Long-Term Safety and Efficacy of Seladelpar in Patients With Primary Biliary Cholangitis (PBC): 2-Year Results From a Long-Term Study

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CYMABAY THERAPEUTICS

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Disclosure

Marlyn J. Mayo, MD

I disclose the following financial relationship(s) with a commercial interest:

- CymaBay Therapeutics: clinical trial agreement, consulting
- Target PharmaSolutions: clinical trial agreement, consulting
- Mallinckrodt: clinical trial agreement, consulting
- Mirum: clinical trial agreement, consulting
- Intercept: clinical trial agreement
- Genfit: clinical trial agreement

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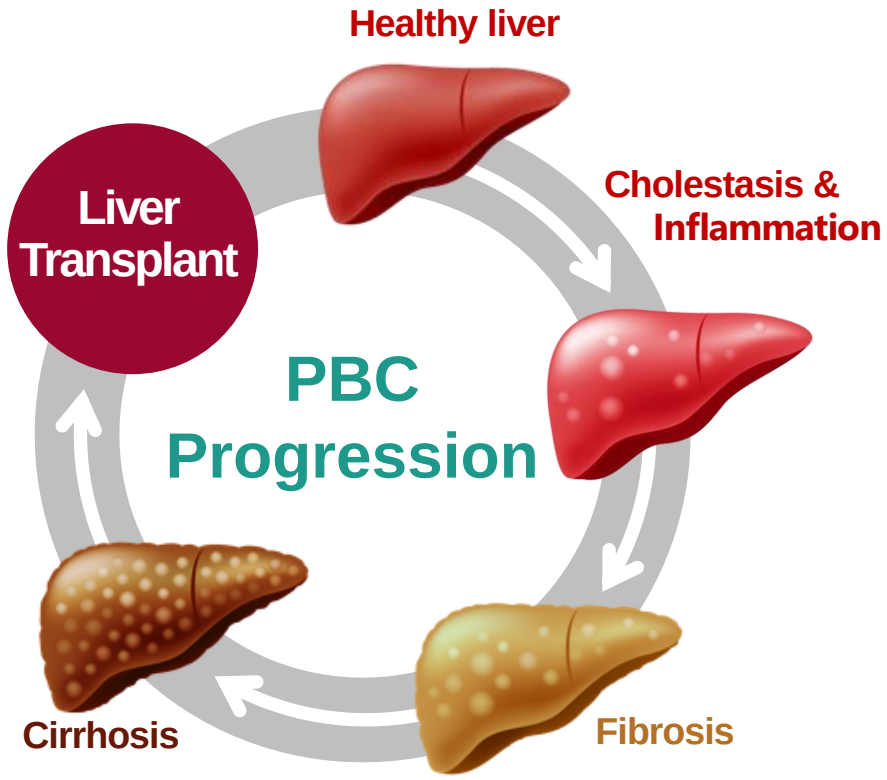
Primary Biliary Cholangitis (PBC)

- Chronic, progressive, autoimmune, cholestatic liver disease
- Affects 1 in 1,000 women over 40 (~130k U.S. patients)
- Impairment of bile flow, portal inflammation and destruction of bile ducts
- Elevated serum markers of cholestasis including alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT) and total bilirubin (TB)
- Clinical symptoms of fatigue and pruritus (itching)

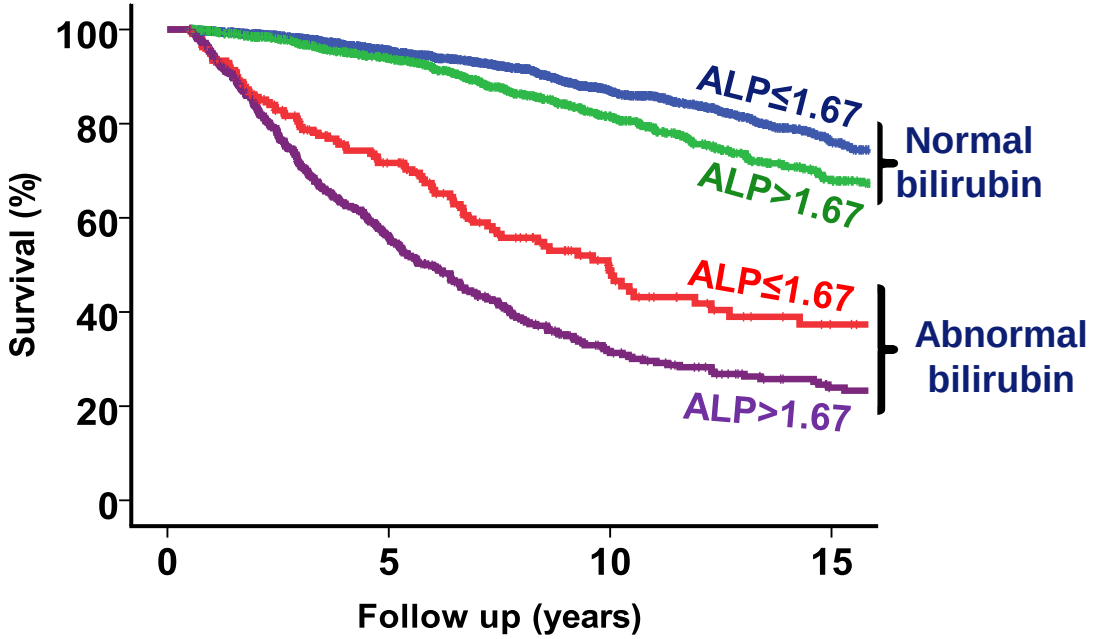


Clinical surrogates for slowing disease progression

ALP ≤ 1.67 x Upper Limit of Normal (ULN) and Normal Total Bilirubin

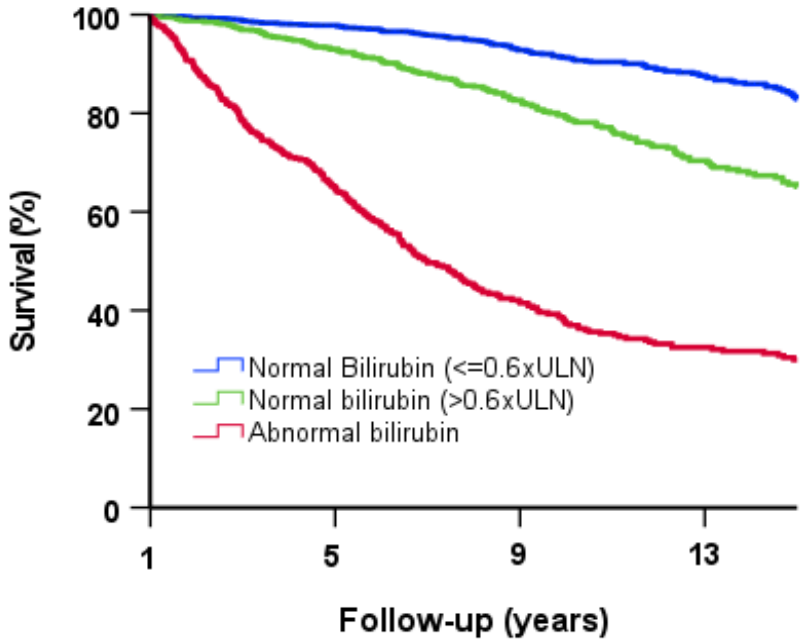
ALP and Bilirubin as Response and Prognostic Risk Factors for PBC

Stratification of ALP using 1.67 x ULN and bilirubin using 1 x ULN



Adapted from Lammers W, *et al.* AASLD 2014 (oral presentation) and Lammers *et al.*, *Gastroenterology* 2014; Courtesy of B. Hansen

Stratification of bilirubin using 0.6x ULN and 1 x ULN



No. at risk

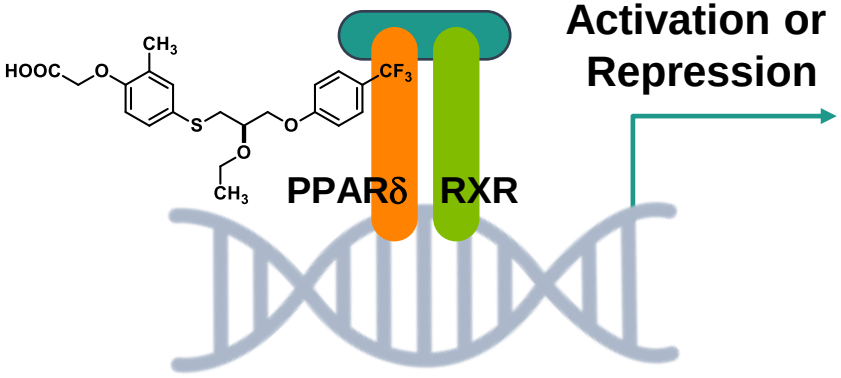
a	1718	1256	737	385
b	837	614	400	209
c	529	285	134	82

Adapted from Perez *et al.*, Am J Gastroenterol 2020; 115:1066-1074; Courtesy of F. Murillo-Perez and B. Hansen

Seladelpar

Once-Daily Oral Selective PPARδ Agonist for Liver Diseases

Human PPARδ EC_{50} = 2 nM



Decrease Bile Acids

- ↓ Cholesterol synthesis/absorption
- ↓ Bile acid synthesis (C4)
- ↑ Bile acid transport

Anti-Inflammatory

- ↓ NFκB-dependent gene activation
- ↓ Inflammatory cytokines
- ↓ hs-C-Reactive Protein

Anti-Fibrotic

- ↓ Profibrotic genes
- ↓ Stellate cell activation
- ↓ Collagen synthesis/deposition

Increase Lipid Metabolism

- ↓ Cholesterol/LDL-C
- ↑ Fatty acid oxidation

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

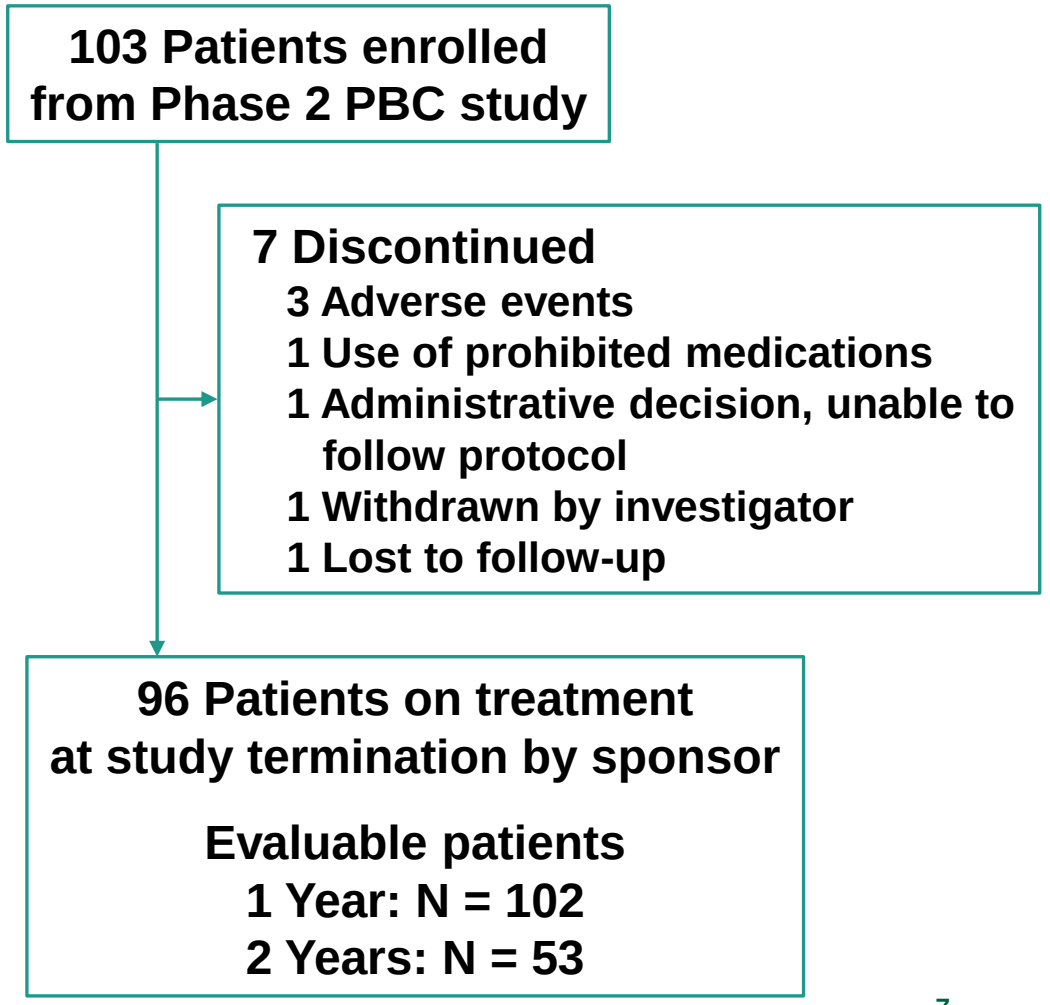
- Composite of ALP < 1.67 x ULN, ≥ 15% decrease in ALP, and Total Bilirubin ≤ ULN; ALP normalization; biochemical; inflammatory markers

Demographics and Baseline Characteristics

Parameters	Total (N = 103) Mean (SD)
Female, n (%)	97 (94.2)
Age, years	57 (9.1)
Age at PBC Diagnosis, years	48 (8.5)
AMA Positive, n (%)	93 (90.3%)
Duration of PBC, years	10 (6.5)
Concomitant UDCA, n (%)	96 (93.2)
UDCA Dose, mg/kg/day	15 (3.6)
ALP (37-116 U/L)*	320 (164.7)
ALT (6-41 U/L)	48 (23.6)
AST (9-34 U/L)	44 (18.6)
GGT (7-38 U/L)	244 (171.3)
Total Bilirubin (0.1-1.1 mg/dL)	0.8 (0.34)
Platelet Count (140-400x10^9/L)	239 (80.5)
Albumin (3.5-5.5 g/dL)	4.1 (0.34)
LDL-C (50-130 mg/dL)	143 (42.7)

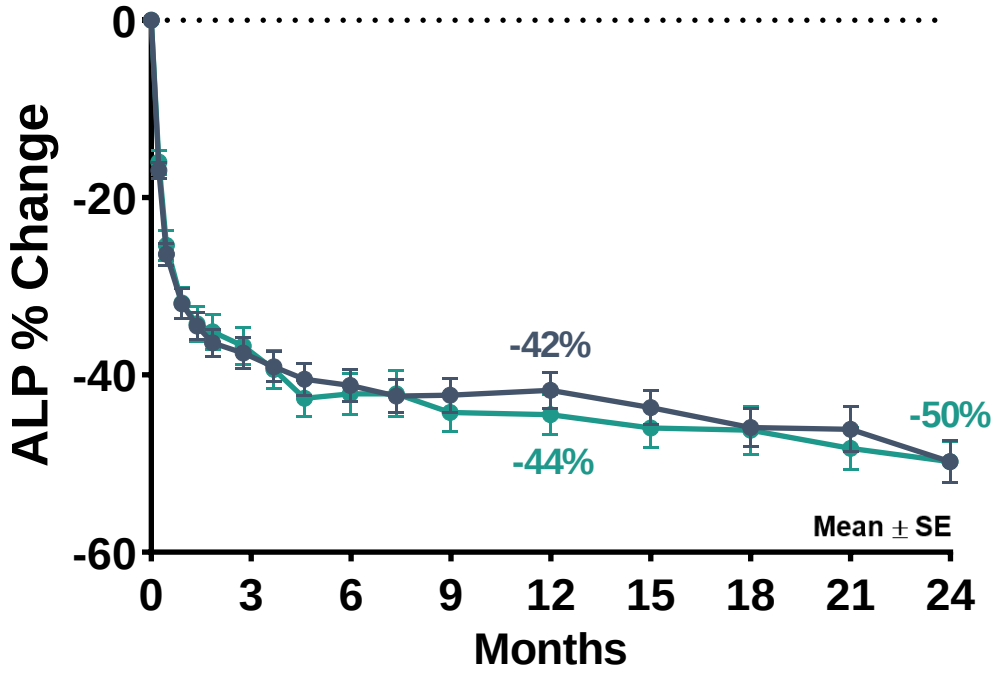
* Normal range

Patient Disposition

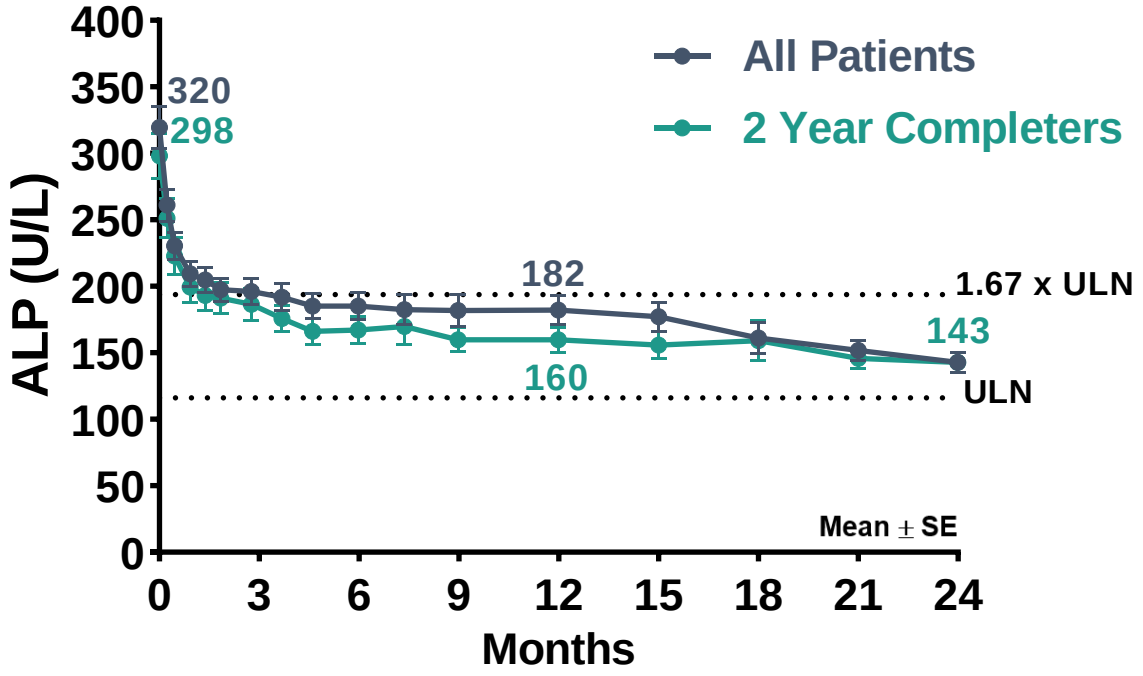


ALP Change Over 2 Years

ALP % Change

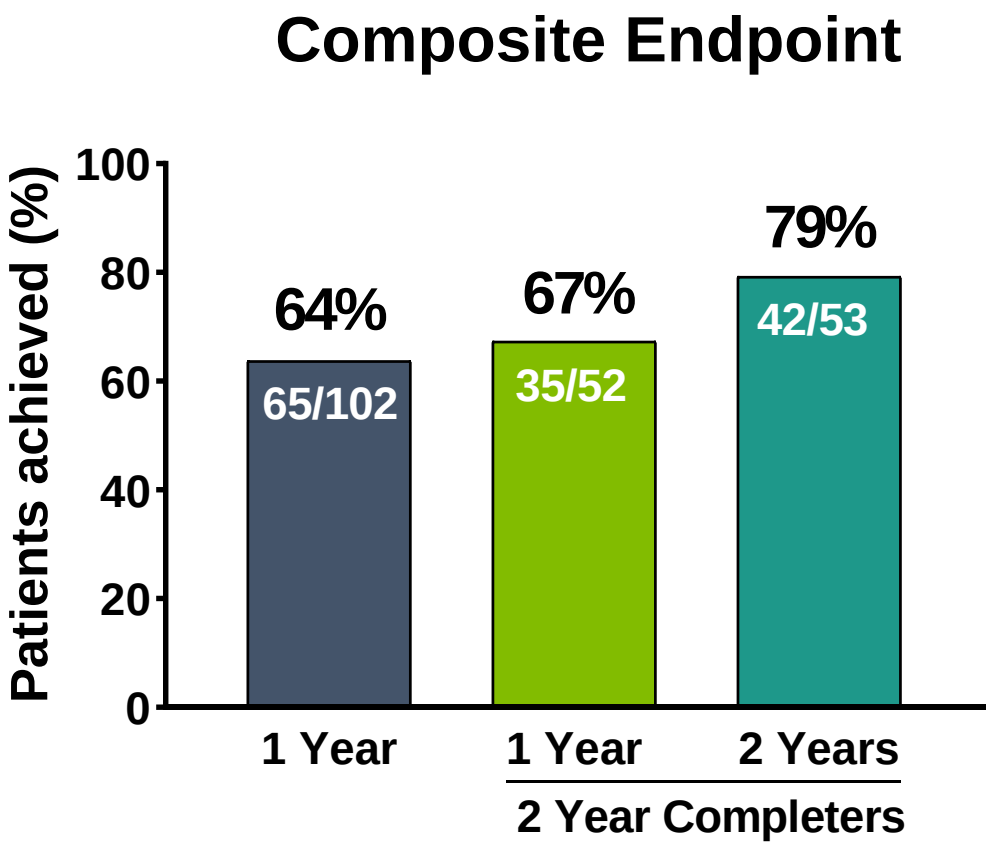


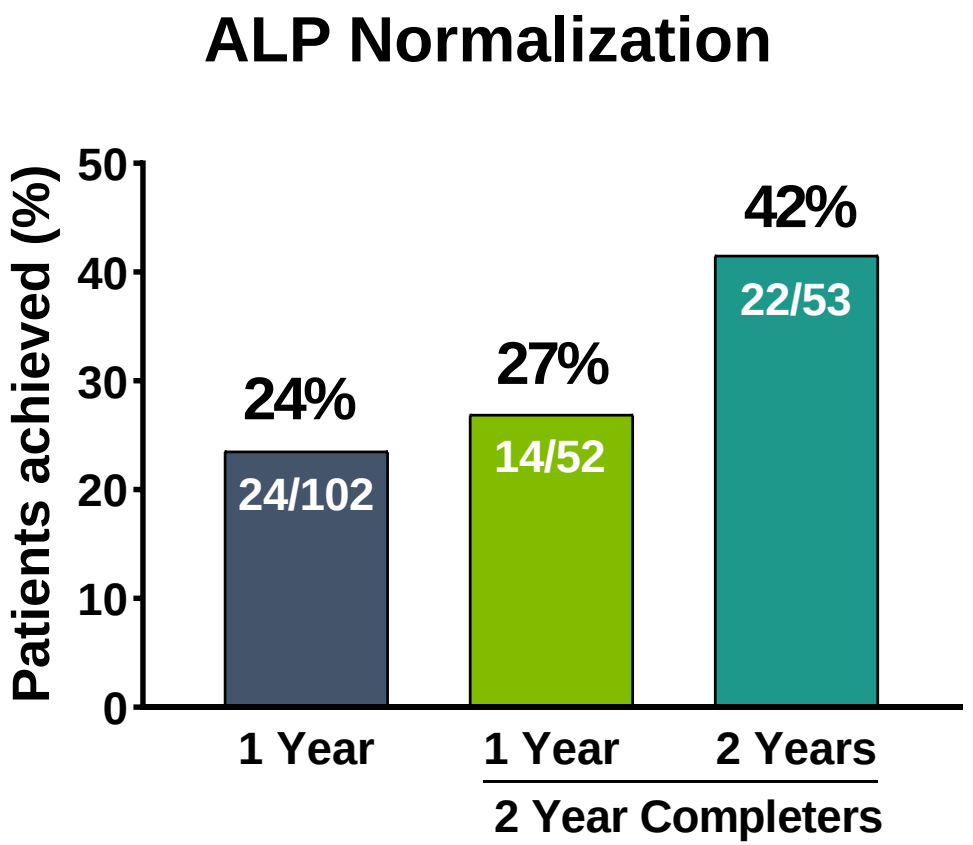
ALP



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





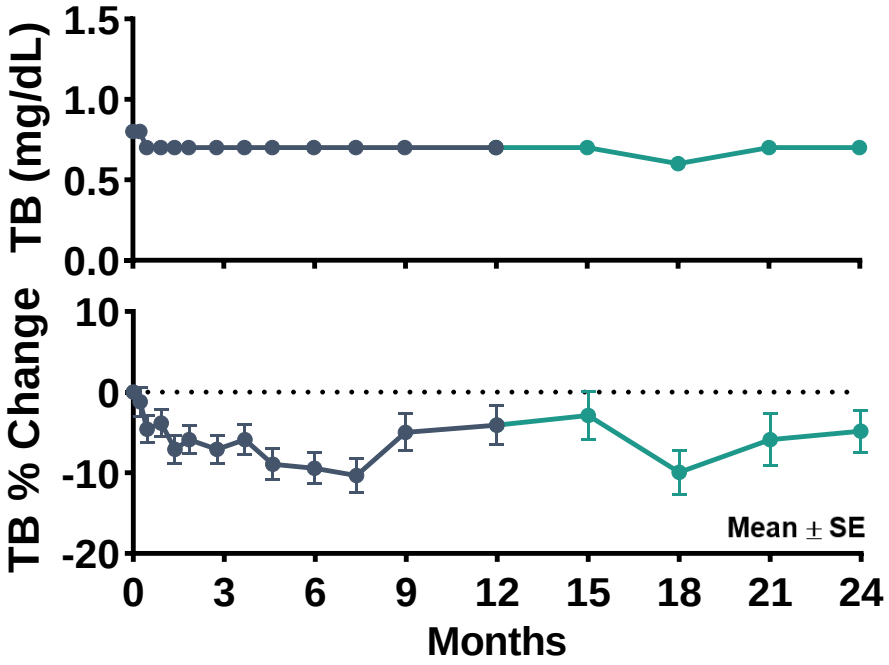
Composite Endpoint: ALP < 1.67x ULN, ≥ 15% decrease in ALP, and total bilirubin ≤ ULN

ALP Normalization: ALP ≤ 116 U/L

Total Bilirubin Change Over 2 Years

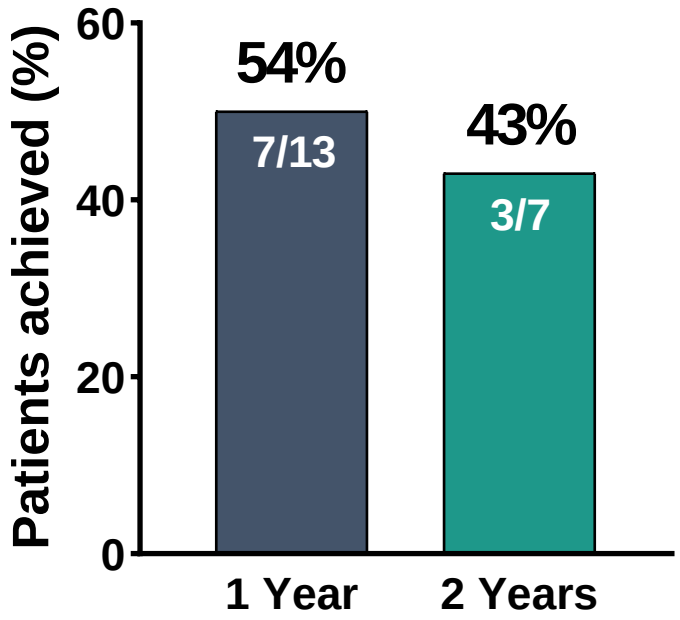
Total Bilirubin (TB)

Observed & % Change



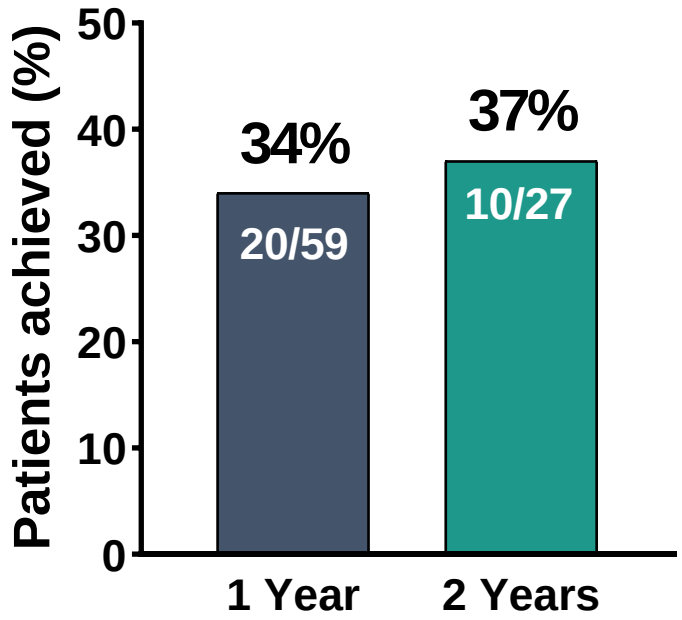
TB ≤ 1 x ULN

In patients with baseline TB > 1 x ULN



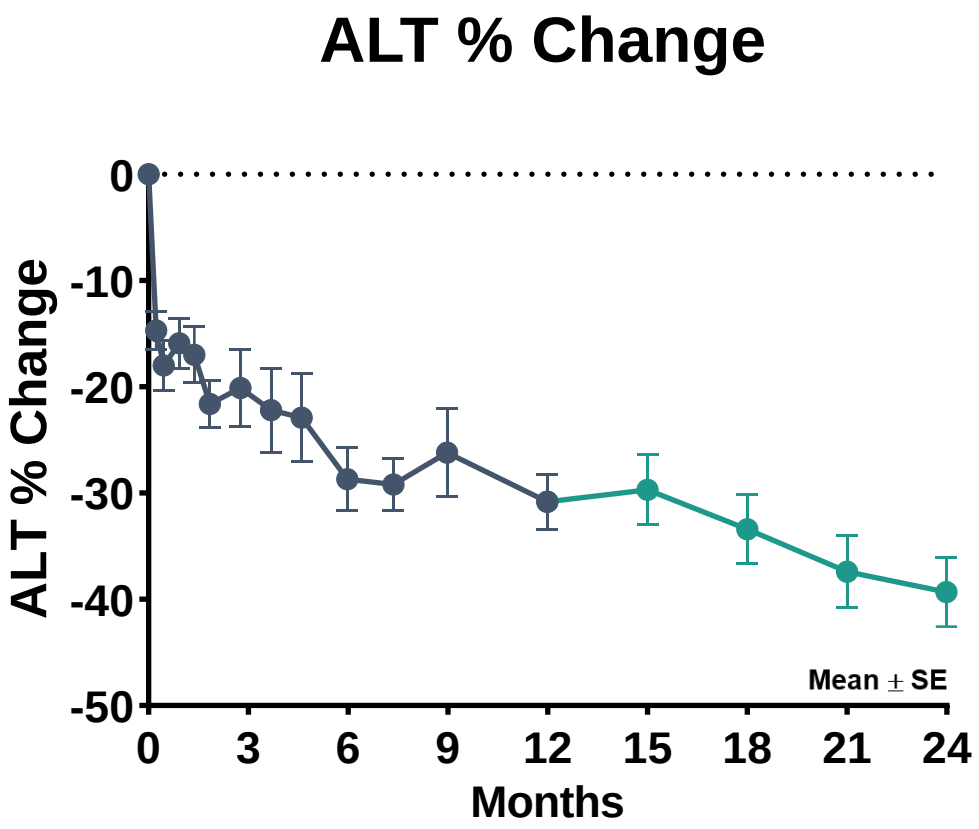
TB ≤ 0.6 x ULN

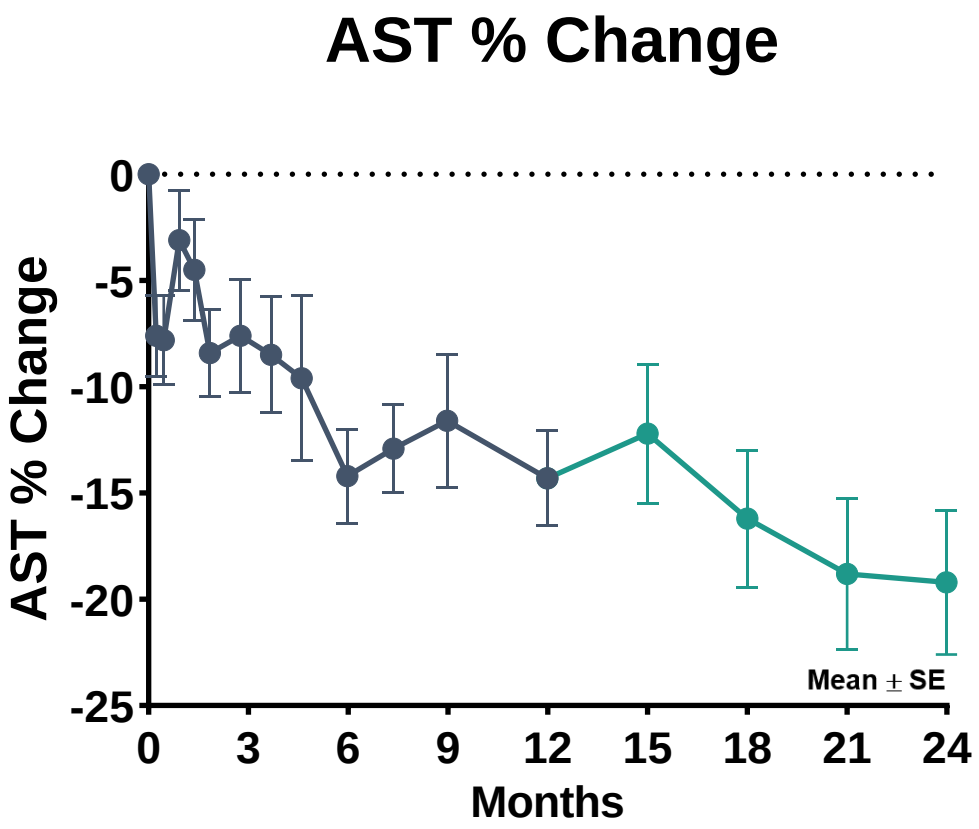
In patients with baseline TB > 0.6 x ULN



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

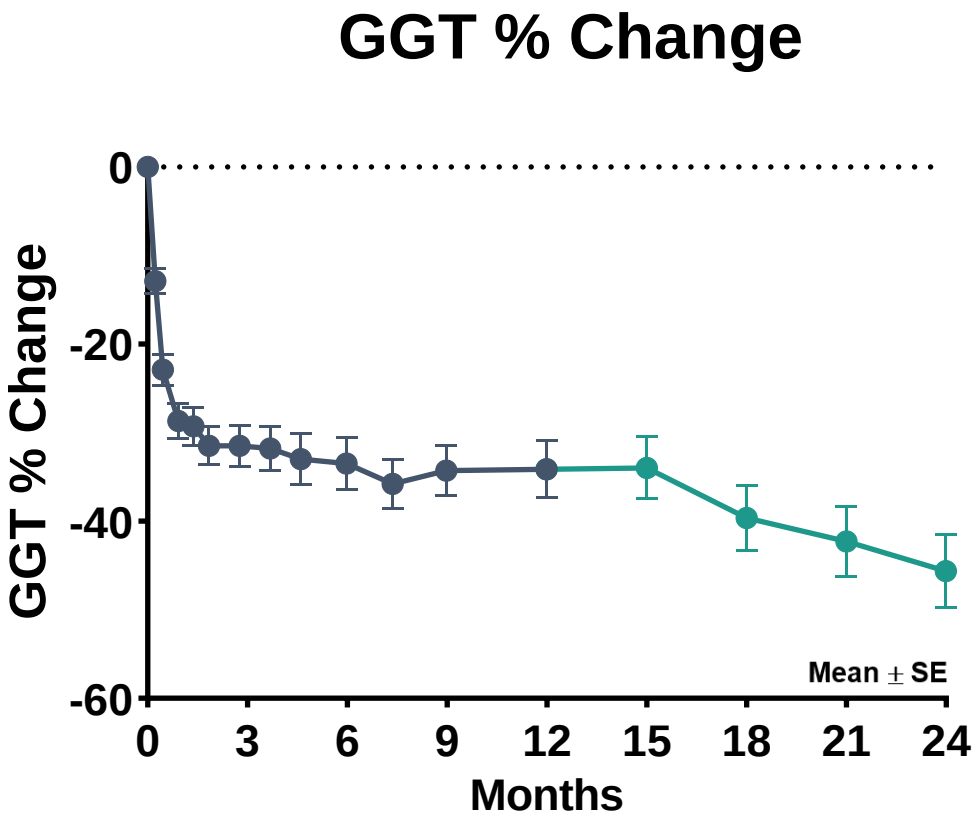
ALT and AST % Change Over 2 Years

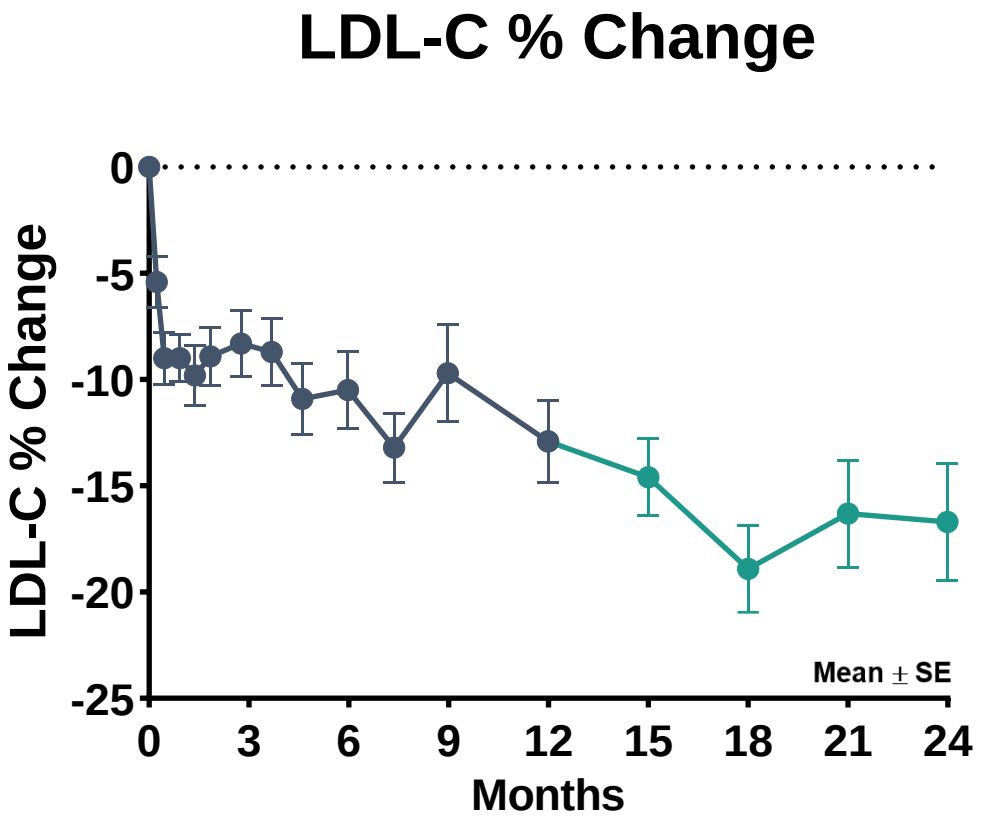




All Patients	M0	M3	M6	M9	M12	M15	M18	M21	M24
N	103	101	102	102	102	99	79	65	53

GGT and LDL-C % Change Over 2 Years





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

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

Conclusions

Long-term treatment with seladelpar for 2 years

- **Appeared safe and well tolerated**
- **Reductions in biomarkers of cholestasis and hepatocellular injury continued to improve throughout the second year of treatment**
- **Nearly 8 out 10 patients achieved the composite endpoint**
- **Over 40% of patients normalized ALP**

A 52-week Phase 3 global study RESPONSE is currently enrolling PBC patients

Seladelpar Long-Term Study Investigators

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