted sample of N=165; 61 OCA-treated patients met COBALT eligibility, SMR weighted sample =192
- Trial arms and external controls were well-balanced at baseline (**Table 1**)

Table 1. Baseline Characteristics (ITT and External Control Populations)

	COBALT		Komodo*	
	Placebo (N=166)	OCA (N=168)	Non-OCA-treated (N=165)	OCA-treated (N=192)
Age (years), Mean (SD)	53.9 (10.4)	53.4 (10.3)	53.8 (5.2)	57.0 (16.4)
Sex (Female), n (%)	149 (89.8)	151 (89.9)	146.5 (88.8)	174.53 (90.9)
Baseline ALP (IU/L), Mean (SD)	499.3 (294.5)	481.3 (276.7)	463.8 (104.4)	441.5 (487.3)
Baseline TB (mg/dL), Mean (SD)	1.65 (0.8)	1.57 (0.8)	1.6 (0.5)	1.56 (1.7)
Baseline ALT (U/L), Mean (SD)	84.0 (50.2)	81.5 (51.9)	77.1 (35.9)	78.5 (70.6)
Baseline AST (U/L), Mean (SD)	81.9 (36.3)	81.1 (41.1)	79.1 (35.8)	85.3 (84.2)
Baseline platelet count (10^9/L), Mean (SD)	197.2 (102.6)	209.9 (101.8)	194.8 (37.3)	200.1 (138.0)
Decompensation at baseline, n (%)	37 (22.3)	32 (19.1)	36.3 (22.0)	50.92 (26.5)
Portal hypertension at baseline, n (%)	82 (49.4)	82 (48.8)	90.0 (54.6)	95.4 (49.7)
UDCA at baseline, n (%)	147 (88.6)	147 (87.5)	143.2 (86.8)	159.7 (83.2)

*Ns represent the weighted populations; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; ITT=intent-to-treat; OCA= obeticholic acid; SD=standard deviation; TB=total bilirubin; UDCA=ursodeoxycholic acid.

COBALT: ITT OCA VS. PLACEBO

- Almost half (44%) of OCA-treated and 54% of placebo patients discontinued IP; 8% and 16% initiated commercial OCA, respectively
- **EMA composite endpoint**: 48 (29%) events occurred in both the COBALT and placebo arms. HR=1.01; 95% CI 0.68, 1.51; p>0.90 (**Figure 1A**)
- **FDA composite endpoint**: 71 (42%) events occurred in the COBALT OCA arm and 80 events (48%) in the COBALT placebo arm. HR=0.84; 95% CI 0.61, 1.16; p>0.30 (**Figure 1B**)

EXTERNAL CONTROL: AS-TREATED OCA (COBALT) VS. KOMODO

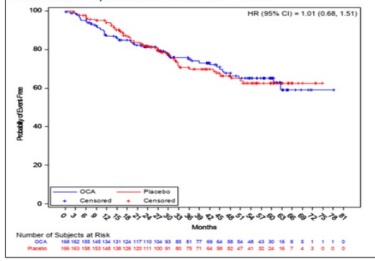
- EMA composite endpoint: 17 (10%) events occurred in the COBALT OCA arm and : 35 (22%) in the Komodo external control arm. HR=0.39; 95% CI 0.22, 0.69; p<0.01 (**Figure 2A**)
- FDA composite endpoint: 28 (17%) events occurred in the COBALT OCA arm and : 46 (28%) in the Komodo external control arm. HR=0.48; 95% CI 0.30, 0.77; p<0.01 (**Figure 2B**)

EXTERNAL CONTROL: AS-TREATED OCA (COBALT) VS. KOMODO CONTINUED

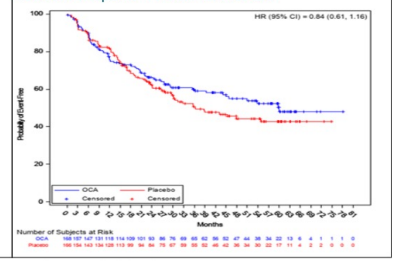
- The EMA endpoint event rates for the COBALT OCA-treated patients (10%) and Komodo OCA-treated patients (11%) were comparable
- The FDA endpoint event rates for the COBALT OCA-treated patients (17%) and Komodo OCA-treated patients (17%) were equivalent

Figure 1. COBALT Trial Primary ITT Analysis: EMA & FDA Endpoint

1A: EMA Endpoint ITT OCA vs. Placebo



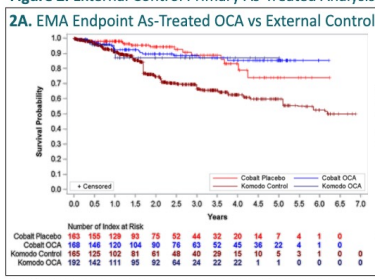
1B: FDA Endpoint ITT OCA vs. Placebo



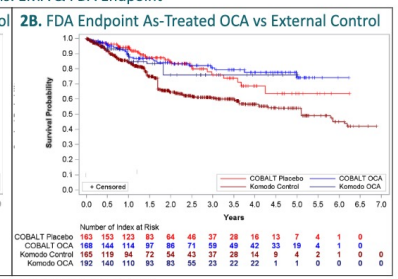
CI=Confidence Interval; EMA=European Medicines Agency; FDA=Food and Drug Administration; HR=Hazard ratio; OCA= Obeticholic Acid.

Figure 2. External Control Primary As-Treated Analysis: EMA & FDA Endpoint

2A. EMA Endpoint As-Treated OCA vs External Control



2B. FDA Endpoint As-Treated OCA vs External Control

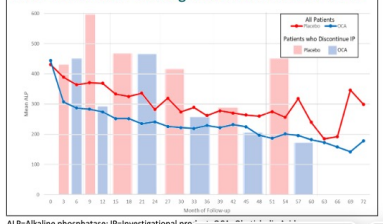


CI=Confidence Interval; EMA=European Medicines Agency; FDA=Food and Drug Administration; HR=Hazard ratio; OCA= Obeticholic Acid.

COBALT AD HOC ANALYSES

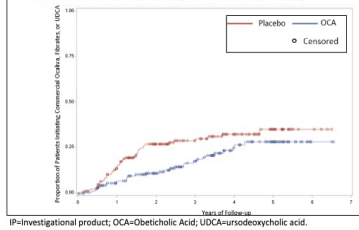
- At each time period, the median ALP of subjects in the placebo group who discontinued investigational product (IP) was higher than the median of all subjects during the same time period, suggesting that Placebo subjects may have functionally unblinded and discontinued IP (**Figure 3**). This pattern was not observed in the OCA group
- Subjects in the placebo group were significantly more likely to initiate Commercial OCA, fibrates and UDCA : 47 (28%) compared to : 33 (20%) subjects in the COBALT OCA group. HR=0.63; 95% CI=0.40, 0.98; p<0.05. (**Figure 4**)

Figure 3. COBALT ALP levels: All Subjects Vs Subjects Who Discontinue Investigational Product over Time



ALP=Alkaline phosphatase; IP=Investigational pr

Figure 4. COBALT: Subjects Who Initiate Commercial OCA, Fibrates or UDCA by Treatment Group



IP=Investigational product; OCA=Obeticholic Acid; UDCA=ursodeoxycholic acid.

Conclusions

- COBALT terminated early due to futility related to recruitment and retention challenges in the setting of commercially available OCA
- The pre-specified ITT analysis of the COBALT trial did not demonstrate a statistically significant difference between the OCA-treated group and placebo on event-free survival for either the EMA or expanded FDA endpoints
- We speculate the results were confounded by high rates of dropout, particularly among placebo subjects who stopped study drug early and initiated other PBC treatments
- Placebo-controlled studies may have limited utility to demonstrate clinical outcomes benefit when the study drug is commercially available or alternative therapies are readily available
- The event rate for OCA-treated subjects in COBALT and OCA-treated subjects in the Komodo database were equivalent; however, events rates in the COBALT Placebo group and Komodo external control differed widely
- A strong OCA benefit was demonstrated when comparing as-treated OCA subjects from COBALT with rigorously matched external controls
- These data provide evidence that OCA decreases the risk of death, liver transplant, and decompensation

Disclosures

KVK: Grant/research/clinical trial support: Concept, CymaBay, Genfit, Gilead, GSK, Hanmi, Intercept, Madrigal, Mirum, Novo Nordisk, NGM Bio, Pfizer, Pliant, Terns, Viking & 89bio. Advisor: CymaBay, Enanta, Genfit, Gilead, HighTide, Inipharm, Intercept, Madrigal, Mirum, NGM Bio, Pfizer & 89bio. Speaker: AbbVie, Gilead & Intercept. Stock: Inipharm. MAB: Advisor: Amgen, Astellas/Seagen, Atara, Brigham & Women's Hospital, Kite, Gilead, Intercept, NIDDK & Vertex; Consultant: Target RWE. GMH: Consultant: Intercept, Ipsen, CymaBay, Gilead, Pliant & HighTide. CC: Employee/ stockholder of Syneos Health. EM, TM, EN, JL: Employees of Intercept. AB, NR: Employee & shareholder of Target RWE. GM: Research funding: Intercept. DJ: Grant, Speaker, Consultant: Intercept; Speaker: Ipsen & Falk; Consultant: Advanz; Consultant & Speaker: Abbott, GSK. PJT: Institutional salary support from (NIHR) Birmingham Biomedical Research Centre (BRC). Poster represents independent research supported by Birmingham NIHR BRC based at University Hospitals Birmingham National Health Service Foundation Trust & University of Birmingham. Views expressed are those of the author(s) not necessarily those of the NHS, NIHR, or Dept. of Health. Grant: Wellcome Trust, Medical Research Foundation, GSK, Guts UK, PSC Support, Intercept, Falk, Gilead & Bristol Myers Squibb; Speaker: Intercept, Falk; Advisor: Intercept, Falk & GSK. BEH: Grants: Intercept, CymaBay, Calliditas, Eiger, Gilead, Mirum & Albireo; Consultant: Intercept, CymaBay, Calliditas, Eiger, Pliant, Enyo, Mirum, Albireo, & Ipsen. RS, DNK: No disclosures. JW, SH: Research support: Intercept. AM: Research funding: Merck. CB: Grant/ research support: Calliditas, Gilead, Intercept, Bristol Myers Squibb, GSK, Cour, Novo Nordisk, CymaBay, Genfit, Pliant, Boston Scientific, Viking & Cara. KM: Advisor: Chiesi (AU). MC: Grant/research support: Intercept, Genetic Spa & Mayoly; Advisor: CymaBay, Ipsen, Calliditas, Mayoly, Albireo, Perspectum, Zydus, Echosens & Genetic Spa. MB: Grant/research support (to institution): Gilead, Abbvie, & Intercept; Advisor: Gilead, Abbvie, Intercept,

Response and On-Treatment Risk Stratification

Despite treatment with UDCA, PBC can remain a progressive disease and has a risk of liver-related complications and death. The risk of developing end-stage complications and potential need for additional treatments should be assessed in all patients[3]

Assess risk of progression based on response to treatment[1,2,4,8,11]

Low risk[4]/ adequate response to UDCA

- ❑ No/early fibrosis[4] **and**
- ❑ ALP ≤ 1.5x ULN[4] **and**
- ❑ Normal bilirubin[4]

Emerging Data

- ❑ Total bilirubin ≤ 0.6x ULN[8]

or

- ❑ Total bilirubin >0.6x – 1x ULN **and** ALP normalization (< 1x ULN)[8]

→ Continue 1st-Line treatment and assess response every 3-6 months[1]

Intermediate-high risk[4] / Intolerance or inadequate response to UDCA[1]

- ❑ High risk using available predictive models (UK-PBC, GLOBE PBC)[2]
- ❑ Increasing fibrosis[2,4]/cirrhosis[1,2,4]

or ALP:

- ❑ ALP > 1.5x ULN[4]
- ❑ persistently elevated serum ALP after 12 months of therapy with UDCA[2]
- ❑ ALP remains > 1.67x ULN 6 months after initiating UDCA[2]

or Bilirubin:

- ❑ rising bilirubin/levels > ULN[4]
- ❑ lack of normalization of bilirubin after 12 months of therapy with UDCA[1,2]
- ❑ increasing total bilirubin despite normal ALP[2]

or Albumin:

- ❑ Albumin < LLN[4]

Emerging Data

- ❑ ALP > 1.0x ULN[8]
- ❑ Total bilirubin > 0.6x – 1x ULN[8]
- ❑ GGT ≥ 3.2x ULN[11]

→ Evaluate risk-benefit of 2nd-Line treatment

- No → Referral to a hepatologist or transplant center further assessment
- Yes → Initiate 2nd-Line Treatment

Consider referral for further assessment[4]

- ❑ Decompensated cirrhosis (Child-Pugh B or C, ascites, variceal bleeding)[4] **or**
- ❑ Compensated cirrhosis + portal hypertension[4] **or**
- ❑ Bilirubin > 2x ULN[4] **or**
- ❑ Severe pruritus[4]
- ❑ AST or ALT > 5x ULN[4]

→ Referral to a hepatologist or transplant center further assessment

Emerging Data from peer-reviewed, primary research literature; not incorporated in guidelines

This educational resource was developed and is provided by Intercept Pharmaceuticals US-PB-MED-00921 03/22

Intercept

Second-Line Treatment Considerations

Initiate 2nd line treatment[1-3]

- ❑ Obeticholic acid (5 mg QD)[1-3,12] for the first 3 months

Boxed WARNING

Routinely monitor for biochemical response, tolerability, and progression of PBC[12]

- ❑ 3 months after initiating therapy[12]

Per discretion of provider:

- ❑ Every 3 months
- ❑ Every 6 months
- ❑ Annually
- ❑ Other_____

Ongoing Routine Monitoring Assessments

Closely monitor patients with[12]:

- ❑ compensated cirrhosis
- ❑ concomitant hepatic disease (e.g., AIH, ALD)
- ❑ severe intercurrent illness

For:

- ❑ new evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia)
- ❑ increases above the upper limit of normal in total bilirubin, direct bilirubin, or prothrombin time

Tolerating treatment

Yes → **Response achieved**

Yes → **Increase to max dose 10 mg once daily[1-3,12]**

No → **If intolerance due to pruritus[12], consider:**

- ❑ Bile acid-binding resins
- ❑ Antihistamines

Additional Pruritus Management

- ❑ Reduce dosage to
  - ❑ 5 mg QOD (if intolerant to 5 mg QD)
  - ❑ 5 mg QD (if intolerant to 10 mg QD)
- ❑ Interrupt treatment for up to 2 weeks; restart at reduced dosage

Pruritus managed

Yes → **Initiate 2nd line treatment[1-3]**

No → **Discontinue treatment in patients who[12]:**

- Develop evidence of hepatic decompensation
- Have compensated cirrhosis and develop evidence of portal hypertension
- Experience clinically significant hepatic adverse reactions
- Develop complete biliary obstruction
- Persistent, intolerable pruritus

→ Refer to a hepatologist or transplant center

No → **Tolerating treatment**

Obeticholic acid is contraindicated in patients with[12]:

- decompensated cirrhosis (e.g., Child-Pugh Class B or C) or prior decompensation event
- compensated cirrhosis who have evidence of portal hypertension (e.g., ascites, gastroesophageal varices, persistent thrombocytopenia)
- complete biliary obstruction

See obeticholic acid full prescribing information (PI)

The content of this page is based on information from obeticholic acid PI[12] and published guidelines[1-3]

To report SUSPECTED ADVERSE REACTIONS, contact Intercept Pharmaceuticals at 1-844-782-ICPT or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

Emerging therapies for PBC

- Approved agents
  - UDCA
  - FXR-agonist: obeticholic acid (OCA)
    - Steroidal carboxylic acid

- **PPAR agonists**
  - Fenofibrates (PPAR alpha agonist) (nonapproved)
  - Bezafibrate (PPAR a, d and g) (nonapproved)
  - Seladelpar (PPAR d agonist) (phase II/III)
  - Elafibrnior (PPAR a and d) (phase II/III)
  - Saroglitizar (PPAR a and g) (phase II

- FXR agonists – phase II
  - EDP-305 (steroidal noncarboxylic)
  - Cilofexor (nonsteroidal carboxylic)
  - Tropifexor (nosteroidal carboxylic)

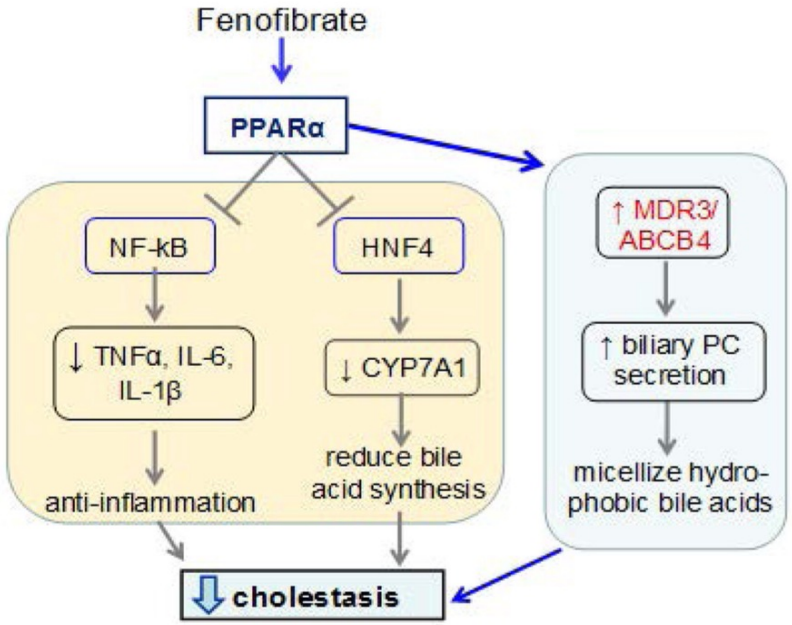
- **Nox 1 and 4 inhibitor (phase II/III)**
  - Antifibrotic

- **IBAT inhibitors** for cholestatic itch
  - Maralixibat (phase II)
  - Linerixibat (phase II/III)

Emerging therapies for PBC

- TGR5 receptor agonists
- CAR and PXR agonists
- *Nor*UDCA
- FGF-19 analog (NGM282)
- Combination: URSO/OCA/fibrates

Fibrates



Proposed pathway of fenofibrate-mediated
reduction of cholestasis via PPARain the liver

Ligand	Human receptor EC_{50} (μM)		
	PPARα	PPARβ/δ	PPARγ
Wy-14,643	5	35	60
Clofibrate[a]	55	IA at 100	~500
Fenofibrate	30	IA at 100	300
Bezafibrate	50	20	60

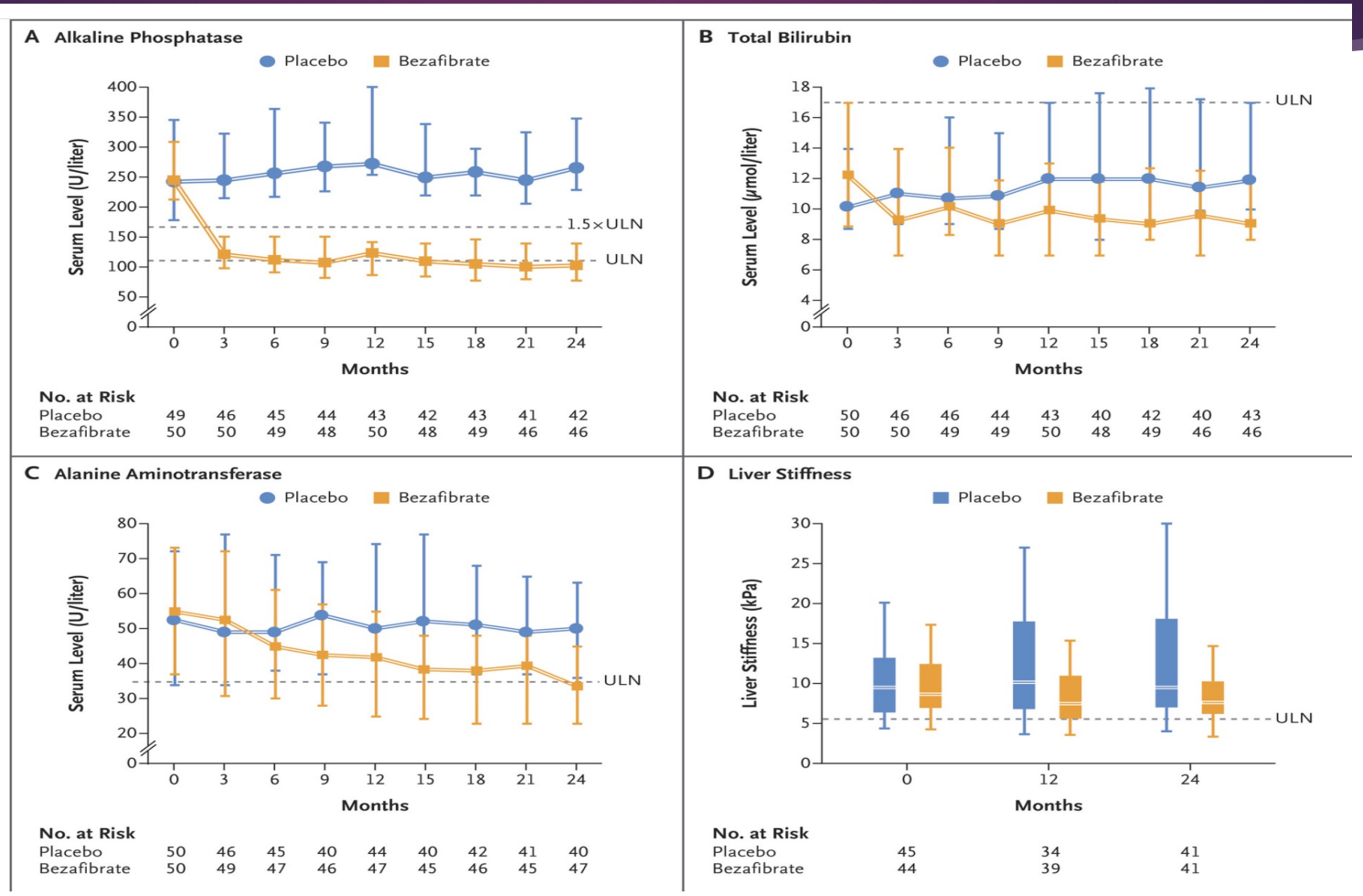
[a] data is for the active metabolite, IA = inactive.

Potency of human PPAR agonists

PPAR Gamma: adipose tissue and heart: **Thiozlidonedones**
PPAR Beta/delta: liver and peripheral tissue: **Elafibranor (phase III in PBC)—alpha/delta**
PPAR alpha: liver, muscle and kidneys: beta oxidation of fatty acid and regulated transcription of lipid metabolism genes the expression of MDR3 and facilitates hepatic export of phospholipids, anti-inflammatory and decreased BA synthesis (**seladelpar (phase III for PBC), bezafibrate (phase III completed) and fenofibrate (off label use)**

Ghonem NS, et a. Hepatology. 2015 Aug;62(2):635-43.

A Placebo-Controlled Trial of Bezafibrate in Primary Biliary Cholangitis



Corpechot et. al.; N Engl. J Med 2018; 378:2171-2181E

A Placebo-Controlled Trial of Bezafibrate in Primary Biliary Cholangitis

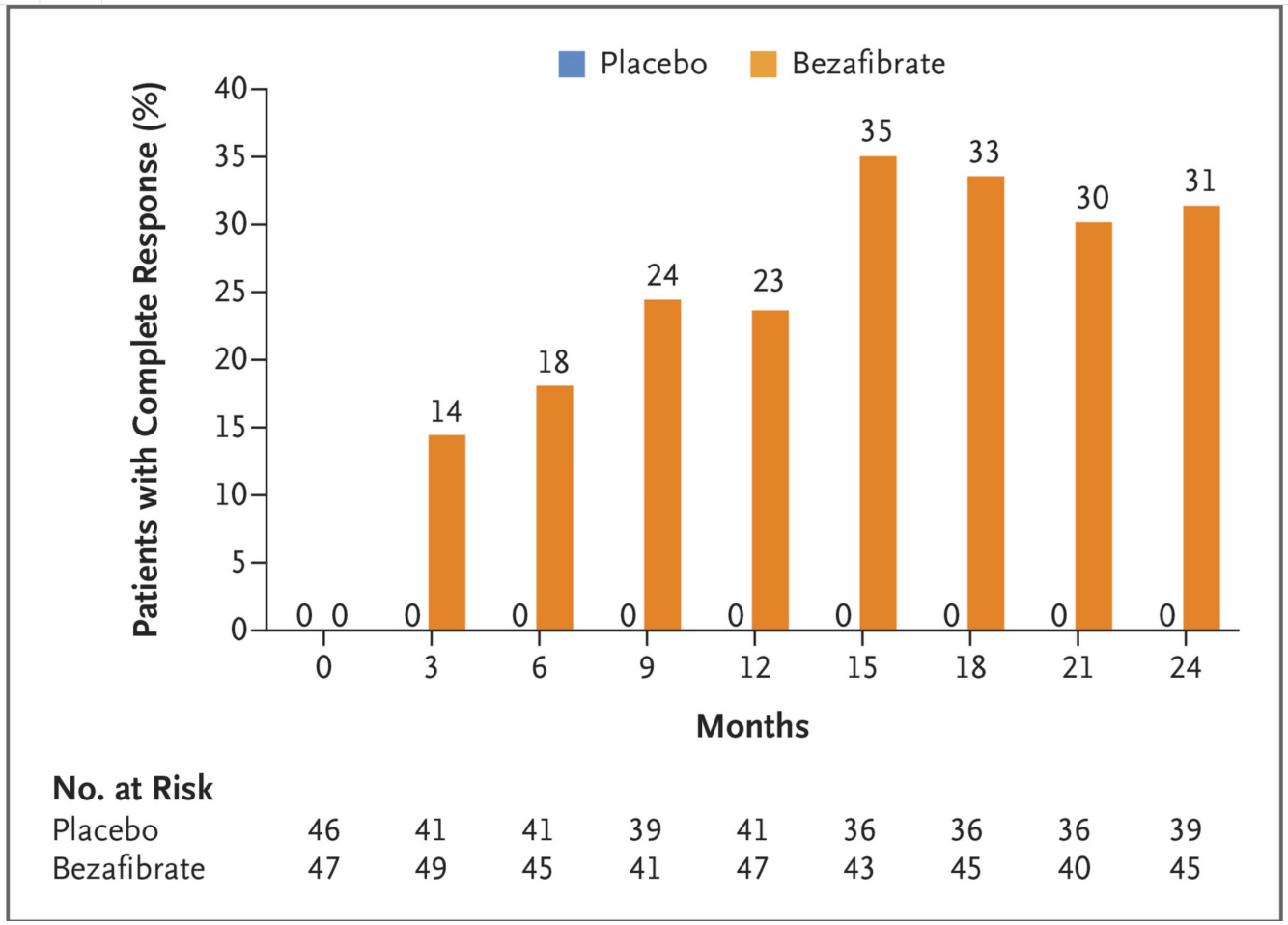


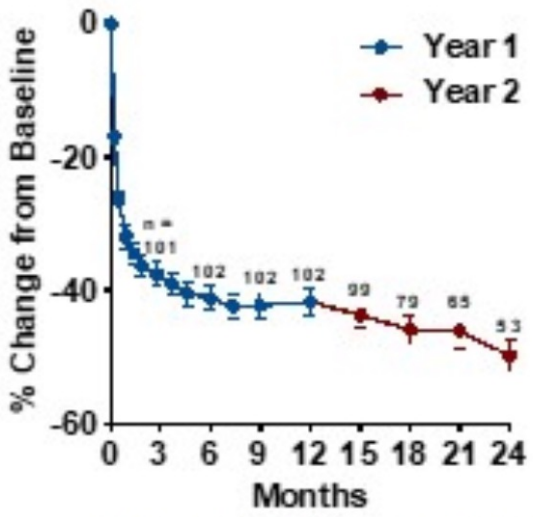
Figure 1. Percentage of Patients with a Complete Biochemical Response According to Time and Trial Group.

Shown are the percentages of patients with available data who had a complete biochemical response, defined as normal serum levels of total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and albumin, and a normal prothrombin index (the patient's prothrombin time expressed as a percentage of the normal value). Bezafibrate and placebo were administered with standard-of-care ursodeoxycholic acid. No patients in the placebo group had a complete biochemical response.

Corpechot et. Al., N Engl J Med 2018; 378:2171-2181E

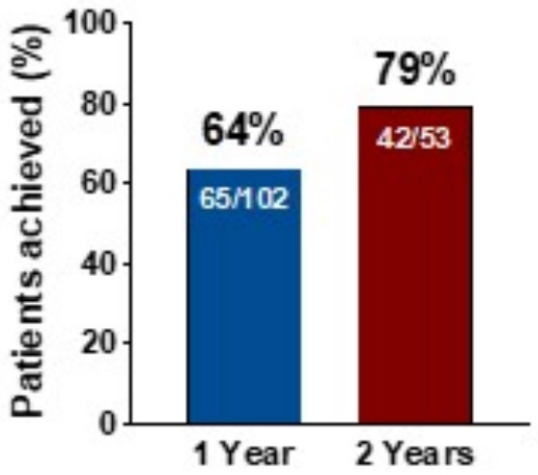
LONG-TERM SAFETY AND EFFICACY OF SELADELPAR IN PATIENTS WITH PRIMARY BILIARY CHOLANGITIS (PBC): 2-YEAR RESULTS FROM A LONG-TERM STUDY

Figure 1A



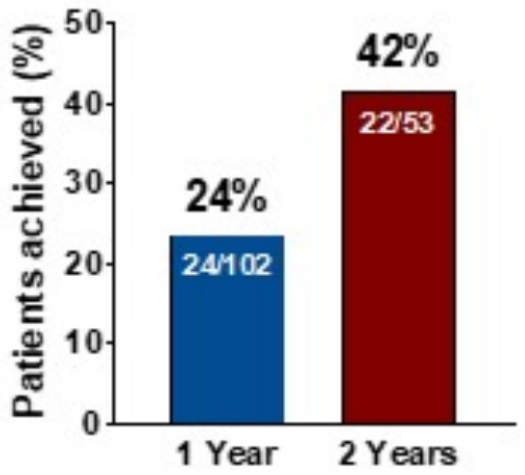
Change from Baseline in ALP over 24 Months

1B



Composite Endpoint (ALP <1.67xULN with ≥15% decrease and normal total bilirubin) at 1 and 2 Years

1C

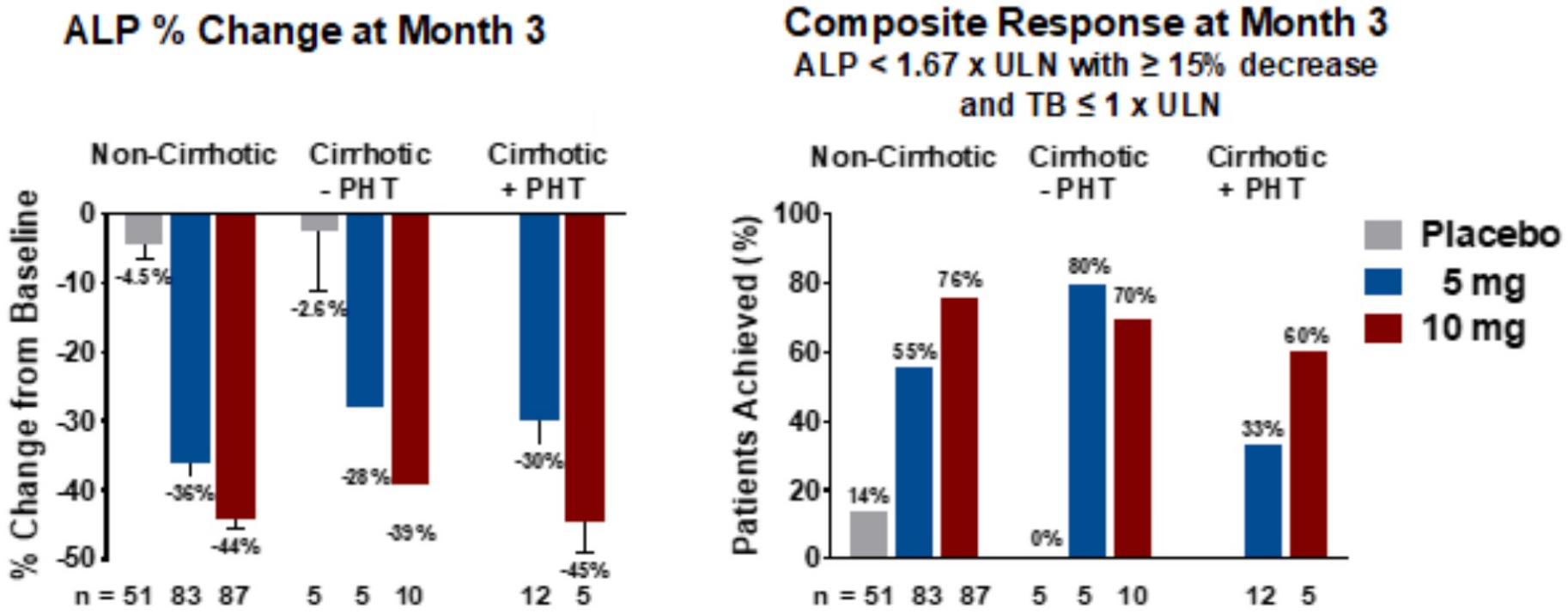


ALP Normalization at 1 and 2 Years

Mayo et. Al., AASLD 2021 #106

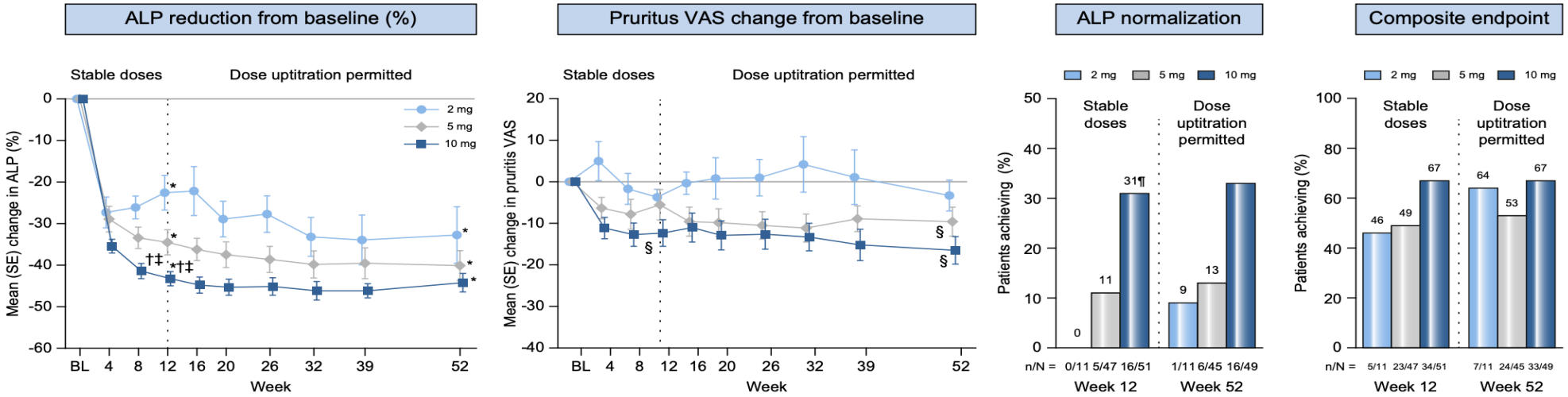
EFFICACY AND SAFETY OF SELADELPAR IN PATIENTS WITH COMPENSATED CIRRHOSIS AND EVIDENCE OF PORTAL HYPERTENSION DUE TO PRIMARY BILIARY CHOLANGITIS (PBC)

Figure



Levy et. al., AASLD 2021 #1269

A phase II, randomized, open-label, 52-week study of seladelpar in patients with primary biliary cholangitis



*$p \leq 0.02$ *vs.* baseline (paired *t* test); † $p \leq 0.01$ *vs.* 2 mg cohort (ANCOVA test of LS means); ‡ $p \leq 0.02$ *vs.* 5 mg cohort (ANCOVA test of LS means); § $p \leq 0.009$ *vs.* baseline (paired *t* test); ¶ $p < 0.01$ *vs.* 5 mg cohort (Fisher's exact test)

Treatment with seladelpar up to 10 mg QD through 1 year resulted in robust, dose-dependent, and clinically significant improvements in biochemical markers of cholestasis and pruritus.

Bowlus et. at.; J. Hepatol. 2022, 77, 353–364

Received: 4 May 2021 | Revised: 11 August 2021 | Accepted: 15 August 2021

DOI: 10.1111/liv.15039

ORIGINAL ARTICLE

Liver INTERNATIONAL WILEY

Seladelpar improved measures of pruritus, sleep, and fatigue and decreased serum bile acids in patients with primary biliary cholangitis

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Abstract

Background & Aims: Primary biliary cholangitis (PBC) can result in life-altering cholestatic pruritus and fatigue, but treatment options are limited. Seladelpar, a peroxisome proliferator-activated receptor-delta (PPARδ) agonist, has demonstrated potent anti-cholestatic effects in clinical studies. This open-label, uncontrolled phase 2 study in PBC patients evaluated the effects of 1-year of seladelpar treatment on measures of pruritus and quality of life.

Methods: Self-reported experiences of 101 PBC patients were collected at baseline and after 1 year of seladelpar treatment using the pruritus visual analog scale (VAS), 5D-itch scale, and PBC-40 questionnaires along with bile acid profiles.

Results: In patients with moderate–to-severe pruritus, substantial improvement in pruritus was seen in 58% and 93% of patients in 5/10 mg and 10 mg treatment groups, respectively. After 1 year, patients reporting improvement substantially outnumbered those who worsened in the total 5-D itch (including individual domains) and PBC-40 (itch and fatigue domains) questionnaires. Improvement in sleep disturbance at 1-year was reported in 81% (5/10 mg) and 78% (10 mg) of the patients with baseline itch-related sleep disturbance by 5-D itch score with similar results using the PBC-40 sleep questionnaire. Seladelpar-treated patients had significant reductions of 46% (5/10 mg) and 31% (10 mg) in the serum bile acid precursor C4 and reductions of up to 38% in serum bile acids.

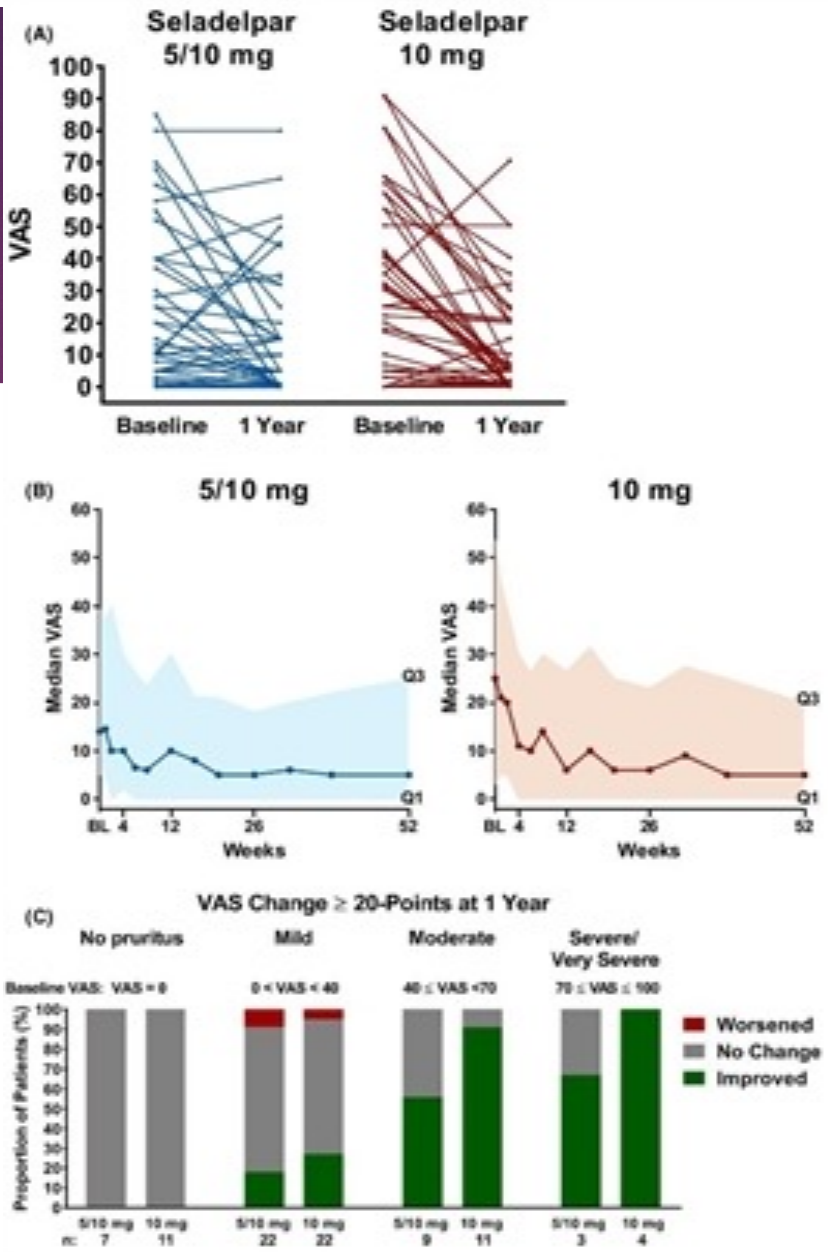

FIGURE 1 Changes in pruritus visual analog scale (VAS) from baseline to 1 year in patients treated with Seladelpar. (A) Changes in VAS for individual patients from baseline to 1 year, (B) Median Changes in Pruritus VAS over 1 year, and (C) Effect of seladelpar on pruritus after 1 year by baseline pruritus severity: In the assessment of pruritus, baseline pruritus VAS was categorized by severity: No pruritus (VAS = 0); Mild (0< VAS <40); Moderate (40≤ VAS <70); Severe/Very Severe (70≤ VAS ≤100). Changes in VAS by minimal clinically important difference of 20-points were evaluated by three categories: improved (VAS ≥20-point decrease), no change (VAS < ±20-points), and worsened (VAS ≥20-point increase)

SELADELPAR IMPROVED THE LIPID PROFILE OF PATIENTS WITH PRIMARY BILIARY CHOLANGITIS (PBC): RESULTS FROM PHASE 2 AND 3 CLINICAL STUDIES

Christopher L. Bowlus, MD[1]; Yun-Jung Choi, PhD[2]; Ke Yang, PhD[2]; Barry Crittenden, MD[2]; Dennis Kim, MD[2]; Charles A. McWherter, PhD[2]

[1]University of California, Davis, Davis, California; [2]CymaBay Therapeutics, Inc., Newark, California

BACKGROUND AND AIMS

- As patients with PBC are living longer, lowering cardiovascular risk is becoming increasingly important[1,2]
- Dyslipidemia, which is a typical modifiable risk factor for cardiovascular disease, is a common feature in patients with PBC[2-4]
- Seladelpar is a peroxisome proliferator-activated receptor delta (PPARδ) agonist that was initially developed as a lipid-lowering agent for patients with dyslipidemia[5]
- It has demonstrated potent

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METHODS

- Data were pooled from patients with PBC with an incomplete response or intolerance to ursodeoxycholic acid (UDCA) who were enrolled in an open-label phase 2 (NCT02955602) or placebo-controlled phase 3 studies (ENHANCE, NCT03602560)
- Key Inclusion Criteria:
  - Diagnosis of PBC
  - Alkaline phosphatase (ALP) ≥1.67× upper limit of normal (ULN)
  - UDCA for the past 12 months or intolerant to UDCA
- Key Exclusion Criteria:

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RESULTS

- A total of 373 patients were enrolled and received placebo (n=87), seladelpar 5 mg (n=142), or seladelpar 10 mg (n=144) (**Table 1**)
- Percentages of patients with body mass index (BMI) >30, diabetes, hypertension, or coronary artery disease were 28%, 9%, 24%, and 2%, respectively (**Table 1**)
- A total of 23% of patients were taking lipid-lowering medications (**Table 1**)
- Mean baseline levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), non-HDL-C, and triglycerides (TG) were 238, 138, 77, 161, and 116 mg/dL, respectively (**Table 1**)
- Elevated levels of TC (≥200 mg/dL), LDL-C (≥130 mg/dL), HDL-C (≥60 mg/dL), and TG (≥150 mg/dL) were found in 77%, 54%, 75%, and 21% of the patients, respectively (**Figure 1**)

TABLE 1. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

	PLACEBO (n=87)	SELADELPAR 5 mg (n=142)	SELADELPAR 10 mg (n=144)	ALL (N=373)
Female, n (%)	85 (98)	133 (94)	133 (92)	351 (94)
Age, years	56 (8)	56 (9)	56 (9)	56 (9)
Age >65 years, n (%)	12 (14)	22 (16)	24 (17)	58 (16)
Duration of PBC, years	8 (6)	9 (7)	9 (6)	9 (6)
AMA positive, n (%)	75 (86)	129 (91)	129 (90)	333 (89)
UDCA dose, mg/kg/day	15 (3)	15 (4)	15 (4)	15 (4)
UDCA intolerant, n (%)	2 (2)	11 (8)	11 (8)	24 (6)
ALP, U/L	293 (106)	311 (143)	293 (120)	300 (126)
TB, mg/dL	0.7 (0.3)	0.8 (0.4)	0.8 (0.3)	0.7 (0.3)
ALT, U/L	44 (21)	47 (23)	47 (21)	46 (22)
GGT, U/L	229 (193)	233 (190)	240 (214)	235 (200)
AST, U/L	38 (17)	41 (17)	42 (16)	41 (17)
Platelet count, 10^3 cells/μL	266 (77)	230 (78)	249 (75)	246 (78)
Albumin, g/dL	4 (0.2)	4 (0.3)	4 (0.3)	4 (0.3)
BMI, kg/m²	28 (6)	27 (6)	28 (6)	28 (6)
BMI >30, n (%)	28 (32)	37 (26)	41 (28)	106 (28)

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RESULTS

- Among patients with evaluable data at Month 6 (placebo, n=23; seladelpar 5 mg, n=71; seladelpar 10 mg, n=70), significant improvements in lipid levels were observed in the seladelpar arms compared with the placebo arm (all *P*<0.05) (**Figures 2-6**)

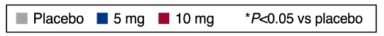


FIGURE 2. MEAN CHANGES FROM BASELINE IN TC

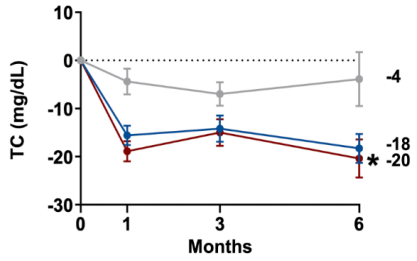
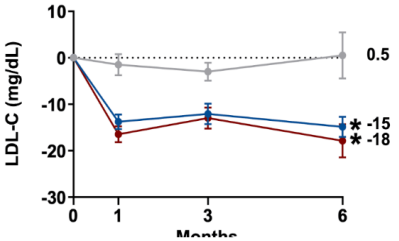


FIGURE 3. MEAN CHANGES FROM BASELINE IN LDL-C



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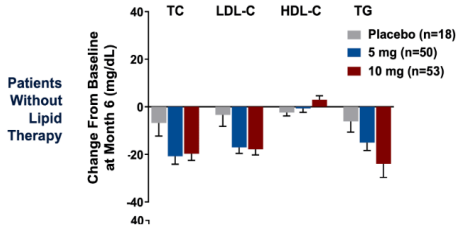
RESULTS

A comparison of lipid lowering in patients with or without concomitant lipid therapy revealed that seladelpar 10 mg achieved similar treatment effects at Month 6 (**Figure 7**)

FIGURE 7. CHANGES FROM BASELINE IN LIPIDS AT MONTH 6 IN PATIENTS WITH OR WITHOUT CONCOMITANT THERAPY



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CONCLUSIONS

- Cardiovascular risk factors were prevalent in this study cohort
- Although 23% were taking concomitant lipid-lowering medications, patients with PBC were characterized by elevated TC, LDL-C, and HDL-C at baseline
- Treatment with seladelpar resulted in significant improvements in TC, LDL-C, HDL-C, and TG in patients with PBC

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ENHANCE: Safety and Efficacy of Seladelpar in Patients With Primary Biliary Cholangitis—A Phase 3, International, Randomized, Placebo-Controlled Study

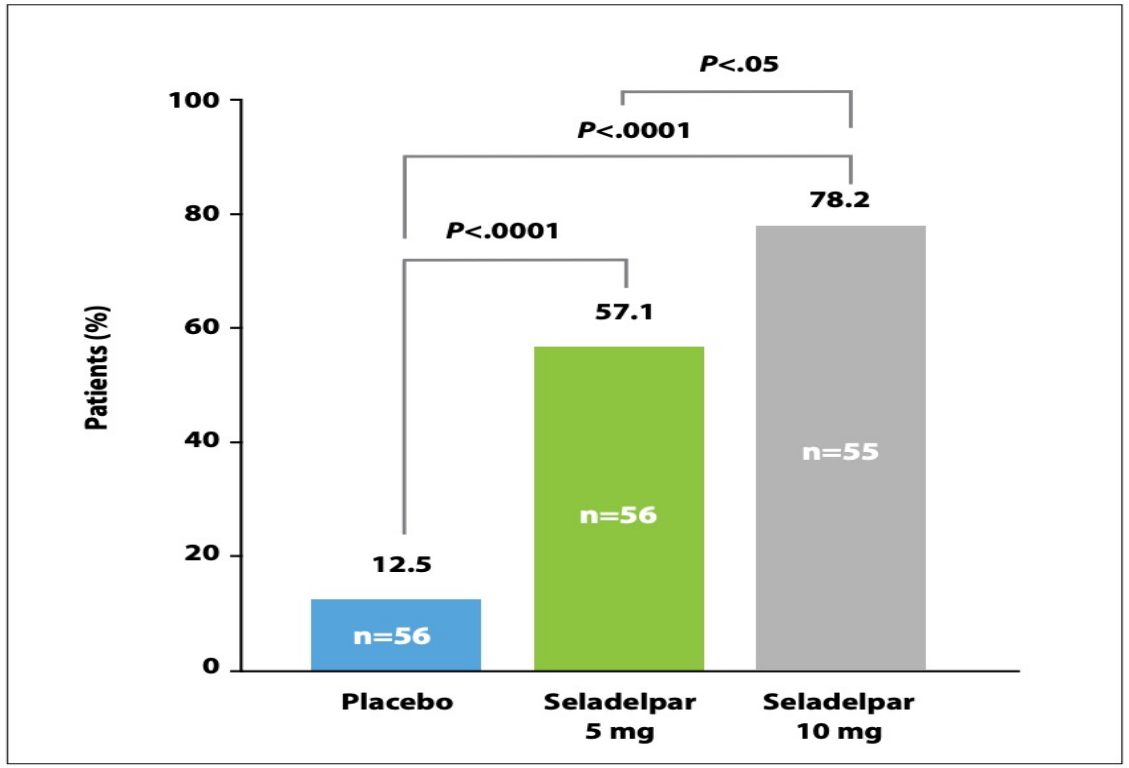


Figure 4. Primary composite endpoint achieved at 3 months with seladelpar. *P* values by Cochran-Mantel-Haenszel test. CymaBay, data on file 2020. Adapted from Hirschfield GM et al. AASLD abstract LO11. *Hepatology*. 2020;72(suppl 1).[2]

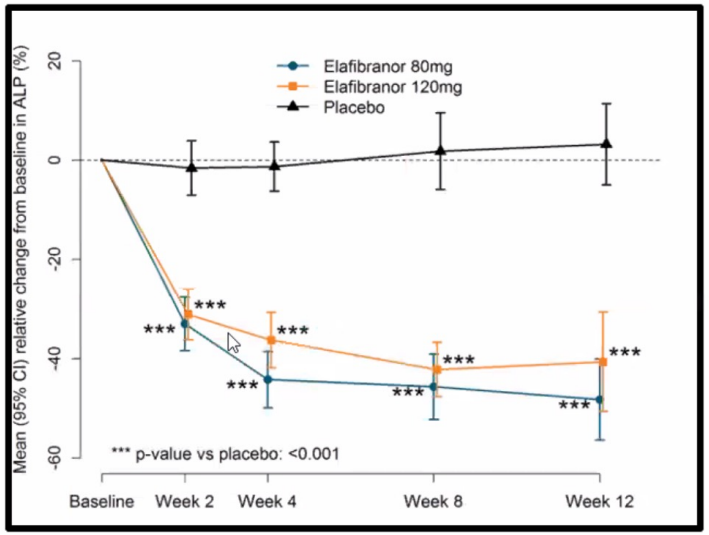
Gastroenterology & hepatology [Gastroenterol Hepatol (N Y)] 2021 Feb; Vol. 17 (2 Suppl 3), pp. 5-6.

RESPONSE: A Placebo-controlled, Randomized, Phase 3 Study to Evaluate the Efficacy and Safety of **Seladelpar** in Patients With Primary Biliary Cholangitis (PBC) and an Inadequate Response to or an Intolerance to Ursodeoxycholic Acid (UDCA)

- Phase III; active but not recruiting
- Composite endpoint of ALP and total bilirubin (Time Frame: 12 months)
  - ALP < 1.67× ULN,
  - ≥ 15% decrease in ALP, and
  - Total bilirubin ≤1.0× ULN
- Secondary outcome
  - Normalization of ALP and improvement in pruirtus
- Awaiting results

PBC – Emerging Therapies: Elafibranor

Elafibranor → Pan-selective PPAR (PPAR- α/δ)



- 12- week double-blind RCT (Phase II)
- ALP decreased significantly in both elafibranor groups Vs. placebo

Composite endpoint: ALP <1.67 ULN, ALP decrease >15%, and Tbili <ULN
80 mg group → 67% patients
120 mg group →79% of patients
Placebo → 6.7% patients

Pruritus improvement →
80 mg: 24% 120 mg: 49% Placebo: 7%

Phase III trial (NCT04526665) → Ongoing

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Research Article
DILI, Autoimmune, Cholestatic and Genetic Diseases

JOURNAL OF HEPATOLOGY

A randomized placebo-controlled trial of elafibranor in patients with primary biliary cholangitis and incomplete response to UDCA

Jörn M. Schattenberg[1,*], Albert Pares[2], Kris V. Kowdley[3], Michael A. Heneghan[4], Stephen Caldwell[5], Daniel Pratt[6], Alan Bonder[7], Gideon M. Hirschfield[8], Cynthia Levy[9], John Vierling[10], David Jones[11], Anne Tailleux[12], Bart Staels[12], Sophie Megnien[13], Remy Hanf[13], David Magrez[13], Pascal Birman[13], Velimir Luketic[14]

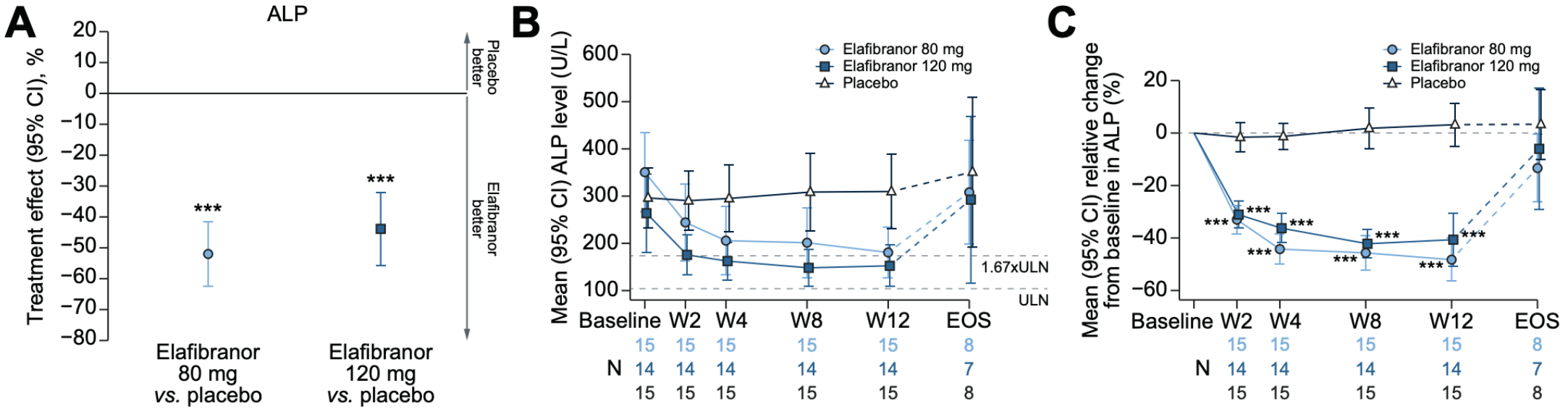

Fig. 1. Effects of elafibranor on ALP levels in the mITT population. (A) Primary efficacy endpoint: treatment effect (±95%CI) of elafibranor 80 mg and 120 mg *vs.* placebo on relative change in ALP at end-of-treatment (week-12); (B) Time course of ALP levels in placebo and elafibranor-treated groups (mean±95%CI); (C) Time course of relative change *vs.* baseline in placebo and elafibranor-treated groups (mean±95%CI). ***p <0.001 *vs.* placebo according to non-parametric ANCOVA with baseline value as covariate. An end-of-study visit was planned following a protocol amendment implemented after the study start and was performed only in a subset of patients (n = 23) after an off-study drug period of 16 to 30 days. ALP, alkaline phosphatase; mITT, modified intention-to-treat.

Study of Elafibranor in Patients With Primary Biliary Cholangitis (PBC) (ELATIVE)

- A Double-blind, Randomized, Placebo-Controlled Study and Open-label Long Term Extension to Evaluate the Efficacy and Safety of Elafibranor 80 mg in Patients With Primary Biliary Cholangitis With Inadequate Response or Intolerance to Ursodeoxycholic Acid. *NCT04526665*
- Phase III, active but not enrolling
- Primary Outcome Measures:Effect of elafibranor (80 mg/day) on cholestasis [Time Frame: From baseline to 52 weeks of treatment]
  - Response to treatment defined as Alkaline phosphatase (ALP) < 1.67 x ULN and TB ≤ ULN and ALP decrease ≥ 15 percent
- Secondary outcomes
  - Normalization of ALP and improvement of pruritus
- Awaiting results

Saroglitazar is a novel peroxisome proliferator-activated receptor (PPAR) agonist with dual agonistic properties (α/γ) Phase 2b/3 recruiting

- A double-blind, phase II proof-of-concept trial, 37 patients with PBC were randomized to saroglitazar 4 mg (n = 13), saroglitazar 2 mg (n = 14), or placebo (n = 10) daily for 16 weeks.
- The primary efficacy endpoint was the reduction in alkaline phosphatase (ALP) level at Week 16.
- A significant reduction of mean ALP levels was observed at Week 16 relative to baseline in both the saroglitazar 4 mg (least-squares [LS] mean =-163.3 U/L, SE = 25.1, p <0.001) and 2 mg (LS mean =-155.8 U/L, SE = 24.4, p <0.001) groups, compared with placebo (LS mean =-21.1 U/L, SE = 28.9). Treatment with saroglitazar resulted in a rapid reduction of ALP concentration at Week 4 that was sustained through the study duration.
- Multicenter, Randomized, Double-blind, Placebo controlled, Phase 2b/3 Safety and Efficacy Study . 192 subjects (64 subjects in each treatment arm) will be randomised in a ratio of 1:1:1 in Saroglitazar Magnesium 1 mg, Saroglitazar Magnesium 2 mg, and Placebo arm, respectively is recruiting

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Nox 1 and 4 inhibitor (Antifibrotic): TRANSFORM

A phase 2b/3 randomized, placebo-controlled, double-blind trial for treatment of primary biliary cholangitis (PBC) with setanaxib: Objectives and study design

4700

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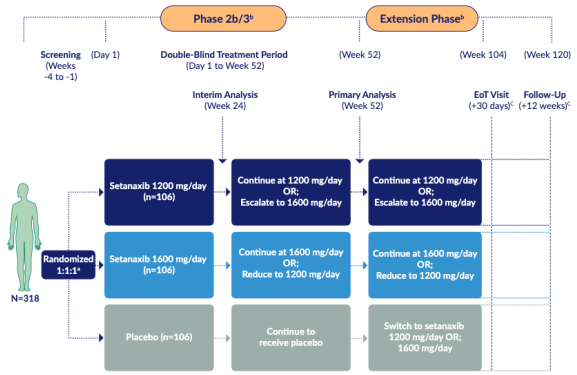
Objective

To describe the methodology of the ongoing phase 2b/3 TRANSFORM trial (NCT05014672), designed to evaluate the effect of setanaxib on biochemical response in patients with primary biliary cholangitis (PBC), elevated liver stiffness, and intolerance or inadequate response to ursodeoxycholic acid (UDCA).

Premise

- PBC is a chronic autoimmune liver disease characterized by the destruction of liver bile ducts following cholestasis.[1,2]
- Fatigue and pruritus are the most common clinical symptoms of PBC, which are often disabling and can have severe impact on patients' quality of life (QoL).[2,3]
- Approximately 40% of patients with PBC have suboptimal responses to UDCA, the current first-line treatment for PBC, and UDCA has not yet been shown to have efficacy in managing symptoms such as fatigue and pruritus.[4,5]
  - There is therefore an unmet need for new second-line treatments that also improve QoL in patients with PBC.
- Setanaxib is an investigational nicotinamide adenine dinucleotide phosphate oxidase (NOX) 1/4 inhibitor that is currently in development for the treatment of PBC.
- A phase 2 trial previously demonstrated anti-cholestatic and anti-fibrotic effects, and reduced fatigue, in patients with PBC following setanaxib treatment in addition to UDCA for 24 weeks.[6,7]

Figure 1: Study design



[a]Stratified by serum alanine phosphatase (ALP) level at baseline (</≥3.0 x upper limit of normal [ULN]); [b]The setanaxib dose levels for phase 3 and the extension phase will be determined by the interim analysis outcome at Week 24; [c]Patients who complete the extension phase will have an end of treatment (EoT) visit and follow-up visit at 30 days and 12 weeks, respectively, after the last setanaxib dose.

Abbreviations:

AESI: adverse event of special interest; ALP: alanine phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; eGFR: estimated glomerular filtration rate; EoT: end of treatment; NOX: nicotinamide adenine dinucleotide phosphate oxidase; PBC: primary biliary cholangitis; PBC-40: primary biliary cholangitis 40-item questionnaire; PDC-E2: pyruvate dehydrogenase complex E2 component; PGIC: Patient's Global Impression of Change; PGIS: Patient's Global Impression of Severity; PROMIS: Patient-Reported Outcomes Measurement Information System; QoL: quality of life; TEAE: treatment-emergent adverse event; TSH: thyroid stimulating hormone; UDCA: ursodeoxycholic acid; UK: United Kingdom; ULN: upper limit of normal; USA: United States of America; WI-NRS: Worst Itch Numerical Rating Scale.

References:

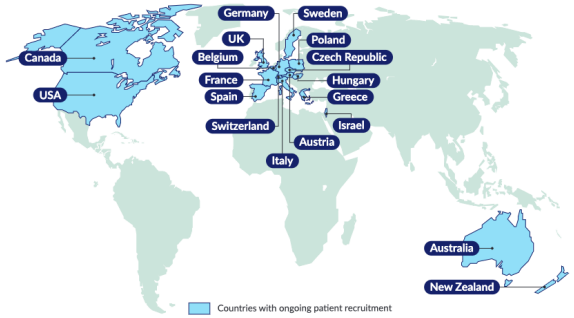
1. Lleo A et al. *Semin Liver Dis* 2020;40:34–48; 2. Purohit T and Cappell MS *World J Hepatol* 2015;7:926–41; 3. Huet P-M et al. *Am J Gastroenterol* 2000;95:760–7; 4. Corpechot C et al. *Hepatology* 2008;48:871–7; 5. Rudic JS et al. *Cochrane Database Syst Rev* 2012;12(12):CD000551; 6. Huang JC et al. *Hepatology* 2019;70:777A–9A; 7. Levy C et al. *Hepatology* 2021;74:782A–3A; 8. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT05014672. Accessed October 2022.

Methods

Trial design

- TRANSFORM (NCT05014672) is a 52-week, randomized, placebo-controlled, double-blind, multi-center, adaptive phase 2b/3 trial of setanaxib in patients with PBC.[8]
  - Patients will be randomized 1:1:1 to receive oral setanaxib 1200 mg/day, setanaxib 1600 mg/day, or placebo for 52 weeks, stratified by serum alanine phosphatase (ALP) level at baseline (</≥3.0 x upper limit of normal [ULN]) (Fig. 1).
- Patients who complete the 52-week double-blind treatment period can enter a 52-week extension phase.
  - An interim analysis will be conducted at Week 24 to determine if each group's setanaxib dose should be continued, escalated to 1600 mg/day or reduced to 1200 mg/day for phase 3 and the extension phase, or if the trial should be discontinued.

Figure 2: Study center locations



Patients

- Recruitment is ongoing to enroll around 318 patients across approximately 150 investigational centers globally (Fig. 2).
- Oral setanaxib will be administered in addition to UDCA in patients with PBC, elevated liver stiffness (≥8.8 kPa), and previous intolerance or inadequate response to UDCA (ALP ≥1.67 x ULN).
  - Key inclusion and exclusion criteria are presented in Table 1.

Trial endpoints

- The primary endpoint will be the proportion of patients achieving a biochemical response to setanaxib at Week 52, defined as: ALP reduction to <1.67 x ULN, ALP reduction of ≥15% from Baseline, and total bilirubin ≤1 x ULN.
  - Secondary endpoints will include the change from Baseline to Week 52 in fatigue, liver stiffness, and pruritus, and the proportion of patients reporting adverse events (Fig. 3).

Acknowledgments:

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Author Contributions:

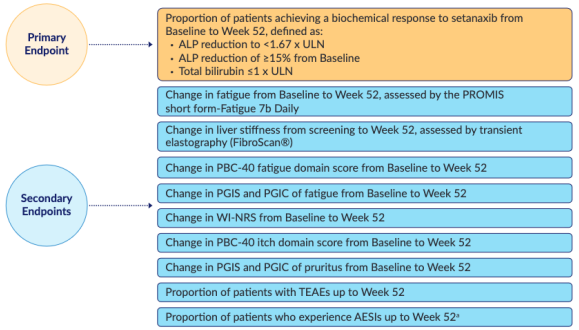
Substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of the data for publication, or revising it critically for important intellectual content: DJ, SC, SvR, CL; Final approval of the publication: DJ, SC, study protocol and had final responsibility for the decision to submit for publication.

Table 1: Key inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Males and females aged ≥18 years	Any historical or current hepatic decompensation event[b]
PBC diagnosis demonstrated by ≥2 of: • Elevated ALP levels • Positive antimitochondrial antibodies titer or positive PBC-specific antibodies[a] • Historical liver biopsy consistent with PBC	Presence of: • Total bilirubin >2 x ULN • Plasma ALT >3 x ULN and/or AST >3 x ULN • International normalized ratio >1.2 unless receiving anticoagulant therapy • eGFR <60 mL/min/1.73 m² • TSH >ULN at screening
Serum ALP ≥1.67 x ULN at screening	Medical conditions that could cause non-hepatic increases in ALP (e.g. Paget's disease)
Liver stiffness ≥8.8 kPa at screening	Cirrhosis with complications, including history or presence of hepatocellular carcinoma
UDCA prescriptional dose use for the past 6 months (at a stable dose for >3 months before screening) OR intolerant to UDCA (last dose of UDCA >3 months prior to screening)	Prior treatment with setanaxib or participation in a previous clinical trial of setanaxib

[a]Anti-GP210 antibodies, anti-SP100 antibodies, or antibodies against the major M2 components (PDC-E2 and 2-oxo-glutaric acid dehydrogenase complex); [b]Defined as variceal or portal hypertension bleed and/or hepatic encephalopathy, spontaneous bacterial peritonitis, ascites requiring treatment, or inclusion on the liver transplantation list.

Figure 3: Key study endpoints



[a]AESIs include drug-induced liver injury, anemia, and hypothyroidism.

Conclusion

Results from the TRANSFORM trial will allow evaluation of the safety and efficacy of setanaxib over two years (main study and extension phase), as well as its potential effects on QoL in patients with PBC and elevated liver stiffness.

Disclosures:

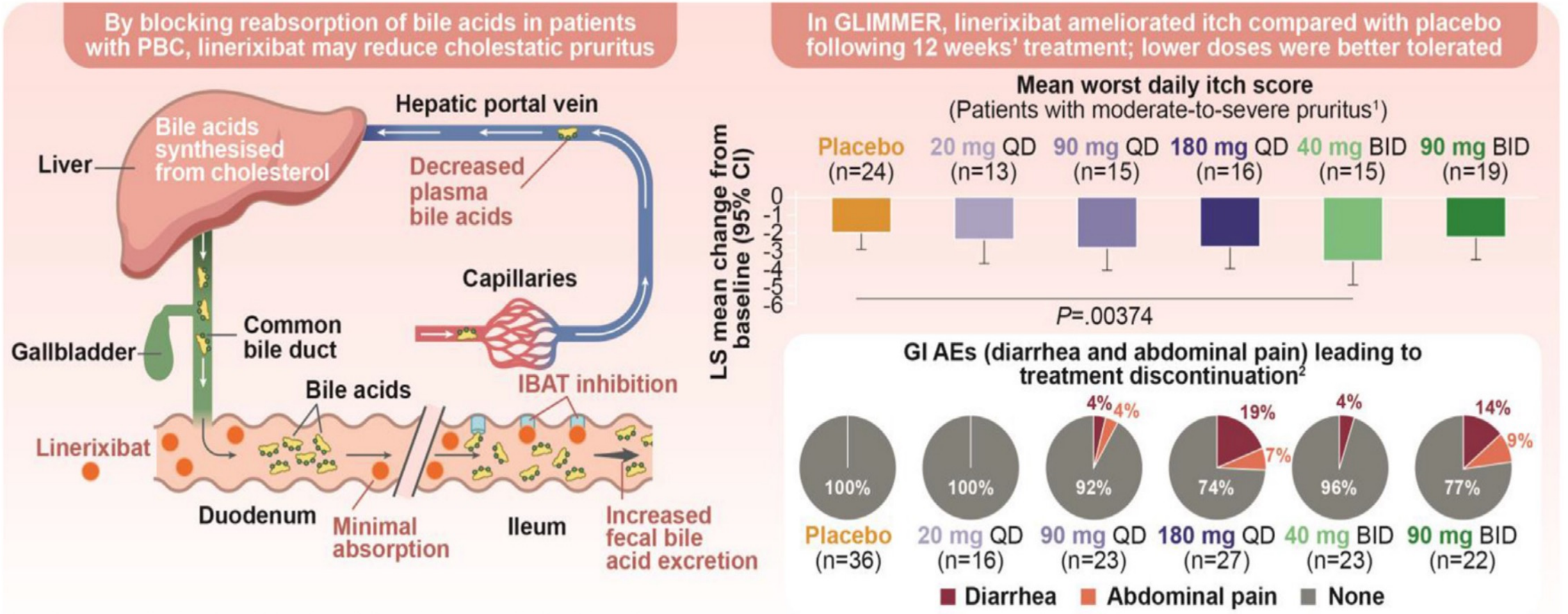
DJ: Consultancy and grant funding from Intercept; Speaker fees from Abbott and Falk; Consultancy fees from Calliditas Therapeutics AB and GSK. SC: Employee and stockholder of Calliditas Therapeutics AB. SvR: Employee and stockholder of Calliditas Therapeutics AB. CL: Grant/research support from Alnylam Pharmaceuticals, Calliditas Therapeutics AB, Cara Therapeutics, CymaBay Therapeutics, Genkyotex, GENFIT, Gilead Sciences, GSK, HighTide Therapeutics, Intercept Pharmaceuticals, Mirum Pharmaceuticals, Mitsubishi Tanabe Pharma Corporation, Novartis, Pliant Therapeutics, and Zydus Pharmaceuticals; Consultancy fees from Calliditas Therapeutics AB, Cara Therapeutics, GENFIT, GSK, Mirum Pharmaceuticals, Pliant Therapeutics, and Teva Pharmaceuticals.

IBAT inhibitors for cholestatic itch

Clinical Gastroenterology and Hepatology 2022;■:■–■

GLIMMER: A Randomized Phase 2b Dose-Ranging Trial of Linerixibat in Primary Biliary Cholangitis Patients With Pruritus

Cynthia Levy,[1,*] Stuart Kendrick,[2,*] Christopher L. Bowlus,[3] Atsushi Tanaka,[4] David Jones,[5] Andreas E. Kremer,[6,7] Marlyn J. Mayo,[8] Nazneen Haque,[2] Robyn von Maltzahn,[9] Matthew Allinder,[10,‡] Brandon Swift,[11] Megan M. McLaughlin,[10] and Gideon M. Hirschfield,[12] on behalf of the GLIMMER Study Group



AE, adverse event; BID, twice daily; CI, confidence interval; IBAT, ileal bile acid transporter; GI, gastrointestinal; LS, least squares; PBC, primary biliary cholangitis; QD, once daily.

[a]Intent-to-treat population; [b]Safety population

Clinical Gastroenterology and Hepatology

IBAT inhibitors

- **Linerixibat**
  - Global Linerixibat Itch Study of Efficacy and Safety in Primary Biliary Cholangitis (PBC) (GLISTEN); phase III, 24 weeks, recruiting
- **Volixibat**
  - A Study to Evaluate Efficacy and Safety of an Investigational Drug Named Volixibat in Patients With Itching Caused by Primary Biliary Cholangitis (VANTAGE), phase II, 28 weeks, recruiting
- Miralixibat, approved for PFIC and Allagille syndrome
- Odevixibat, approved in 3 months of age or older patient with PFIC

Medical Management of PSC

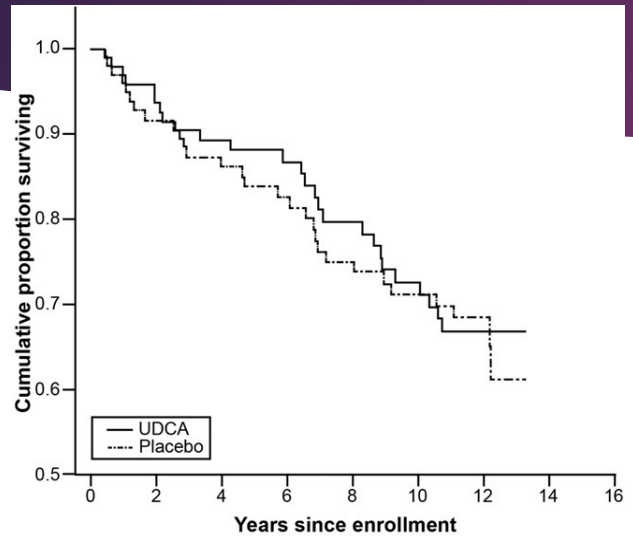
- At this time, there are no proven medical therapies for PSC, and the goals of treatment are primarily symptom and complication management

- Liver transplantation is the only effective treatment currently available for end-stage PSC

UDCA and ALP level in PSC

- Data from patients enrolled in the Scandinavian PSC UDCA trial (Lindström L, et. al. Clin Gastroenterol Hepatol. 2013 Jul;11(7):841-6.)
  - Patients with normal levels of ALP or reduced by ≥ 40% after 1 year in the trial had longer survival times, regardless of whether they receive UDCA or placebo

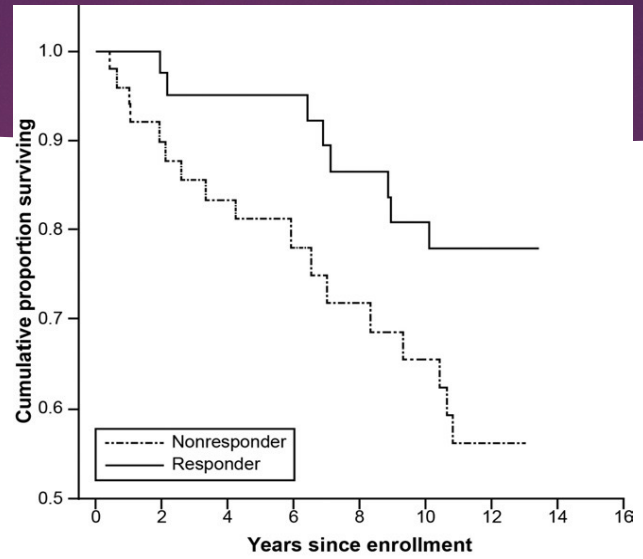
Scandinavian PSC UDCA trial



Numbers at risk

Years	0	2.5	5	7.5	10	12.5
UDCA	97	84	78	56	51	20
Placebo	101	84	72	59	56	19

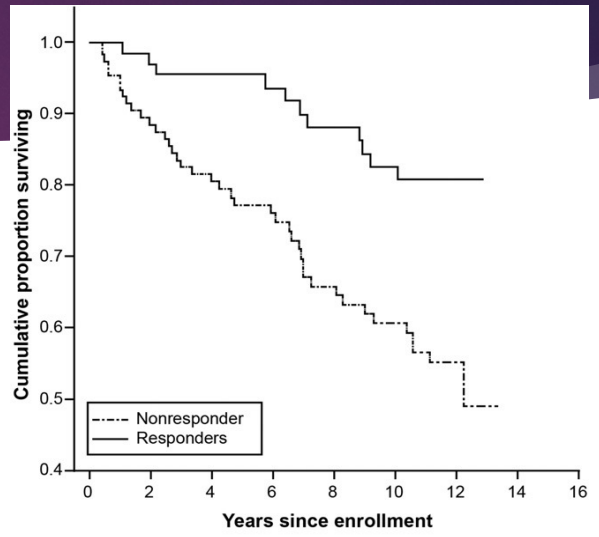
P = .77, log-rank test



Numbers at risk

Years	0	2.5	5	7.5	10
Responder	43	40	34	24	23
Nonresponder	51	45	35	19	15

P = .033, log-rank test
Tx with UDCA



Numbers at risk

Years	0	2.5	5	7.5	10	12.5
Responders	79	72	69	56	53	17
Nonresponders	116	93	78	56	52	21

P = .0001, log-rank test
Regardless of UDCA Tx

Lindström L, Hultcrantz R, Boberg KM, Friis-Liby I, Bergquist A. Association between reduced levels of alkaline phosphatase and survival times of patients with primary sclerosing cholangitis.
Clin Gastroenterol Hepatol. 2013 Jul;11(7):841-6.

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Prospective Evaluation of Ursodeoxycholic Acid Withdrawal in Patients With Primary Sclerosing Cholangitis

Ewa Wunsch,[1] Jocelyn Trottier,[2] Malgorzata Milkiewicz,[3] Joanna Raszeja-Wyszomirska,[1,4] Gideon M. Hirschfield,[5] Olivier Barbier,[2] and Piotr Milkiewicz[1,4]

Ursodeoxycholic acid (UDCA) is no longer recommended for management of adult patients with primary sclerosing cholangitis (PSC). We undertook a prospective evaluation of UDCA withdrawal in a group of consecutive patients with PSC. Twenty six patients, all treated with UDCA (dose range: 10-15 mg/kg/day) were included. Paired blood samples for liver biochemis-

Hepatology. 2014 Sep;60(3):931-40.

Patient and methods

- 29 patients with PSC established by EASL criteria
- Treated with UDCA (10-15 mg/kg/day) for at least 12 months before withdrawal
- Clinical data, HRQoL questionnaires, and paired blood samples for liver biochemistry, FGF19, and bile acids were collected 1 day before UDCA withdrawal and 3 months after withdrawal

Results
Liver Biochemistry

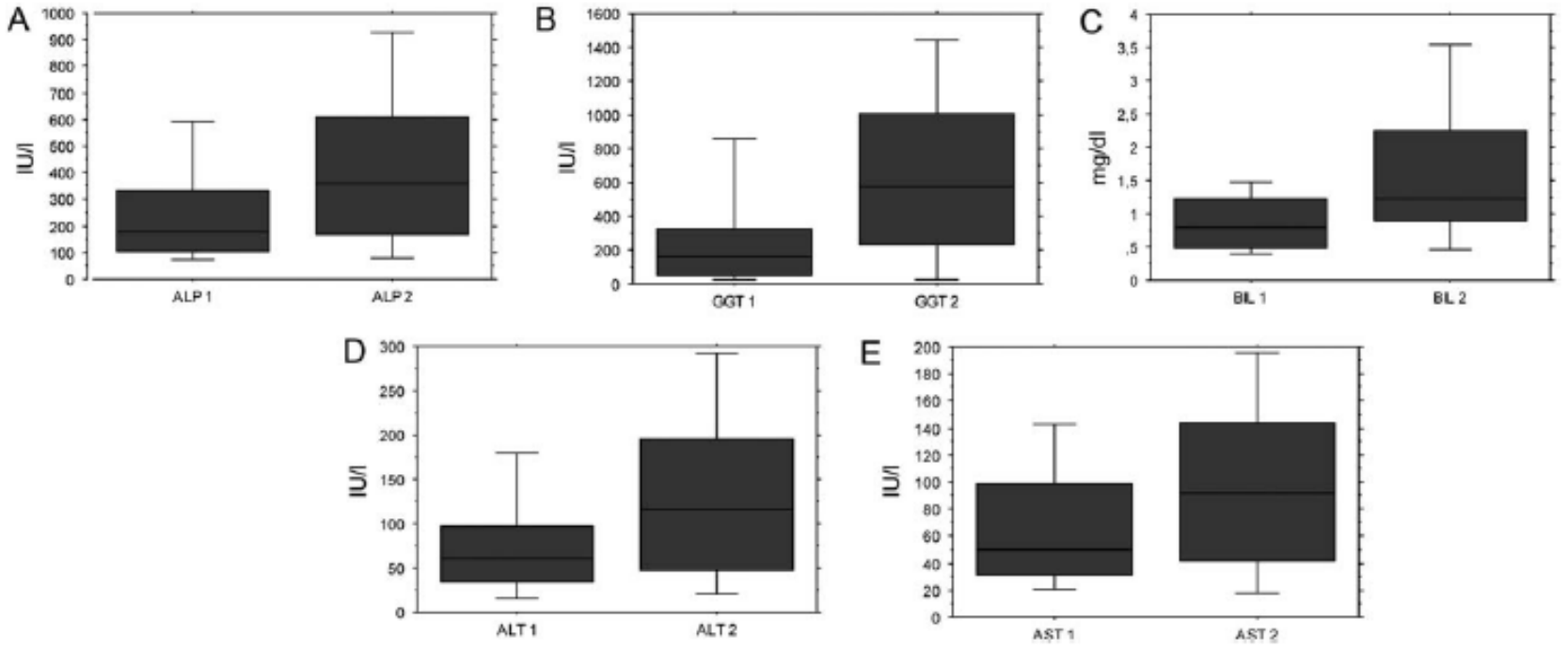


Fig. 1. Changes in liver biochemistry tests after UDCA withdrawal with respect to (A) ALP, (B) GGT, (C) total bilirubin, (D) ALT, and (E) AST. 1, Results of individual tests before UDCA withdrawal. 2, Results of individual tests 3 months after UDCA withdrawal.

Results

- PSC Mayo Risk Score significantly increased at the end of the study, in comparison with the day of enrollment
  - (-0.2 ±1.0 vs. -0.7 ± 0.9, respectively; P<0.003)
- 42% of patients reported increased pruritus measured by the itching domain of the PBC-40
- Deterioration in overall general health (a domain of the short form-36 QOL instrument in 60% of patients)
- One patient dropped out of the study (resumed UDCA) as a result of severe pruritus

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases

Ursodeoxycholic Acid in Primary Sclerosing Cholangitis: If Withdrawal Is Bad, Then Administration Is Good (Right?)

See Article on Page 931

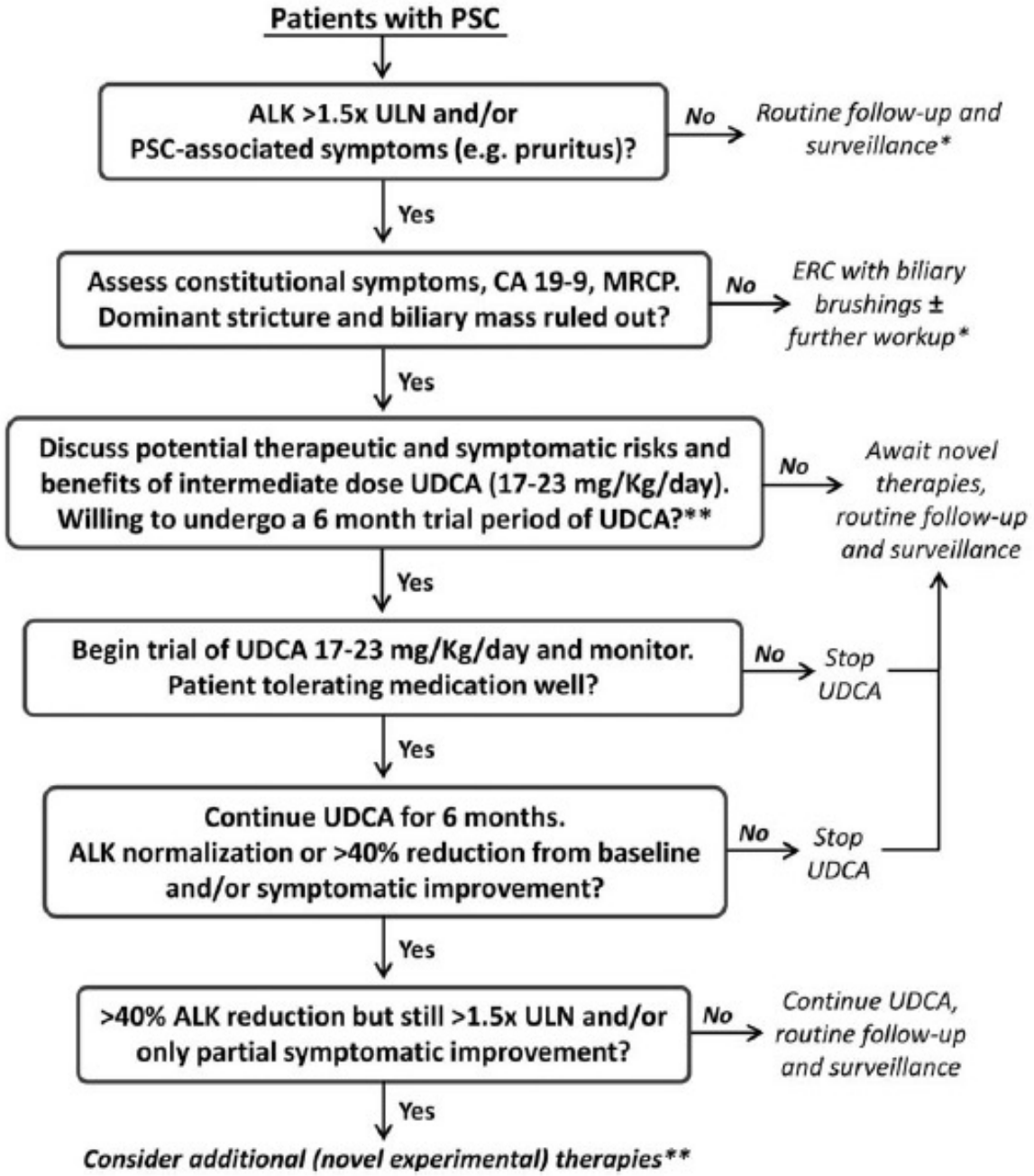
and fatigue, as well as worries related to the unpredictable disease course (personal clinical observations).[8,9]

Prevailing hypotheses, based on both clinical and ani-

Tabibian JH, Lindor KD. Hepatology. 2014 Sep;60(3):785-8.

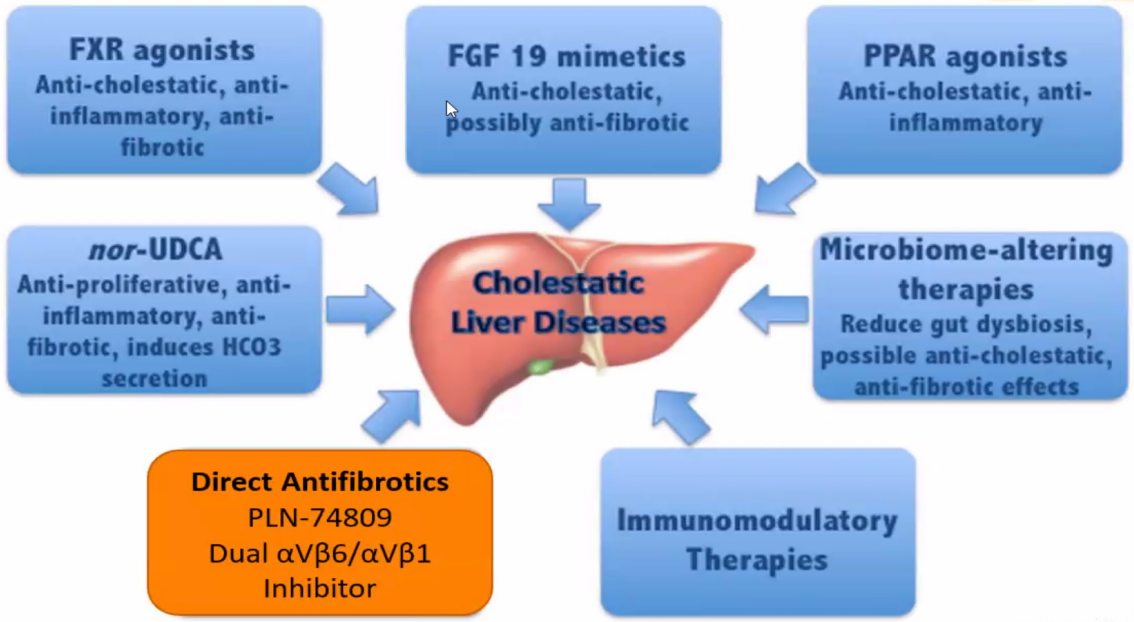
Proposed algorithm for UDCA use in clinical care and trials in PSC

Upcoming AASLD practice guideline—recommends use of UDCA –medium dose



Tabibian JH, Lindor KD. Hepatology. 2014 Sep;60(3):785-8.

Upcoming therapies in PSC



Adapted from Santiago et al Therap Adv Gastroenterol 2018

Upcoming therapies in PSC

- Pliant
- Berberine
- FXR agonists
- NorUDCA

Sample Table

Text	Text	Text	Text
Text	Text	Text	Text
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Text	Text	Text	Text

Sample Chart