AASLD THE LIVER MEETING® 2018 SAN FRANCISCO NOVEMBER 9-13

Efficacy and Safety of Seladelpar in Primary Biliary Cholangitis

52-Week Analysis of a Dose-Ranging Phase 2 Study

Bowlus CL, Neff G, Aspinall R, Galambos M, Goel A, Hirschfield G, Kremer AE, Mayo MJ, Swain M, Borg B, Dörffel Y, Gordon S, Harrison S, Jones D, Thuluvath P, Levy C, Sheridan D, Stanca C, Bacon B, Berg C, Hassanein T, Odin J, Shiffman M, Thorburn D, Vierling J, Bernstein D, Buggisch P, Corless L, Landis C, Peyton A, Shah H, Wörns M-A, Gitlin N, Steinberg S, Bergheanu S, Amato G, Choi, Y-J, Rosenbusch S, Varga M, McWherter C, Boudes P

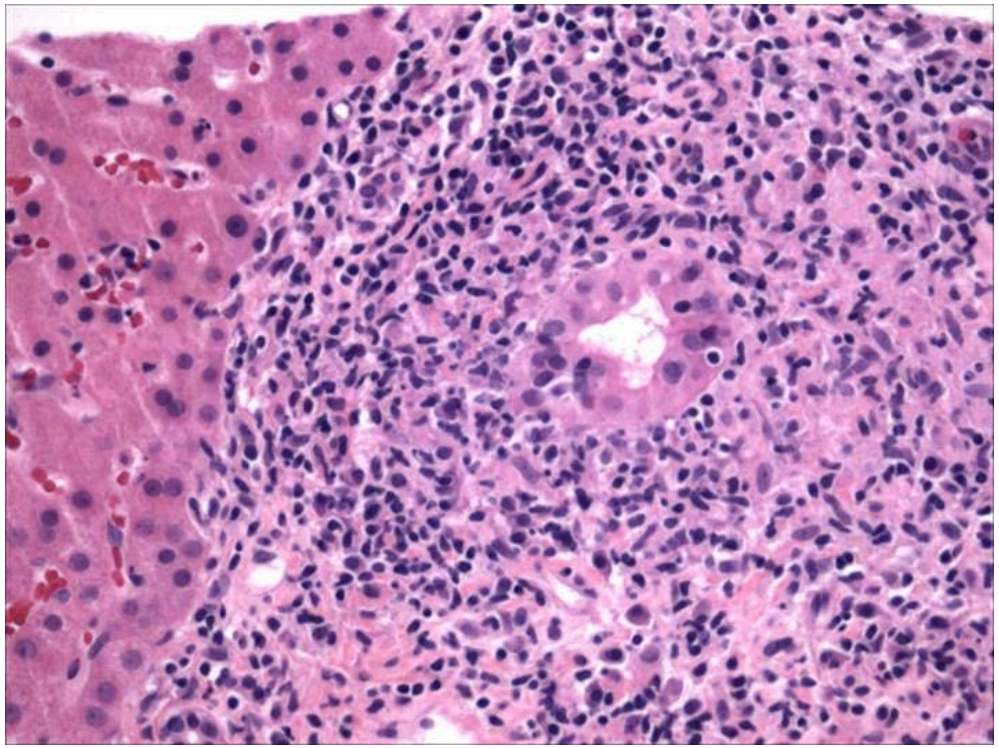
CYMABAY THERAPEUTICS

AASLD AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

Primary Biliary Cholangitis (PBC)

A Progressive, Debilitating Liver Disease

- Most common autoimmune liver disease[1]
  - 1 in 1000 women over the age of 40 are estimated to have PBC[2]
- Inflammation and destruction of the biliary epithelial cells of intrahepatic bile ducts
- Chronic, slowly progressive, cholestatic liver disease[3]
- Ultimately causes cirrhosis[3]



1. Hirschfield GM. *Best Pract Res Clin Gastroenterol*. 2011;25:701-712.
2. Primary Biliary Cholangitis. NORD. https://rarediseases.org/rare-diseases/primary-biliary-cholangitis/.Accessed October 24, 2018.
3. Hohenester S, et al. *Semin Immunopathol*. 2009;31:283-307.

Current Licensed Therapies for PBC

Limited Treatment Alternatives

Ursodeoxycholic Acid (UDCA)
1st Line

- ▲ First-line therapy for PBC
- ▼ ~40% inadequate responders: AP > 1.67 x ULN
- ▼ Additional 5% are intolerant to therapy

Obeticholic Acid (Ocaliva®)
2nd Line

- ▲ Combination therapy for UDCA-inadequate responders
- ▲ Monotherapy for UDCA-intolerant patients
- ▲ Established AP/bilirubin as biomarkers for conditional approval
- ▼ ~50% inadequate responders
- ▼ Can cause or worsen pruritus

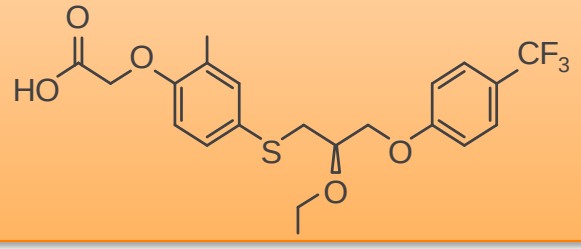
Significant need remains for (1) improved efficacy and (2) better tolerability

AP, alkaline phosphatase.

Invernizzi P, et al. *Dig Liver Dis*. 2017;49(8)841-846.

Seladelpar

Once-Daily Oral PPARδ Agonist for Inflammatory Liver Diseases



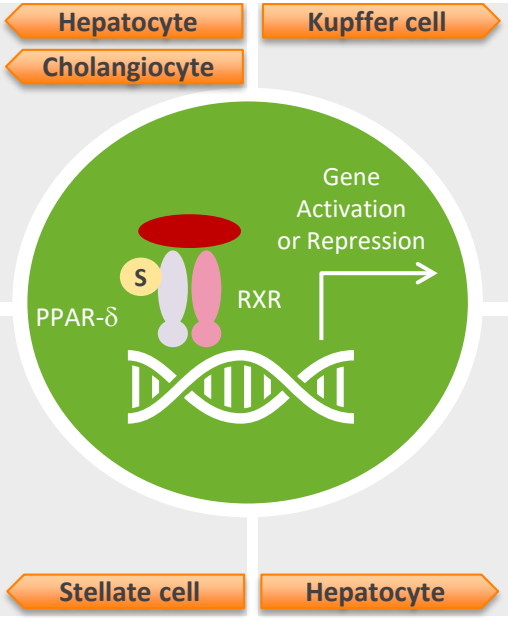
Human PPAR-δ EC_{50}=2 nM
600-fold selective over PPAR-α
Inactive against PPAR-γ

Bile Acid Homeostasis

- ↓ Cholesterol synthesis
- ↓ Bile acid synthesis (C4)
- ↑ Transport

Fibrosis

- ↓ Connective tissue growth factor (CTGF)
- ↓ Stellate cell activation
- ↓ Collagen deposition



Inflammation

- ↓ NFκB-dependent gene activation
- ↓ Inflammatory cytokines
- ↓ hs-C-reactive protein (CRP)

Metabolic Benefits

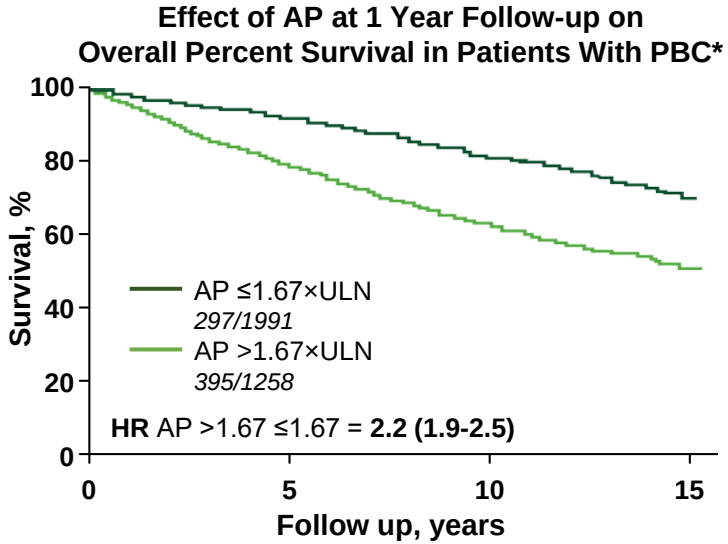
- ↓ LDL-C
- ↓ Cholesterol
- ↓ Lipids and increase in insulin sensitivity

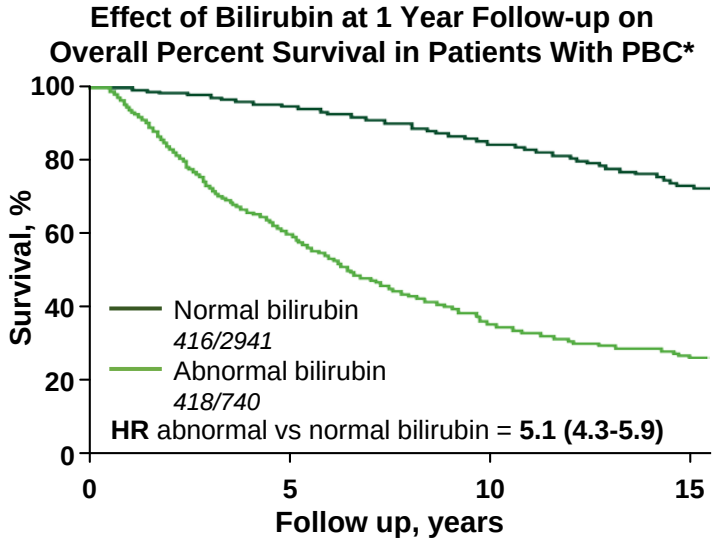
CymaBay, Data on File 2018.

Seladelpar Phase 2 Study in PBC

Objective

- To evaluate the safety and efficacy of daily seladelpar treatment for up to 52 weeks from an ongoing open-label phase 2 study in PBC (NCT02955602)
- As of July 2018, results presented for 34 patients completing 52 weeks of treatment
- The 52 week time-point with a composite of AP and bilirubin as surrogates was used for regulatory approval of obeticholic acid

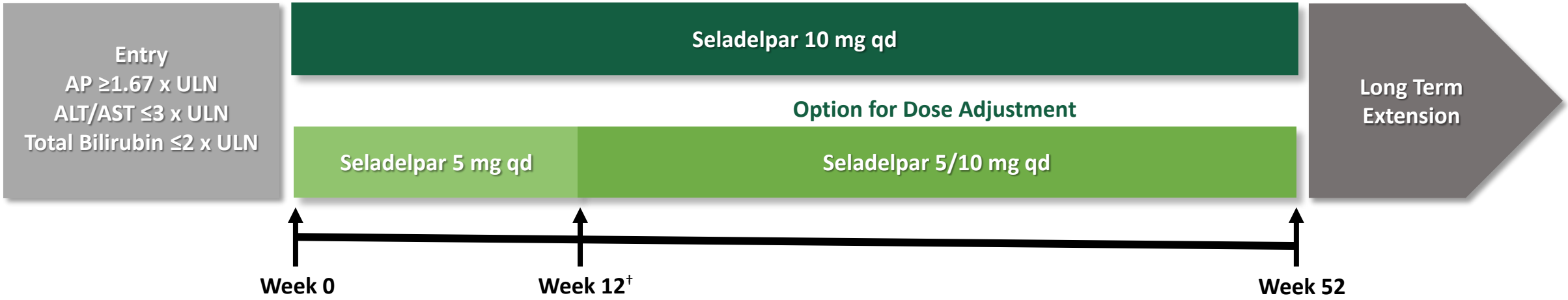




*Global PBC study group

Study Design and Eligibility Criteria

Open Label, Dose Ranging, Stable UDCA Dose or Intolerant to UDCA*



Primary End Point	• AP % change from baseline
Secondary End Points	• Responder analysis defined as a composite of: • AP < 1.67 x ULN, ≥ 15% decrease in AP, total bilirubin ≤ ULN • AP normalization • Changes in liver, metabolic, and inflammatory markers • Pruritus visual analogue scale (VAS)

*UDCA therapy for prior 12 months. †At week 12 a dose adjustment in the 5/10 mg group was made based on patient response and tolerability.
CymaBay, Data on File 2018.

Seladelpar Phase 2 Study in PBC

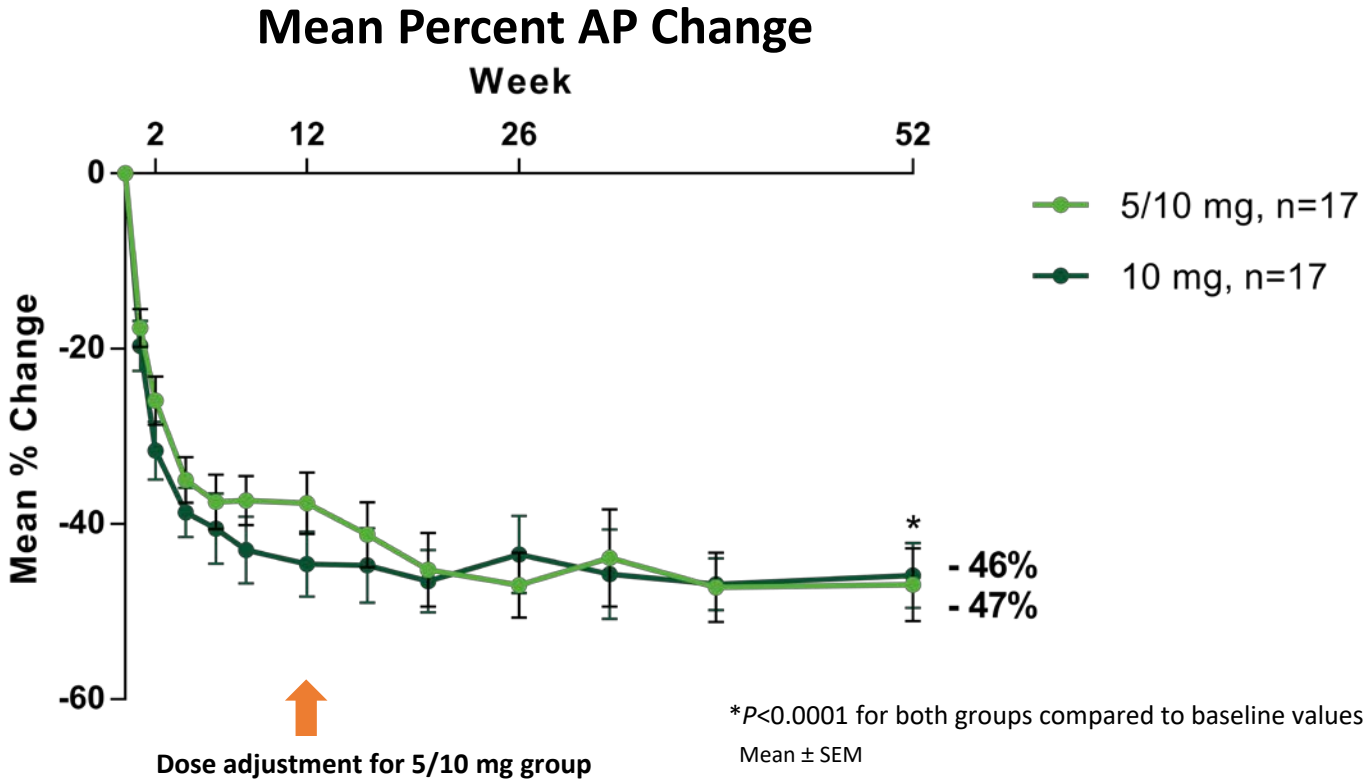
Baseline Demographics of mITT Population

Parameters Mean (SD)	(Reference Range)	Seladelpar 5/10 mg (n=17)	Seladelpar 10 mg (n=17)
Age, years		49 (5)	48 (11)
Female/male		17/0	16/1
History of Pruritus, n (%)		11 (65)	14 (82)
Pruritus VAS	(0-100)	19 (22)	37 (31)
AP	(37-116 U/L)	351 (166)	279 (74)
ALT	(6-41 U/L)	41 (17)	52 (25)
Total bilirubin*	(0.10-1.10 mg/dL)	0.56 [0.50, 0.70]	0.75 [0.57, 1.14]
UDCA Dose, mg/kg/day		15 (4)	17 (3)

*Median [Quartiles: 25, 75]. mITT, modified intention to treat; VAS, visual analogue scale.
CymaBay, Data on File 2018.

Seladelpar Phase 2 Study in PBC

Rapid and Sustained Activity Through Week 52



*P<0.0001 for both groups compared to baseline values

Mean ± SEM

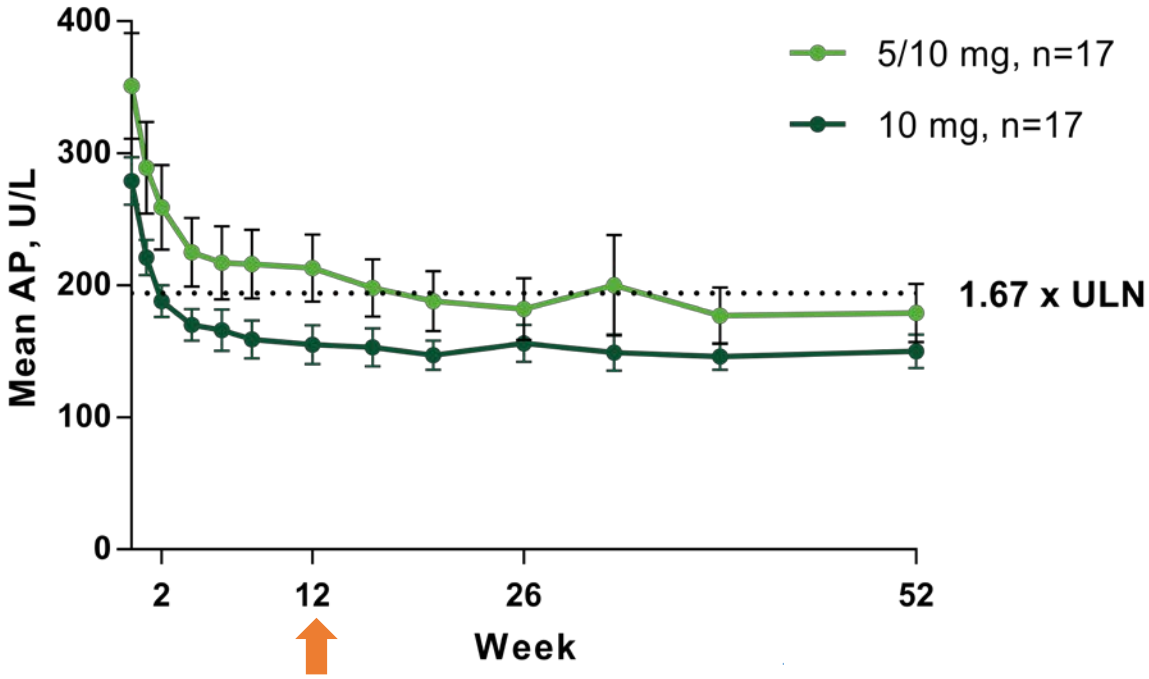
Decreases in AP >45% observed at 5/10 mg and 10 mg

CymaBay, Data on File 2018.

Seladelpar Phase 2 Study in PBC

Meaningful and Sustained Activity Through Week 52

Mean AP from Baseline to Week 52



Mean ± SEM

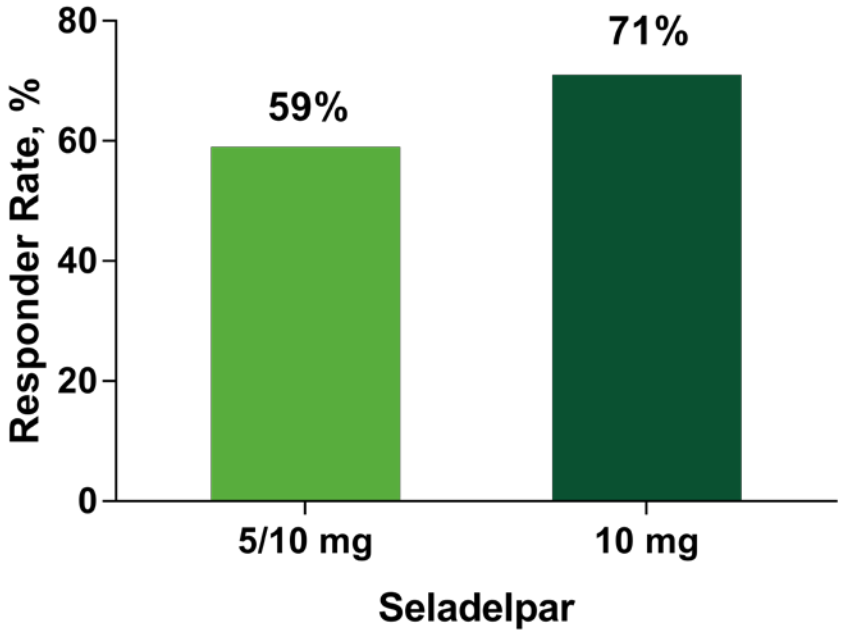
Substantial improvement with AP < 1.67 x ULN

CymaBay, Data on File 2018.

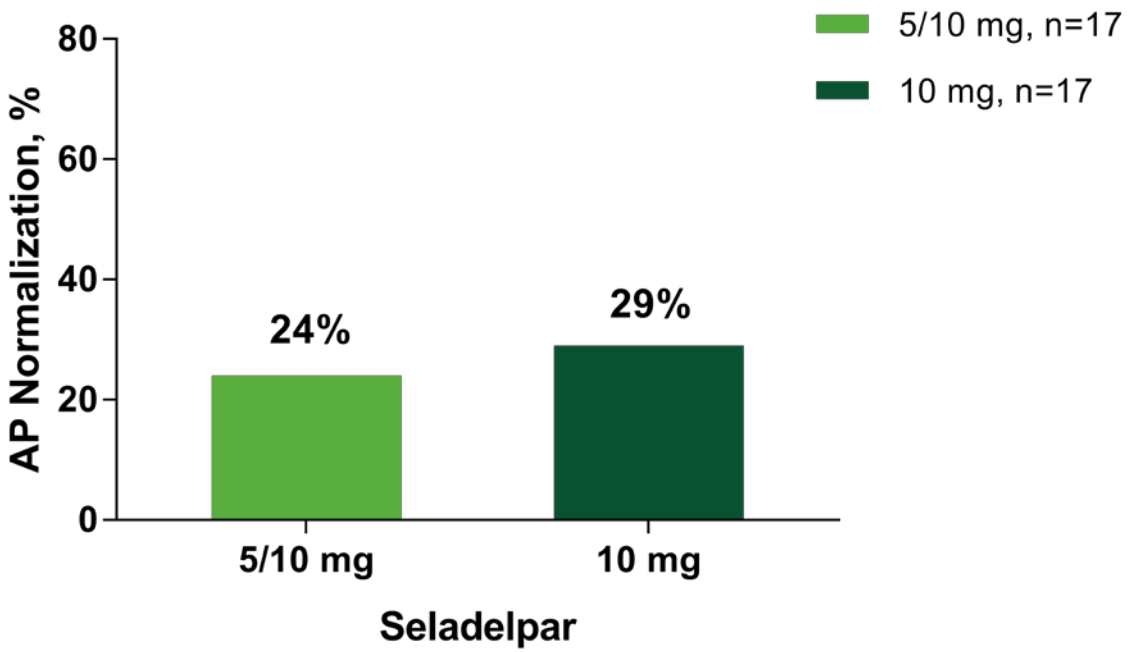
Seladelpar Phase 2 Study in PBC

Responder Analysis at Week 52

Composite Responder Rate



AP Normalization



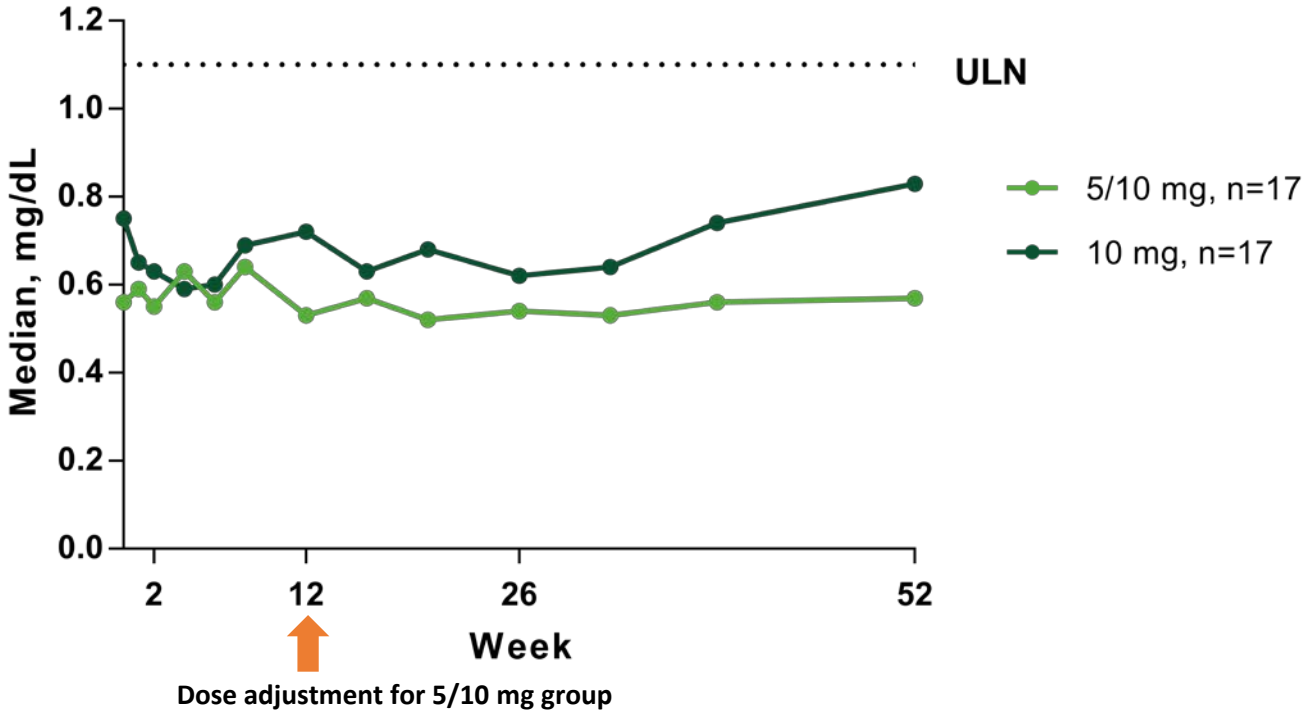
Up to 71% of patients achieved the composite efficacy end point

CymaBay, Data on File 2018.

Seladelpar Phase 2 Study in PBC

Stable Total Bilirubin Levels Through Week 52

Median Total Bilirubin

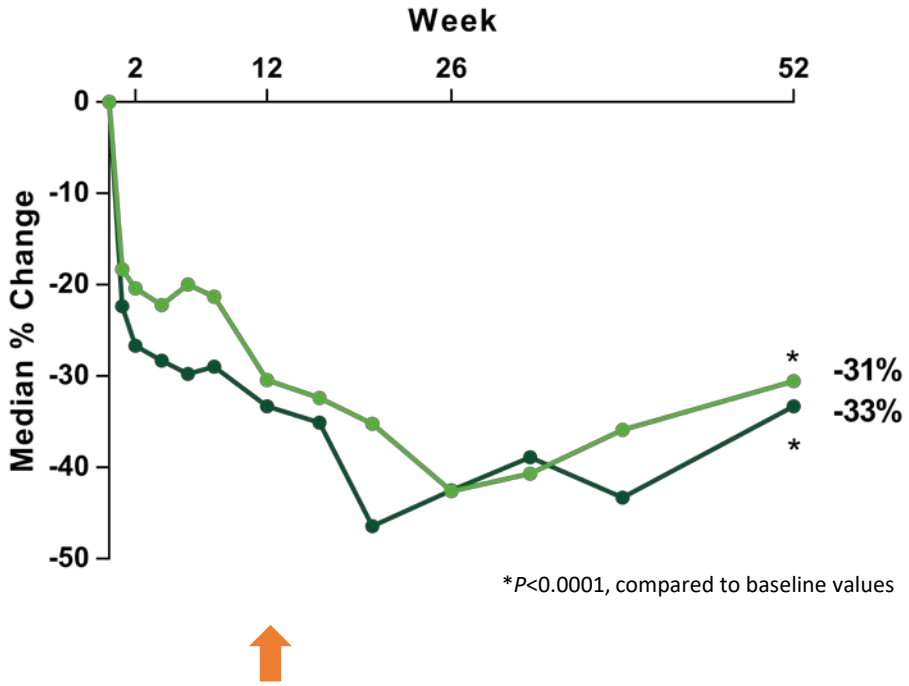


Median total bilirubin remains normal with 5/10 mg and 10 mg

Seladelpar Phase 2 Study in PBC

Significant Decreases in Transaminase Through Week 52

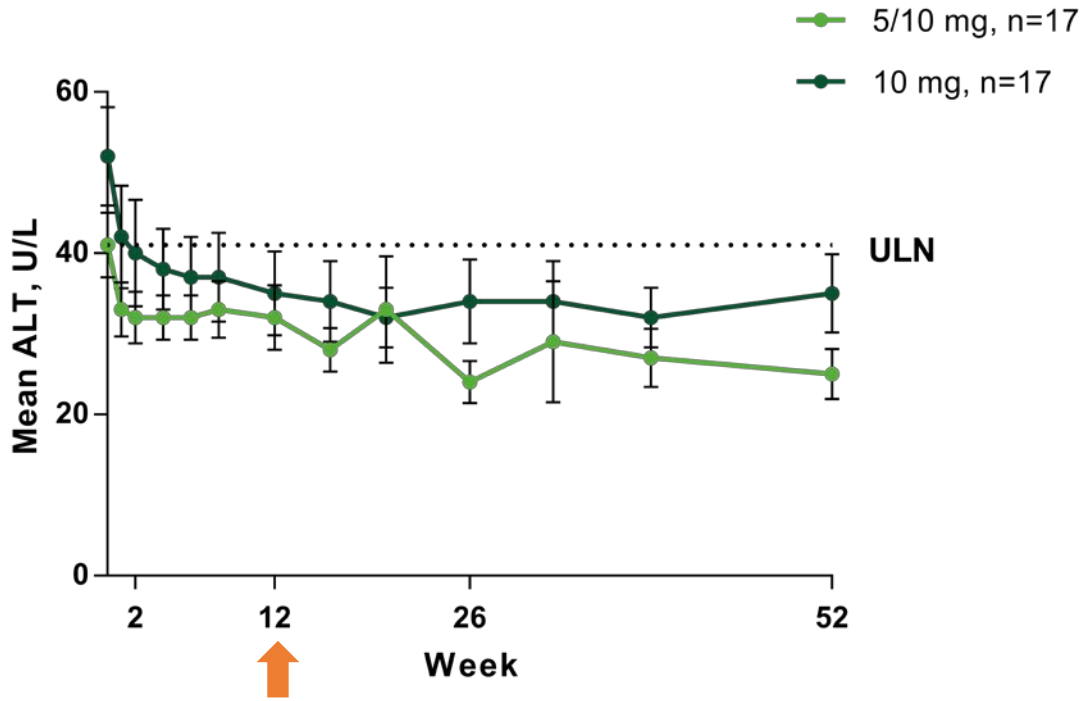
Median Percent ALT Change



*P<0.0001, compared to baseline values

Dose adjustment for 5/10 mg group

Mean ALT



Dose adjustment for 5/10 mg group

Mean ± SEM

No transaminase safety signal was observed

CymaBay, Data on File 2018.

Seladelpar Phase 2 Study in PBC

Additional Markers of Interest

Percent Change in Other Biochemical Markers from Baseline to Week 52

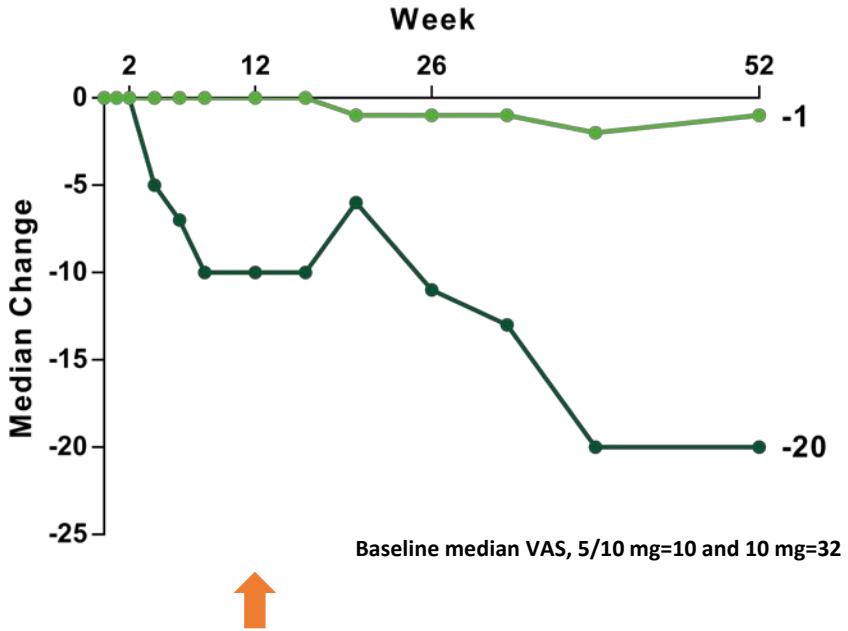
Parameter Mean (SD) (Reference range)	Seladelpar 5/10 mg (n=17)			Seladelpar 10 mg (n=17)		
	Baseline	% change from baseline	*P*-value	Baseline	% change from baseline	*P*-value
LDL-C (50-130 mg/dL)	140 (28)	-13% (13)	0.0005	143 (47)	-21% (20)	0.0006
HDL-C (35-60 mg/dL)	82 (21)	+4 (23)	NS	74 (27)	+9 (22)	NS
GGT (Female: 7-38, Male: 11-52 U/L)	140 (28)	-37% (34)	0.0004	286 (223)	-32% (32)	0.0008
hs-CRP* (0.0 – 3.0 mg/L)	3 [2, 6]*	-14% (-69, 180)†	NS	3 [2, 6]*	-7% (-81, 200)†	NS

*Median (Quartiles: 25, 75). †Median (Min, Max).
CymaBay, Data on File 2018.

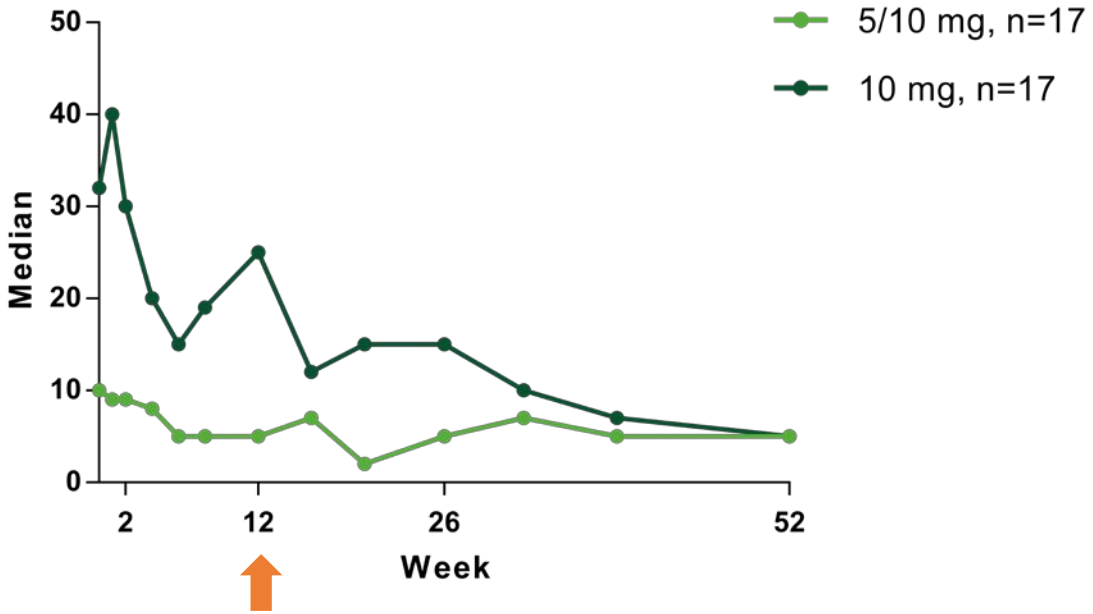
Seladelpar Phase 2 Study in PBC

Patient Reported Pruritus: VAS Through Week 52

Median Change in VAS



Median VAS



- In patients with baseline itch, the median changes in VAS were -30% and -66% in the 5/10 mg and 10 mg groups, respectively

Treatment was not associated with increased pruritus

CymaBay, Data on File 2018.

Seladelpar Phase 2 Study in PBC

Safety Population Adverse Event (AE) Profile

AE Category	Seladelpar 5/10 mg (n=64) n (%)	Seladelpar 10 mg (n=55) n (%)
Any AE	50 (78)	38 (69)
Any AE ≥ grade 3	6 (9)	4 (7)
Any treatment-related AE	20 (31)	13 (24)
Any treatment-related AE ≥ grade 3	0	0
Any AE with outcome of death	0	0
Any serious AE (SAE)	6 (9)	5 (9)
Any treatment-related SAE	0	0
Any AE leading to discontinuation from seladelpar	2 (3)	1 (2)
Most Common AEs (≥ 10%)		
Pruritus	14 (22)	10 (18)
Fatigue	8 (13)	4 (7)
Diarrhea	9 (14)	3 (6)
Nausea	9 (14)	3 (6)

CymaBay, Data on File 2018.

Seladelpar Phase 2 Study in PBC

Safety Summary

- There were 11 serious AEs in the study; none were deemed related to seladelpar
- No ≥ grade 3 ALT elevations
- No discontinuations for transaminase elevations
- Three discontinuations
  - One discontinuation for a grade 1 gastroesophageal reflux was deemed related to seladelpar
  - Two discontinuations (pneumonia & worsening of pruritus) were deemed unrelated to seladelpar
- Overall, no increase in pruritus

CymaBay, Data on File 2018.

Seladelpar for PBC

Summary and Next Steps

- Seladelpar maintained a potent anti-cholestatic effect over 52 weeks
- Up to 71% of patients achieved the composite efficacy end point
- Overall, seladelpar was generally safe, well tolerated, and not associated with pruritus

A 52-week phase 3 global PBC study (ENHANCE) has been initiated to further confirm these results

Acknowledgements

We gratefully acknowledge study patients, investigators, site staff, and CB8025-21629 team!

- **USA**
  - Guy Neff, Michael Galambos, Goel Aparna, Marlyn Mayo, Brian Borg, Stuart Gordon, Stephen Harrison, Paul Thuluvath, Cynthia Levy, Carmen Stanca, Bruce Bacon, Tarek Hassanein, Joseph Odin, Mitchell Shiffman, John Vierling, David Bernstein, Charles Landis, Adam Peyton, Norman Gitlin
- **UK**
  - Richard Aspinall, David Jones, David Sheridan, Douglas Thorburn, Lynsey Corless
- **Germany**
  - Andreas Kremer, Yvonne Dörffel, Christoph Berg, Peter Buggisch, Markus-Alexander Wörns
- **Canada**
  - Gideon Hirschfield, Mark Swain, Hemant Shah
- **CymaBay**
  - Sasha Steinberg, Gianni Amato, Yun-Jung Choi, Scott Rosenbusch, Monika Varga, Charles McWherter, Pol Boudes, Sandrin Bergheanu

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Thank You

ENHANCE

A study of Primary Biliary Cholangitis