Primary Biliary Cholangitis: Practice Updates and New Treatments in Development

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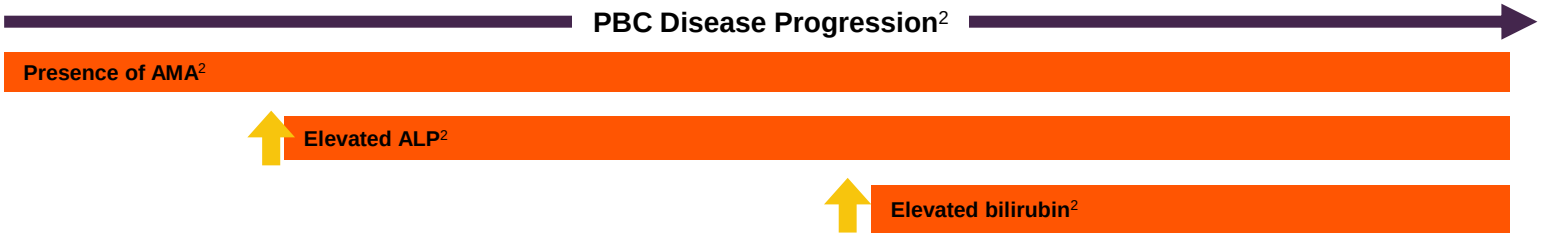
PBC Diagnosis Is Predominantly Based on Elevated ALP and the Presence of Anti-mitochondrial Antibodies[1]



AASLD Guidelines:

PBC diagnosis can be established when 2 of these 3 criteria are met[1,3]

1. Biochemical evidence of cholestasis based on **elevated ALP level**
2. Presence of **AMA** or other PBC-specific autoantibodies, including sp100 or gp210, if AMA is negative
3. Histologic evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts if biopsy is performed

Liver biopsy can be used to further substantiate the diagnosis but is no longer considered necessary in most patients[1]

AASLD, American Association for the Study of Liver Diseases; ALP, alkaline phosphatase; AMA, anti-mitochondrial antibodies; PBC, primary biliary cholangitis.

1. Lindor KD et al. *Hepatology*. 2019;69(1):394-419; 2. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172; 3. Kaplan MM, Gershwin ME, et al. *N Engl J Med*. 2005;353(12):1261-1273.

Goals of Therapy and Initial Treatment for PBC

- Goals of Therapy[1]
- Prevent end-stage liver disease
- Management of associated symptoms (e.g., fatigue and pruritus)

UDCA: First-line therapy[2,3]

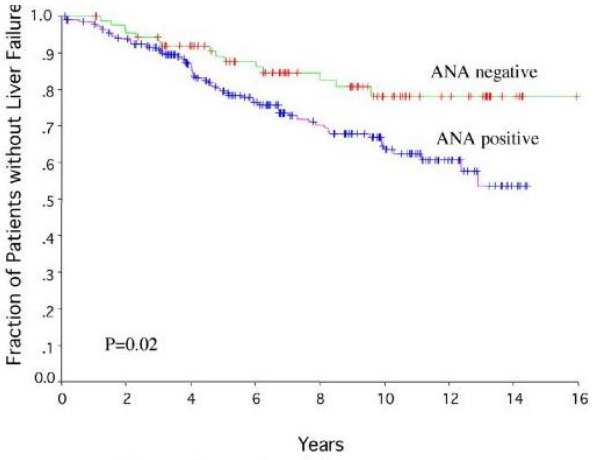
40% of patients do not respond adequately

3%-5% of patients may be intolerant

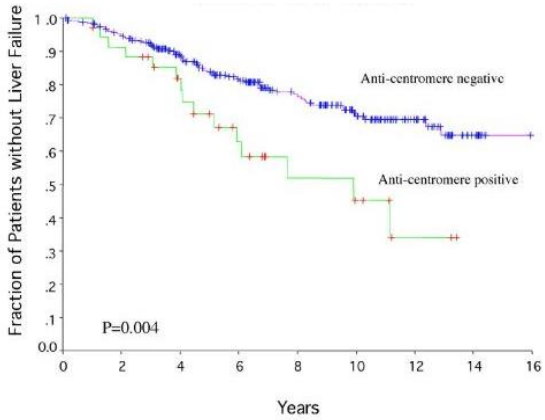
PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

1. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172; 2. Lindor KD et al. *Hepatology*. 2019;69(1):394-419;
3. Invernizzi P et al. *Dig Liver Dis*. 2017;49(8):841-846.

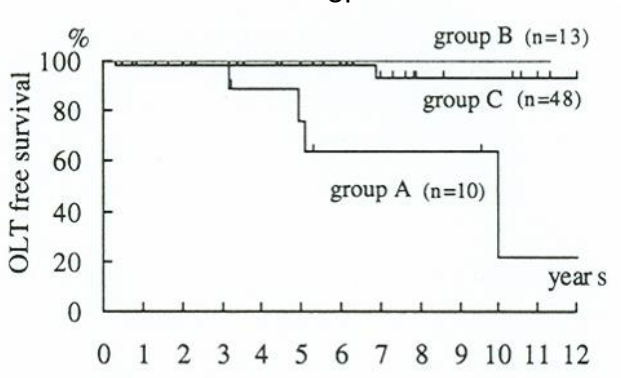
Predictors of Prognosis; Serologic Markers



Anti-Centromere Antibodies



ANA/gp210



Yang W, Yu JH, Nakajima, et al. Do antinuclear antibodies in primary biliary cirrhosis patients identify increased risk for liver failure? *Clin Gastroenterol Hepatol.* 2004;2(12):1116-22; Nakamura M, Shimizu-Yoshida Y, Takii Y, et al. Antibody titer to gp210-C terminal peptide as a clinical parameter for monitoring primary biliary cirhossis. *J Hepatol.* 2005;42(3):386-92.

ALP and Bilirubin Are Important Markers of Disease Progression and Response to Treatment[1]

Biochemical response to UDCA is typically measured by liver biochemical values for ALP and bilirubin[2]

Elevated **ALP** is an early and ongoing indicator of PBC progression[1,2]

- Lowering ALP is associated with longer transplant-free survival

Bilirubin is an important predictor of survival in PBC[1]

- Elevations usually occur in later stages

ALP, alkaline phosphatase; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

1. Lammers WJ et al. *Gastroenterology*. 2014;147(6):1338-1349. 2. Lindor KD et al. *Hepatology*. 2019;69(1):394-419.

Response to UDCA Is Currently Outlined by Multiple Criteria[1]

- There is currently no consensus on the criteria for non-response; however, decreasing ALP levels has emerged as an important treatment goal[2]

	Time (months)	Treatment Failure[1,*]
Rochester	6	ALP ≥2.0 × ULN or Mayo score ≥4.5
Barcelona	12	Decrease in ALP ≤40% and ALP ≥1.0 × ULN
Paris-I	12	ALP ≥3.0 × ULN or AST ≥2.0 × ULN or bilirubin >1 mg/dL
Rotterdam	12	Bilirubin ≥1.0 × ULN and/or albumin <1.0 × ULN
Toronto	24	ALP >1.67 × ULN
Paris-II	12	ALP ≥1.5 × ULN or AST ≥1.5 × ULN or bilirubin >1 mg/dL

*This is not an all-inclusive listing.

ALP, alkaline phosphatase; AST, aspartate aminotransferase; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid; ULN, upper limit of normal.

1. European Association for the Study of the Liver. *J Hepatol*. 2017;67(1):145-172; 2. Younossi ZM et al*. Am J Gastroenterol*. 2019;114(1):48-63.

Serum ALP After 6 Months of UDCA Initiation Demonstrates Utility in Identifying POISE Insufficient Response Within 1-2 Years.

Cutoff value of 2.5 xULN proposed at 6 months for adding second-line therapy.

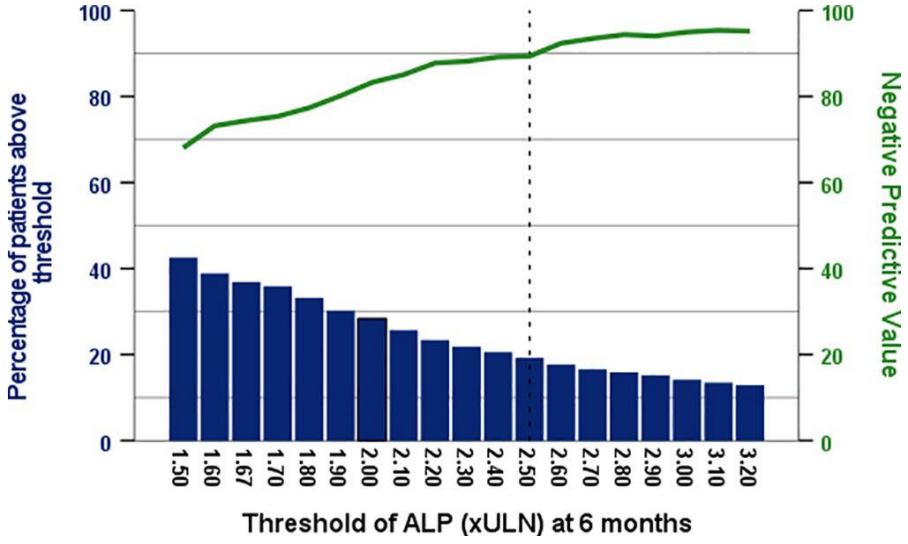


Table 1. Determination of response based on POISE criteria. Response and ALP were calculated in sub-groups of patients with available liver biochemistry in respective time fram

	Response	Insufficient Response
1 year (n=1362)	768 (56.4%)	594 (43.6%)
ALP (xULN) at 6 months (n=744)	1.05 (0.82-1.33)	2.37 (1.72-3.69)
1-2 years (n=2709)	1693 (62.5%)	1016 (37.5%)
ALP (xULN) at 6 months (n=1121)	1.07 (0.83-1.41)	2.55 (1.82-3.77)

Data presented as n (%) or median (25-75th percentiles)

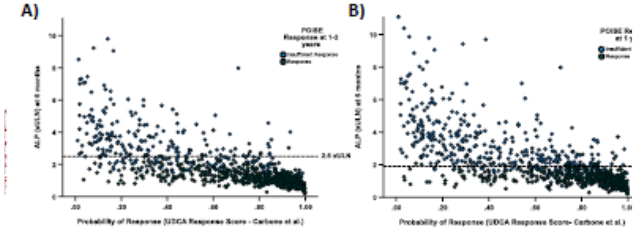
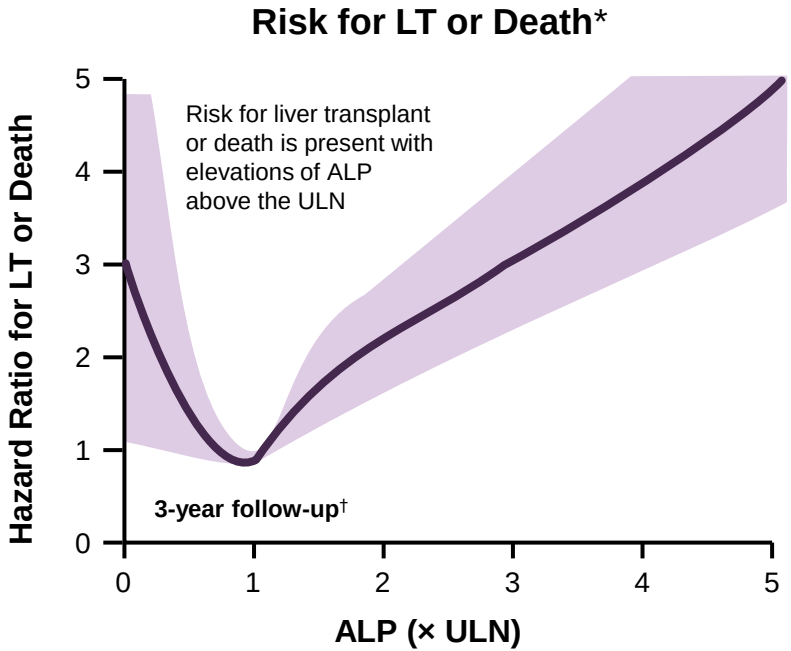


Figure 4. Scatter plot of probability of response determined by UDCA response score calculated at baseline and ALP at 6 months stratified by A) response at 1-2 years and B) response at 1 year.

SUMMARY OF FINDINGS

- There are patients that respond to therapy beyond 1 year
- Serum ALP after 6 months of UDCA initiation demonstrates utility in identifying insufficient response
- We propose a cut-off value of 1.9 xULN at 6 months as a threshold for adding second-line therapy as it relates to response at 1 year and current standard of care
  - 67% of patients would have early identification

Reconsider ALP and Bilirubin Treatment Goals?



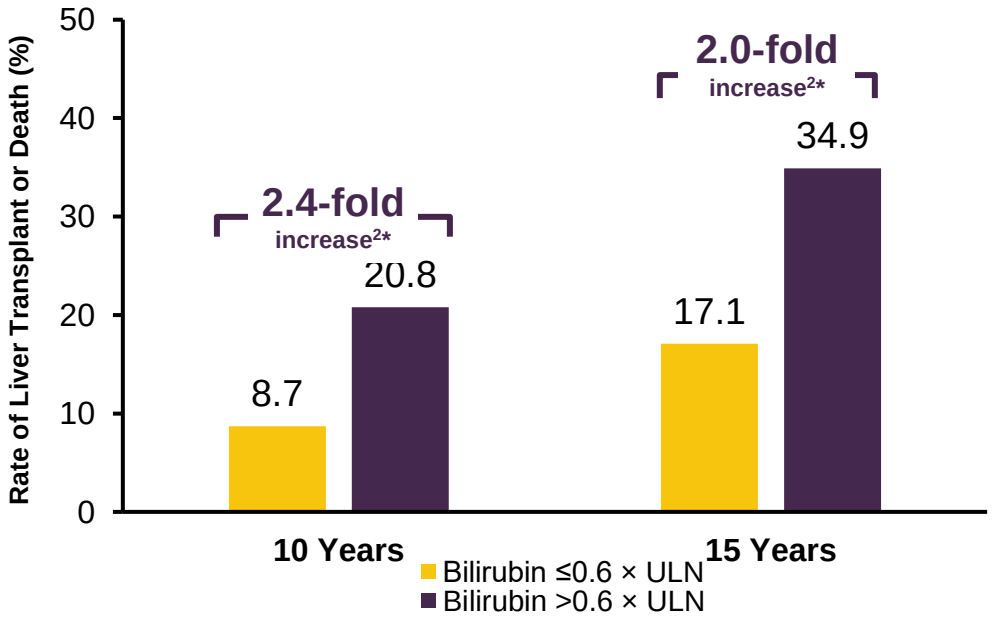
ALP >1.0 × ULN is associated with **2× greater risk** for transplant or death vs ALP ≤1.0 × ULN at 1-year follow-up (*P*<0.001)

Bilirubin levels >1.0 × ULN are associated with **5× greater risk** for transplant or death vs bilirubin ≤1.0 × ULN at 1-year follow-up (*P*<0.001)

*Hazard ratios of liver transplant or death were estimated by applying a cubic spline function of ALP and bilirubin at baseline and yearly up to 5 years of follow-up.
†2573/3865 patients were included in this analysis.
ALP, alkaline phosphatase; LT, liver transplant; ULN, upper limit of normal.
Lammers WJ et al. *Gastroenterology*. 2014;147(6):1338-1349.

Do You Aim for a Bilirubin of ≤0.6 × ULN?

Surpassing the 0.6 × ULN threshold significantly increased risk for liver transplant or death1



Bilirubin >0.6 × ULN was associated with increased risk for liver transplant or death at 10 and 15 years compared with ≤0.6 × ULN[1]

*Calculation based on percent rates of liver transplant or death extrapolated from survival estimate curve at 10 years.
ULN, upper limit of normal.

1. Murillo Perez CF et al. *Am J Gastroenterol*. 2020;115(7):1066-1074; 2. Data on file: Intercept Pharmaceuticals, Inc.

Should GGT Be Included in Treatment Decisions?

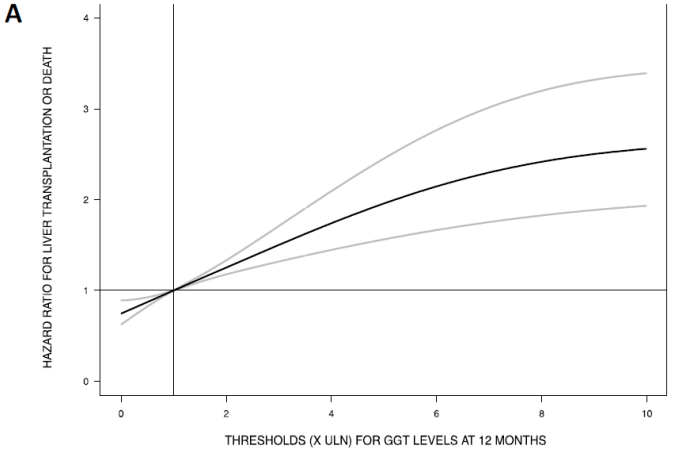


Figure A
GGT levels and hazard ratio for liver transplantation or liver-related death in PBC

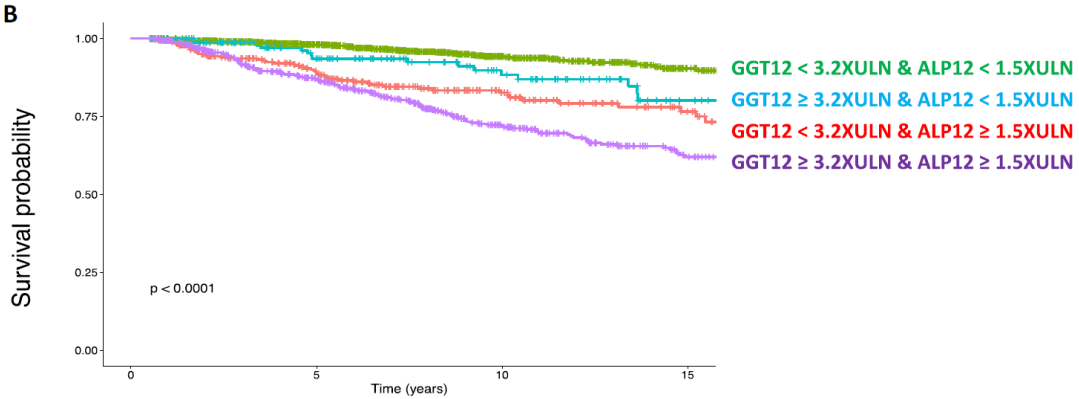
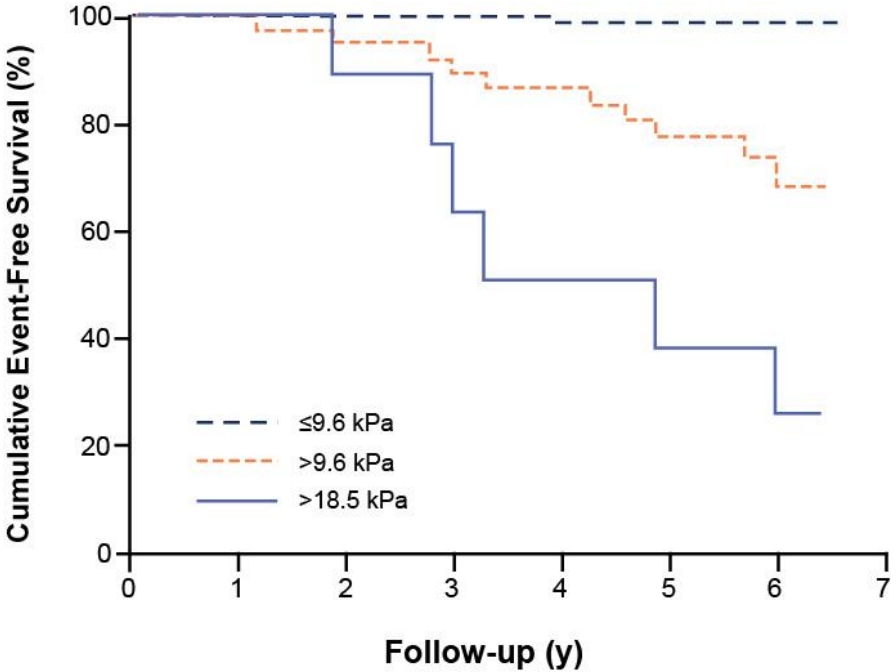


Figure B
The transplant-free survival in relations to the combined GGT and ALP levels in PBC patients

Presented at ILC Virtual Congress 2020. FRI124. August 28-30, 2020.

Impact on Survival of Liver Stiffness Measurement in PBC

150 PATIENTS



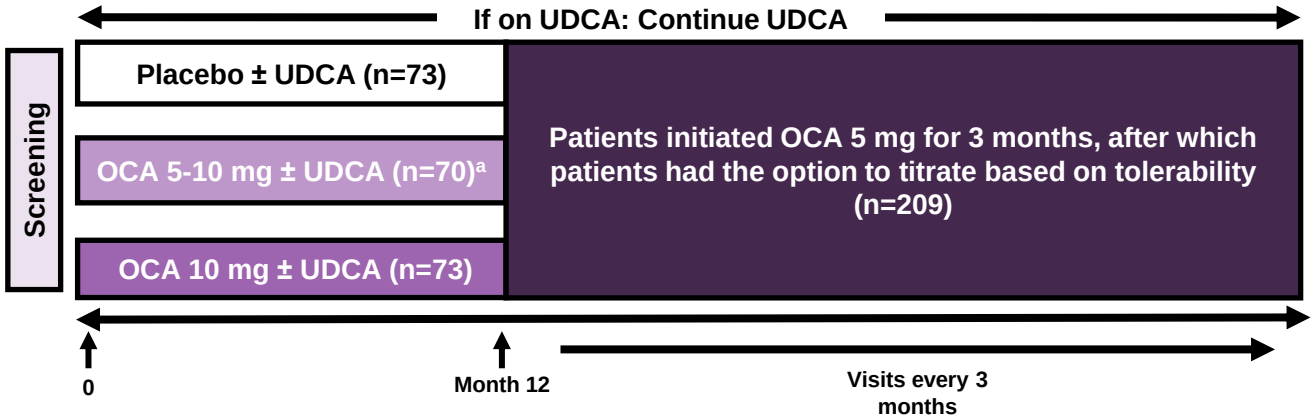
Corpechot C et al. Utility of Noninvasive Markers of Fibrosis in Cholestatic Liver Diseases. *Clin Liver Dis*. 2016;20:143-158.

Treatment of PBC

- UDCA approved in 1999
- OCA approved in 2016
  - Based on “POISE” criteria
  - ALP<1.67XULN, 15% decline and normal bilirubin
  - Long-term OLE extension study completed
  - Label Update for OCA in May 2021
- Elafibranor, seladelpar in Phase 3 trials

Obeticholic Acid: POISE Long-Term Safety Extension Study

- Patients on placebo crossed over to OCA treatment at 12 months
- Patients followed for up to an additional 5 years
- Events measured included death and liver transplant



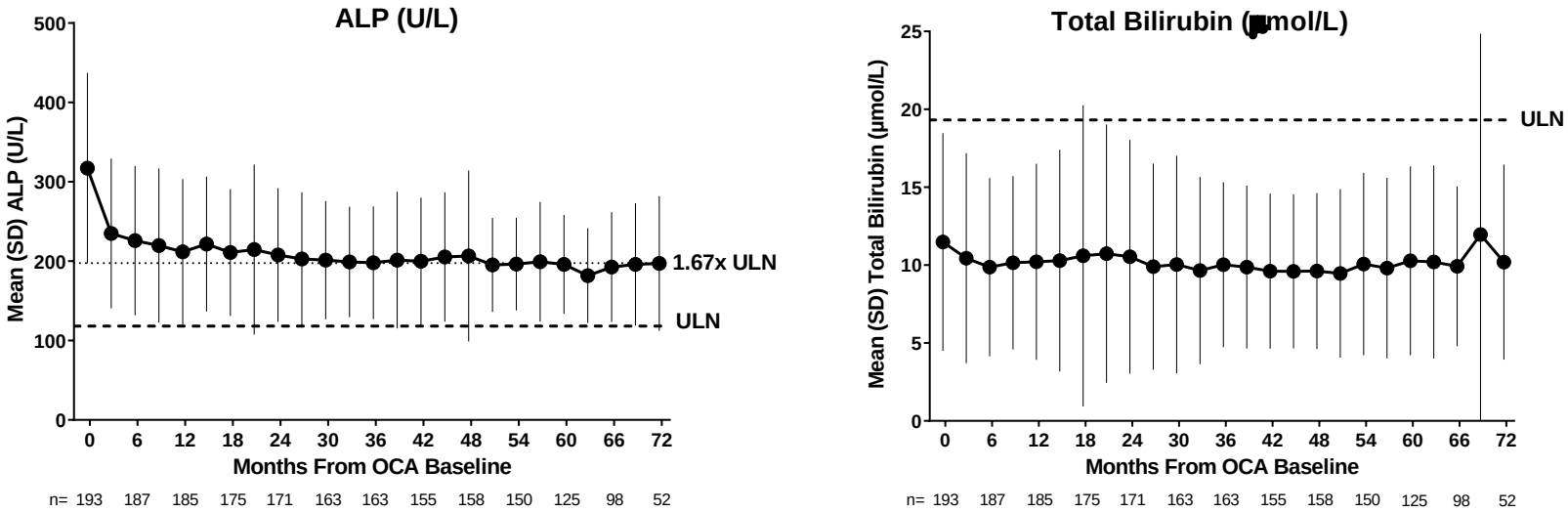
[a]OCA 5-10 mg group: 5 mg OCA for 6 months then titrated to 10 mg OCA if tolerated and ALP ≥1.67x ULN or bilirubin >ULN, or <15% reduction in ALP.

Sustained Reductions in ALP and Bilirubin With OCA Treatment

POISE LTSE

POISE was a pivotal phase-3 12-month randomised controlled trial of OCA in patients with PBC followed by a five year open label extension (LTSE). The primary endpoint was achievement of ALP <1.67 xULN, ALP reduction ≥15% from baseline, and total bilirubin ≤ULN, achieved by 46% of patients in the 5–10-mg group vs. 10% in the placebo group (P<0.001)[1]

Results from the POISE LTSE[2]



ALP = alkaline phosphatase; LTSE = long-term safety extension; OCA = obeticholic acid; SD = standard deviation; ULN = upper limit of normal.

1. Nevens F et al. *N Engl J Med*. 2016;375(7):631–643. 2. Nevens F et al. *Presented at AASLD.* 2019. Boston, MA (Oral LO6).

May 2021 Update to Obeticholic Acid Licenced Dosing – US and Europe

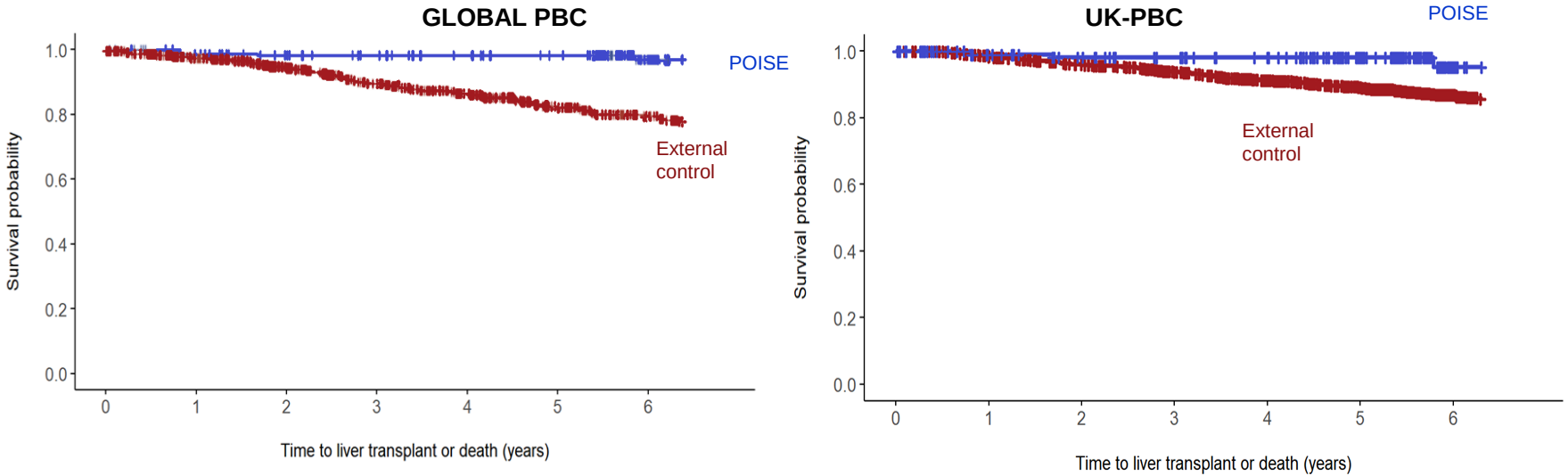
	US PI[1]	EU SmPC[2]
Without cirrhosis	5mg once daily → 10 mg once daily Titration at 3 months	5mg once daily → 10 mg once daily Titration at 6 months
Compensated cirrhosis without CSPH	5mg once daily → 10 mg once daily Titration at 3 months	5mg once daily → 10 mg once daily Titration at 6 months
Compensated cirrhosis with CSPH	**Contraindicated**	5mg once daily → 10 mg once daily Titration at 6 months
Decompensated cirrhosis	**Contraindicated**	5mg once weekly → 5mg twice weekly → 10mg twice weekly

Titration is dependent of patients not achieving adequate biochemical response and not experiencing tolerability issues at the lower dose
CSPH = clinically significant portal hypertension; OCA = OCALIVA (obeticholic acid); PI = prescribing information; SmPC = summary of product characteristics.

1. Ocaliva [Full Prescribing Information]. New York, NY: *Intercept Pharmaceuticals*, Inc.; 2021; 2. Ocaliva (obeticholic acid) *Summary of Product Characteristics.* 2021. Available at https://www.medicines.org.uk/emc/product/2561/smpc. [accessed June 2021].

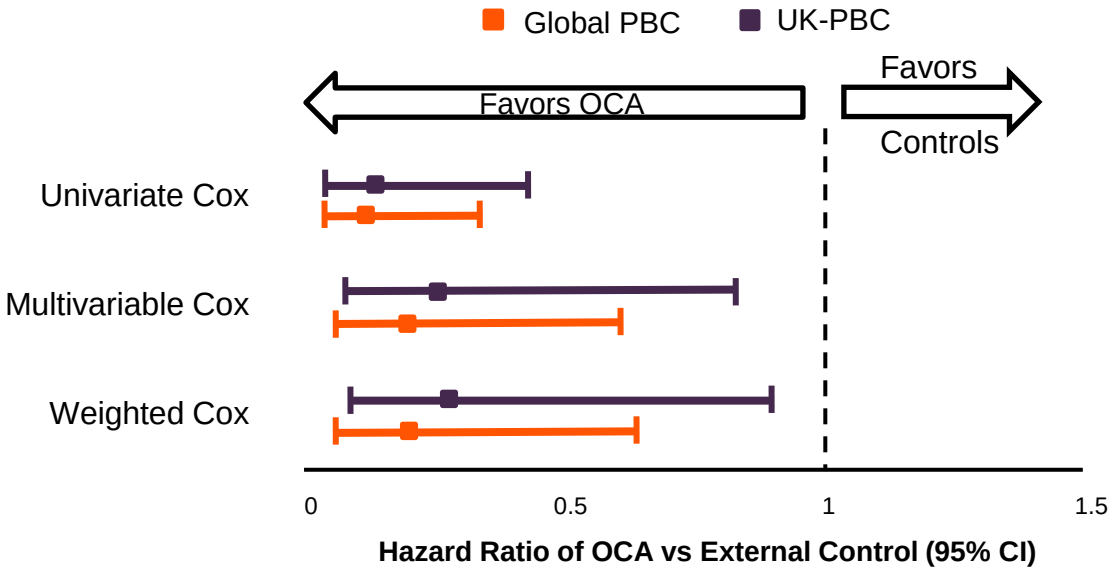
OCA-Treated Trial Patients Demonstrated Improved Transplant-Free Survival

Weighted Kaplan-Meier Plots



Total number of events	POISE n=3	GLOBAL PBC n=146	UK-PBC n=281
Liver transplantation	0	52	119
Death	3	94	162

OCA Associated With Lower Risk for Liver Transplant or Death



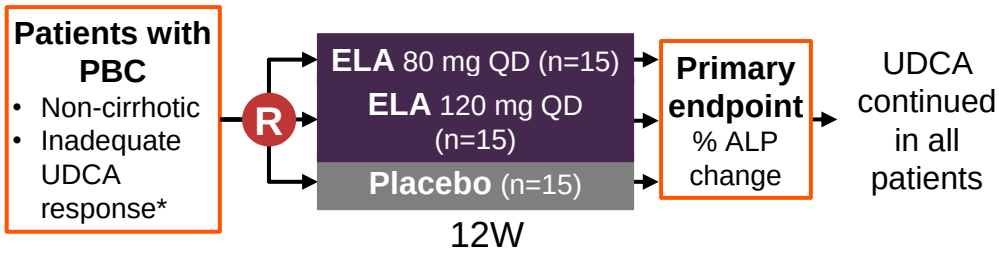
	HR (95%CI)	P value
Univariate Cox	0.14 (0.04-0.42)	<0.001
	0.12 (0.04-0.34)	<0.001
Multivariable Cox	0.24 (0.08-0.76)	0.015
	0.20 (0.06-0.61)	0.005
Weighted Cox	0.28 (0.09-0.91)	0.034
	0.20 (0.06-0.64)	0.007

Elafibranor Demonstrates Favourable Efficacy and Safety in Patients With Primary Biliary Cholangitis and Inadequate Response to UDCA

BACKGROUND & AIMS

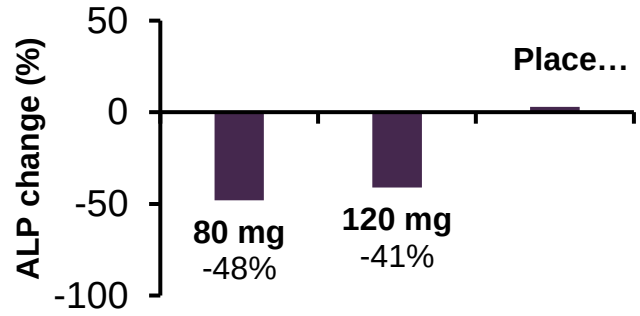
- Up to 40% of UDCA-treated patients have suboptimal response and are at high risk of disease progression
- **Aim:** This phase 2a, double-blind, placebo-controlled study investigated elafibranor (ELA), a dual PPARα/δ agonist, as a new anti-cholestatic treatment for PBC

METHODS



RESULTS

Primary endpoint: ELA demonstrated significant decreases in mean ALP at Week 12



- Highly significant treatment effect vs. placebo (both p<0.001)
  - 80 mg: -52% (95% CI -62.5, -41.5)
  - 120 mg: -44% (95% CI -55.7, -32.1)

*Defined as ALP >1.67x ULN.

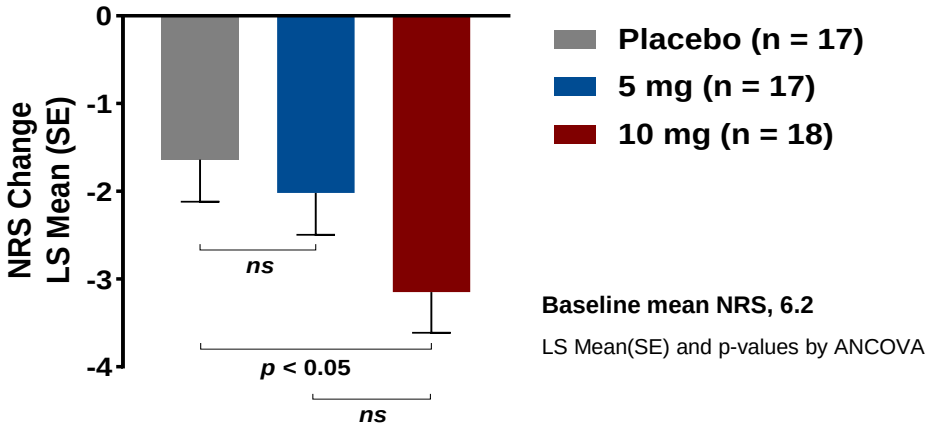
Jörn S et al. *ILC*. 2019; LB-02.

ENHANCE: Change in Pruritus Numerical Rating Scale (NRS) at Month 3

Subjects with Baseline NRS ≥ 4

Proportion of Patients with Relief from Itch*

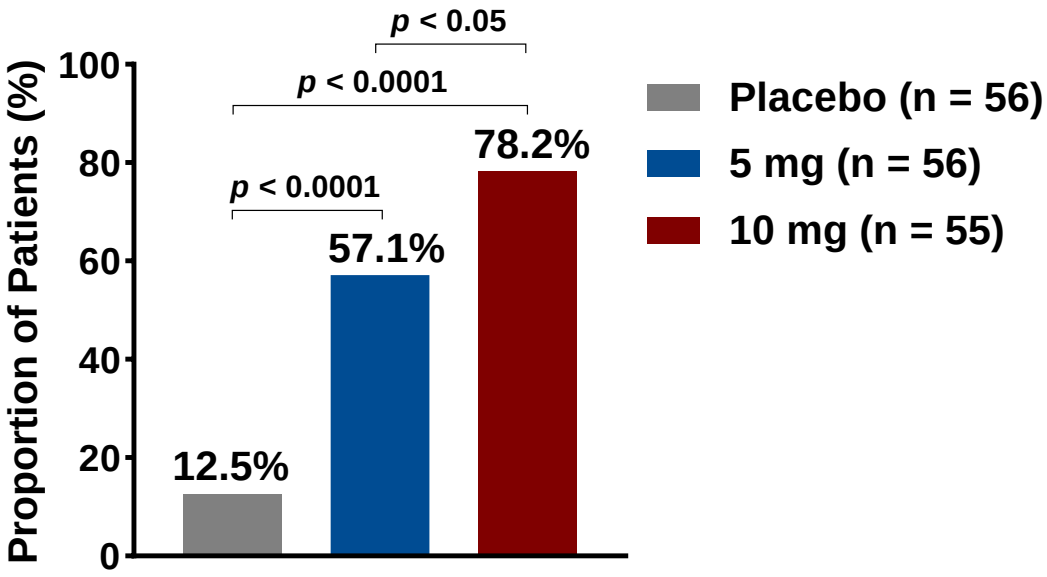
Placebo	Seladelpar 5 mg	Seladelpar 10 mg
6%	18%	39%



*At Month 3, NRS <4 and decrease in NRS ≥4.

ENHANCE: Composite Responder Rate at Month 3

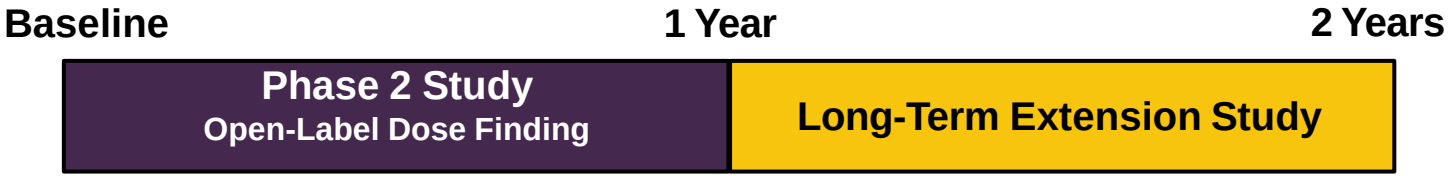
ALP < 1.67 x ULN, ≥ 15% Decrease in ALP and Total Bilirubin ≤ ULN



p-values by Cochran-Mantel-Haenszel (CMH) test.

Long-Term Extension Study

2 Year Treatment with Seladelpar in Patients with PBC



Entry criteria

- Inadequate response or intolerant to UDCA
- ALP ≥ 1.67 x ULN; ALT/AST ≤ 3 x ULN; Total Bilirubin ≤ 2 x ULN

Treatment

- Once daily oral seladelpar at 5 or 10 mg

Objectives

- To evaluate safety and efficacy

Primary efficacy endpoint

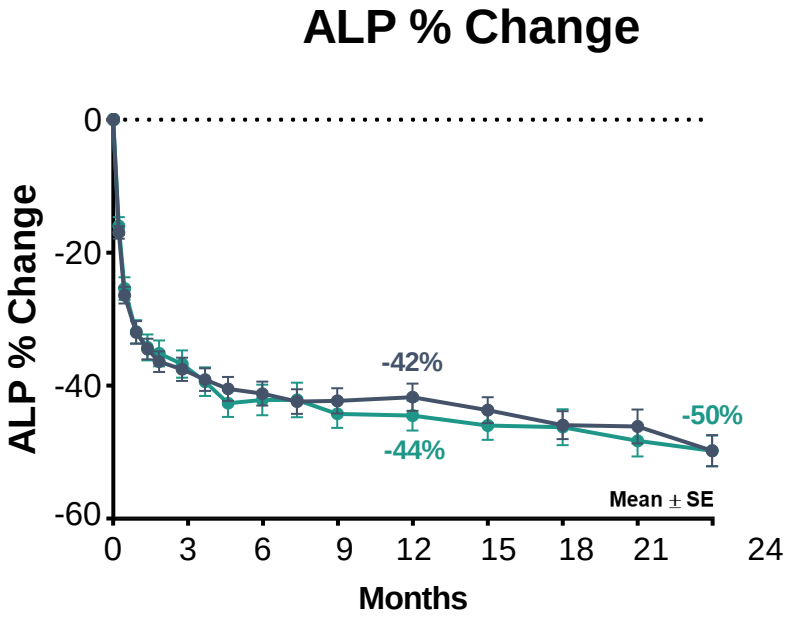
- % Change in ALP from baseline

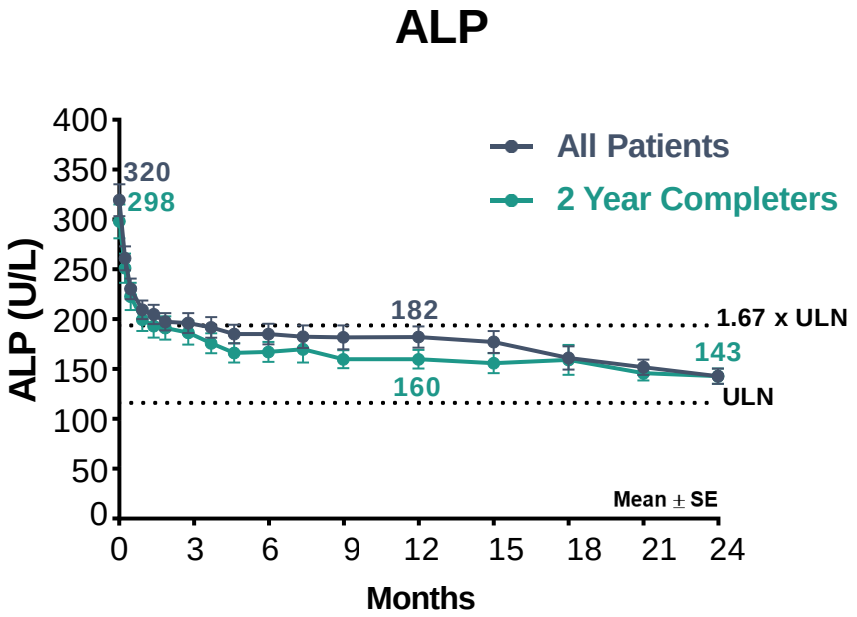
Secondary efficacy endpoints

- Composite of ALP < 1.67 x ULN, ≥ 15% decrease in ALP, and Total Bilirubin ≤ ULN; ALP normalization; biochemical; inflammatory markers

Abstract 106.

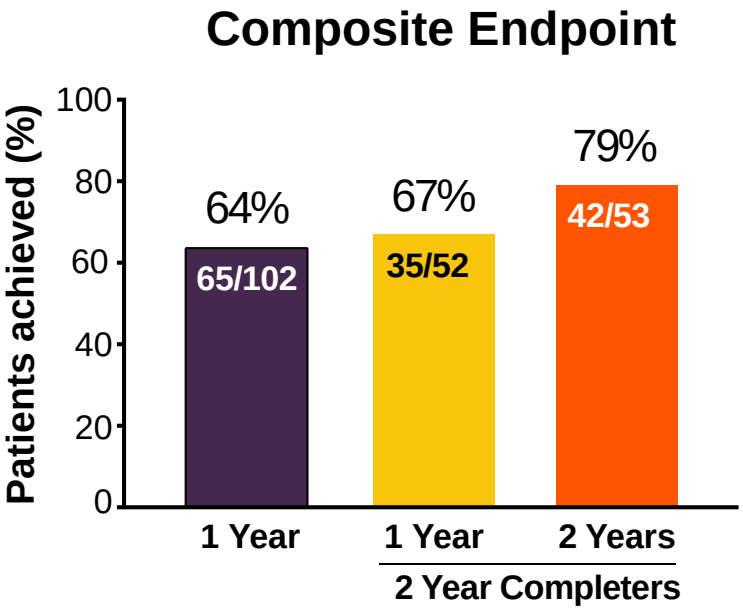
ALP Change Over 2 Years

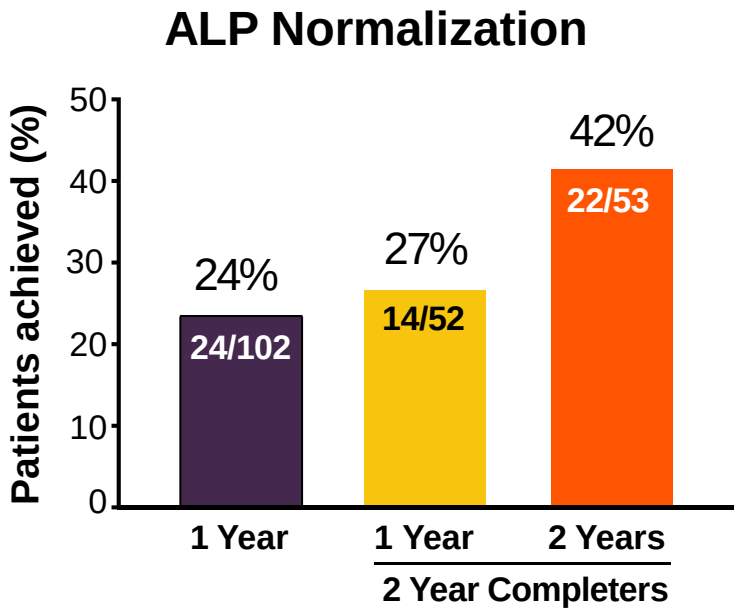




N	M0	M3	M6	M9	M12	M15	M18	M21	M24
All Patients	103	101	102	102	102	99	79	65	53
2 Year Completers	53	52	52	52	52	53	53	53	53

Composite Endpoint and ALP Normalization





Composite Endpoint: ALP < 1.67x ULN, ≥ 15% decrease in ALP, and total bilirubin ≤ ULN

ALP Normalization: ALP ≤ 116 U/L

Adverse Events

Safety Population (All Patients Entering Year 2)

Adverse Events (AE)	Total (N = 103)
Patients with at least 1 AE	99 (96%)
Treatment-related AE	38 (37%)
Treatment-related AE ≥ Grade 3	1 (1%)
AE leading to discontinuation*	3 (3%)
SAE†	21 (20%)
Liver-related SAE	0
Treatment-related SAE	0
AE with outcome of death‡	1 (1%)
Treatment-related AE occurring ≥ 5%	**Total (N = 103)**
Nausea	8 (8%)
Pruritus	8 (8%)
Diarrhea	5 (5%)

Any AE ≥ 15%	Total (N = 103)
Pruritus	26 (25%)
Nausea	22 (21%)
Fatigue	20 (19%)
Urinary tract infection	19 (18%)
Arthralgia	18 (17%)
Diarrhea	17 (17%)
Nasopharyngitis	15 (15%)

* 2 patients with grade 2 increased liver function test; 1 patient with malignant neoplasm
† 26 SAE in 21 patients (20 preferred terms)
‡ Unrelated TEAE resulting in death occurred approximately 7 months after the last dose in the seladelpar 10 mg group due to of a malignant neoplasm of unknown primary location

Summary

- Treatment goals in PBC are evolving
- “Complete” biochemical response criteria are being re-defined
- GGT may be added as another biochemical variable
- Possible double and triple therapies in the future
- Fatigue and pruritus may become alternate regulatory targets
- Historical controls being proposed for standard approval