CYMABAY THERAPEUTICS

Improving the Lives of Patients with Liver Diseases

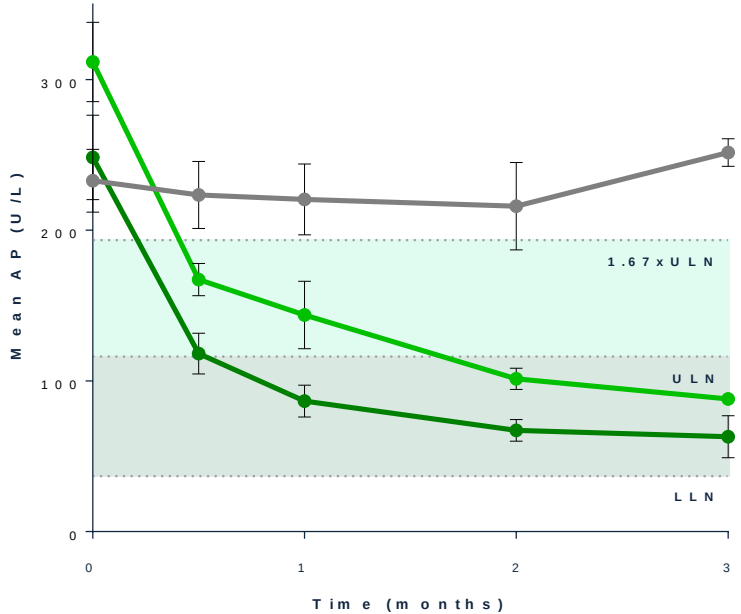
PBCers conference May 2018

Pol Boudes, MD, Chief Medical Officer

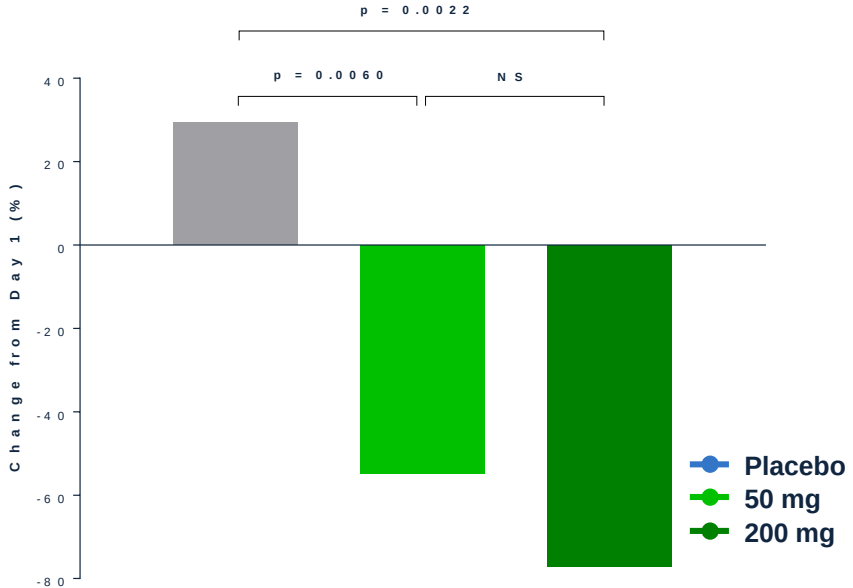
AASLD 2016: Proof-of-Concept in High Dose Study

Benefit/risk supported rationale for lower dose study

Efficacy: Alkaline Phosphatase



Mechanism: Bile Acid Synthesis (C4)



Safety: Study stopped after 3 reversible asymptomatic transaminase elevations

Jones et al. AASLD 2016 & Lancet GE&H 2017

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New Phase 2 Seladelpar '*Low Dose*' Study

Open label, randomized, dose ranging

AP ≥ 1.67 x ULN; ALT/AST ≤ 3 x ULN; Total Bilirubin ≤ 2 x ULN *

Main

Seladelpar 5 mg qd (n = 12)

Seladelpar 10 mg qd (n = 12)

Extension (Option for Dose Adjustment)

Seladelpar (5, 10 or 25 mg)

Seladelpar (5, 10 or 25 mg)

18 weeks

12 Week Interim Analysis

Main

Seladelpar 25 mg qd (n = 12)

Extension (Option for Dose Adjustment)

Seladelpar (5, 10 or 25 mg)

18 weeks

* UDCA therapy for prior 12 months

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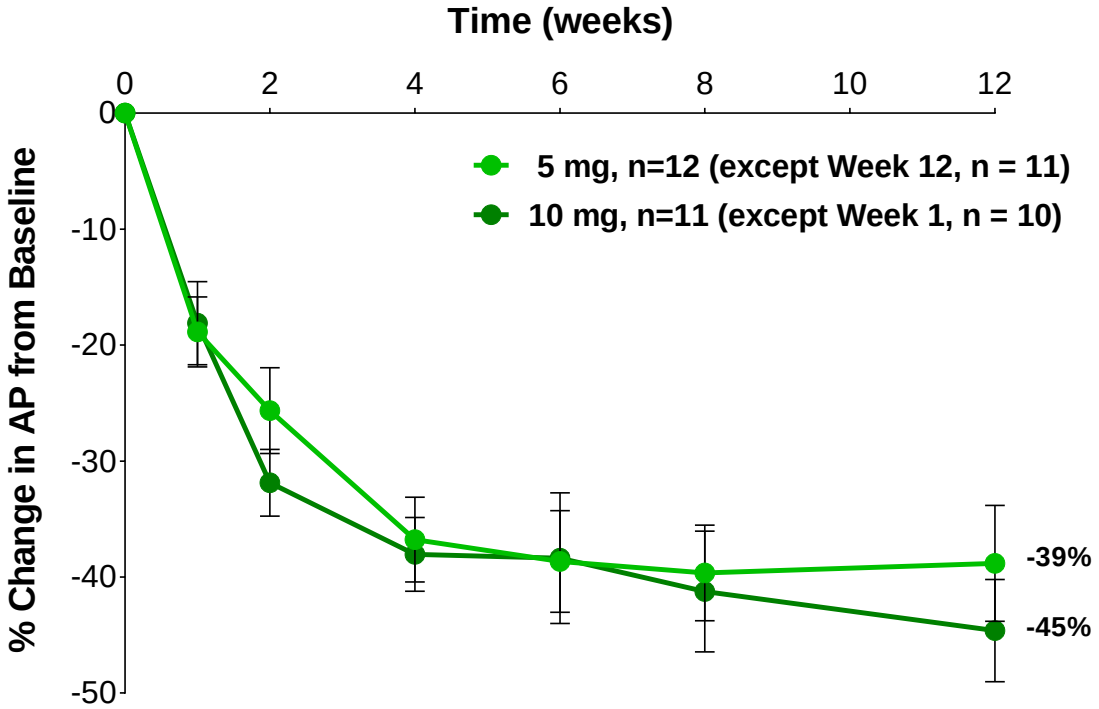
AASLD 2017: Phase 2 Seladelpar '*Low Dose*' Study

5 mg and 10 mg Doses Both Result in Rapid and Robust Decreases in AP

Mean percent AP change from baseline to Week 12



Mean ± SE

Hirschfield et al., AASLD 2017

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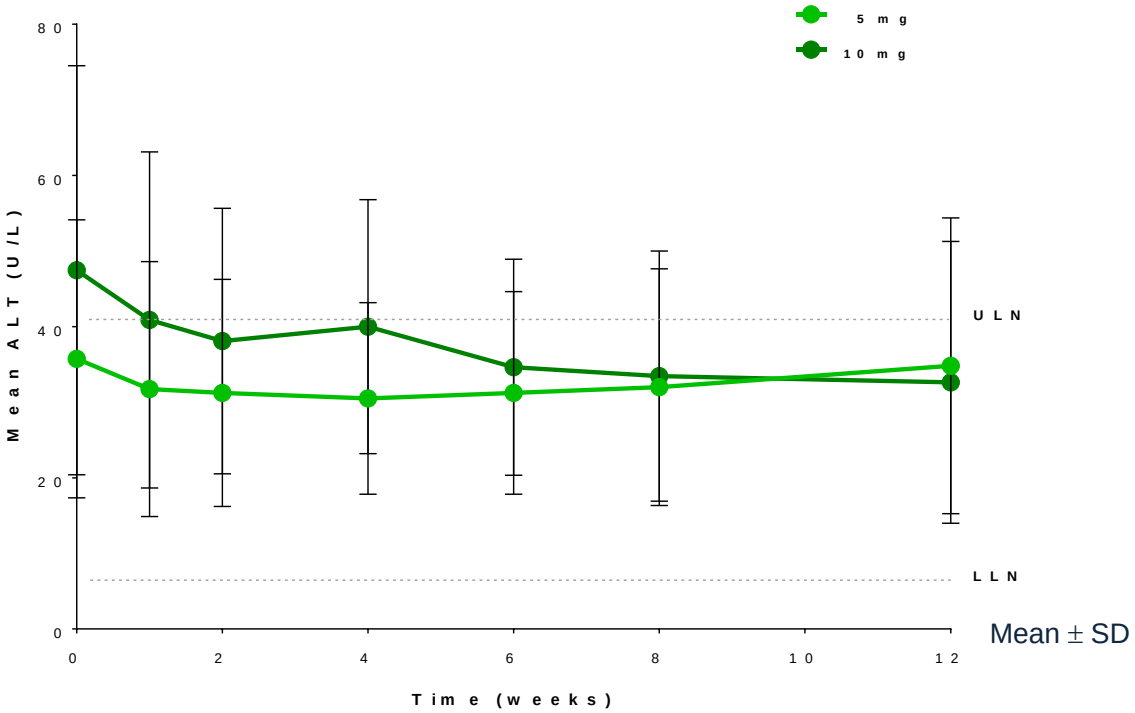
AASLD 2017: Phase 2 Seladelpar '*Low Dose*' Study

Decreases in ALT Provide an Additional Indication of Efficacy

ALT changes from baseline to Week 12



Mean ± SD

Hirschfield et al., AASLD 2017

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AASLD 2017: Phase 2 Seladelpar '*Low Dose*' Study
Modified to Extend Duration and Expand Database

- ***Extended to 52 weeks***
- ***Increased 5 mg and 10 mg groups to 49 patients each***
- ***Dosing above 10 mg not planned***
- ***To assess minimally effective dose, added a 2 mg arm***

Hirschfield et al., AASLD 2017

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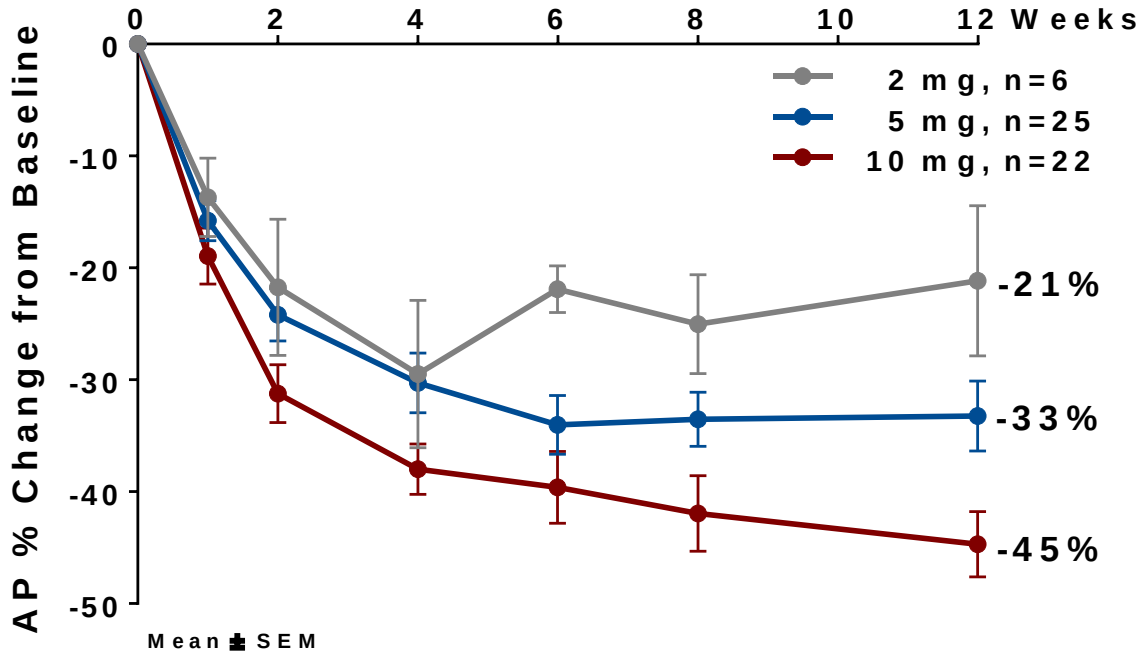
EASL 2018: Phase 2 Seladelpar '*Low Dose*' Study

Dose response and clinical activity with robust decreases in AP

Mean percent AP change from baseline to Week 12



Hirschfield et al, EASL, International Liver congress 2018

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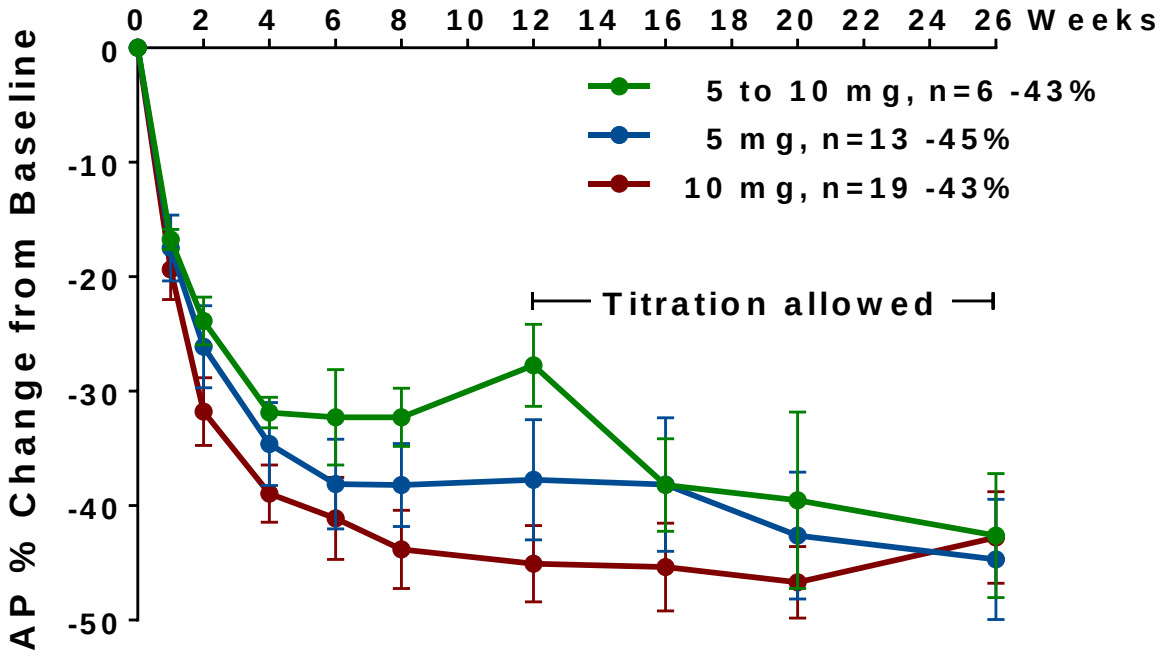
EASL 2018: Phase 2 Seladelpar '*Low Dose*' Study
Sustained activity to Week 26

AP changes from baseline to Week 26



Hirschfield et al, EASL, International Liver congress 2018

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EASL 2018: Phase 2 Seladelpar 'Low Dose' Study

AP responders from baseline to Week 26

At Week 26 n (%)	Seladelpar Titration 5 mg or 5 to 10 mg n=19	Seladelpar 10 mg n=19
Baseline AP (U/L)	348	272
Primary Composite Endpoint		
Responder Rate	13 (68%)	15 (79%)
AP < 1.67 x ULN	13 (68%)	15 (79%)
AP decrease ≥ 15%	18 (95%)	17 (89%)
Total bilirubin ≤ ULN	18 (95%)	17 (89%)
AP Normalization		
AP ≤ ULN at Week 26	5 (26%)	6 (32%)

Hirschfield et al, EASL, International Liver congress 2018

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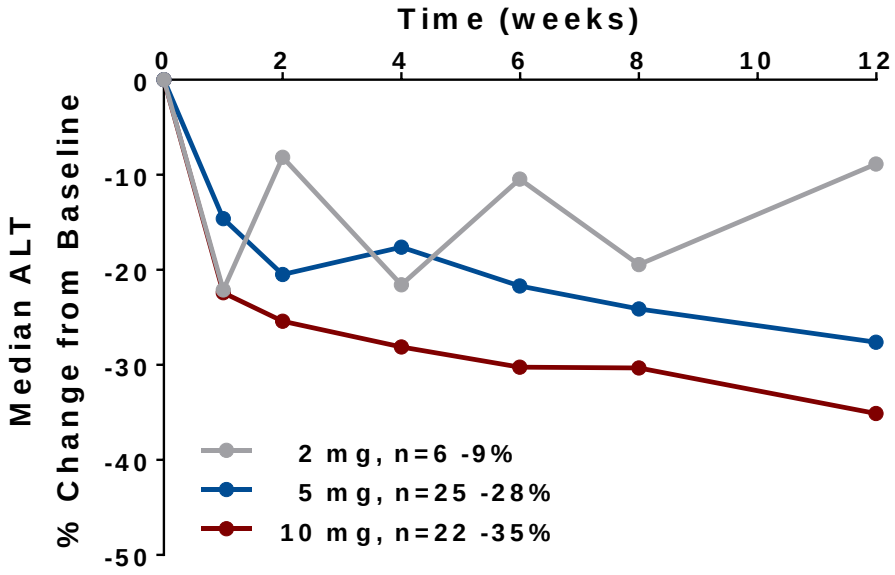
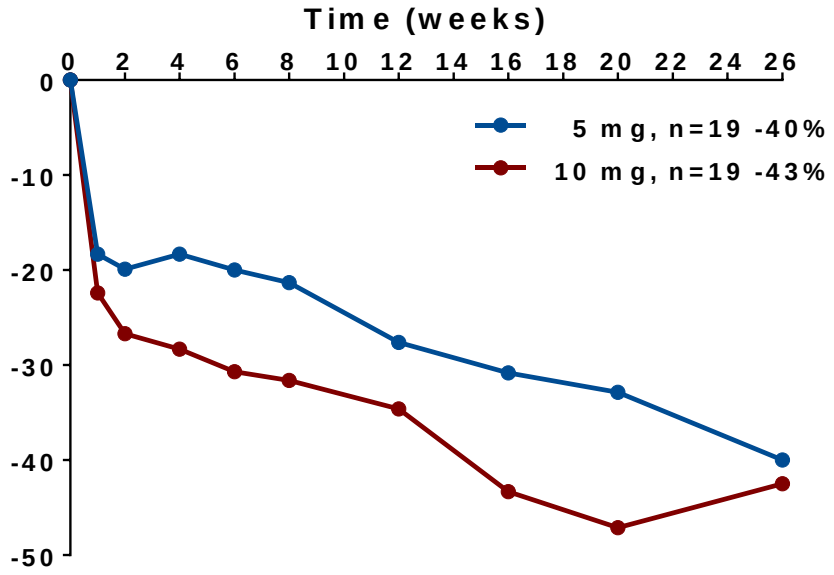
EASL 2018: Phase 2 Seladelpar *Low Dose* Study

Robust anti-inflammatory effects: ALT

Week 12 Cohort



Week 26 Cohort



Hirschfield et al, EASL, International Liver congress 2018

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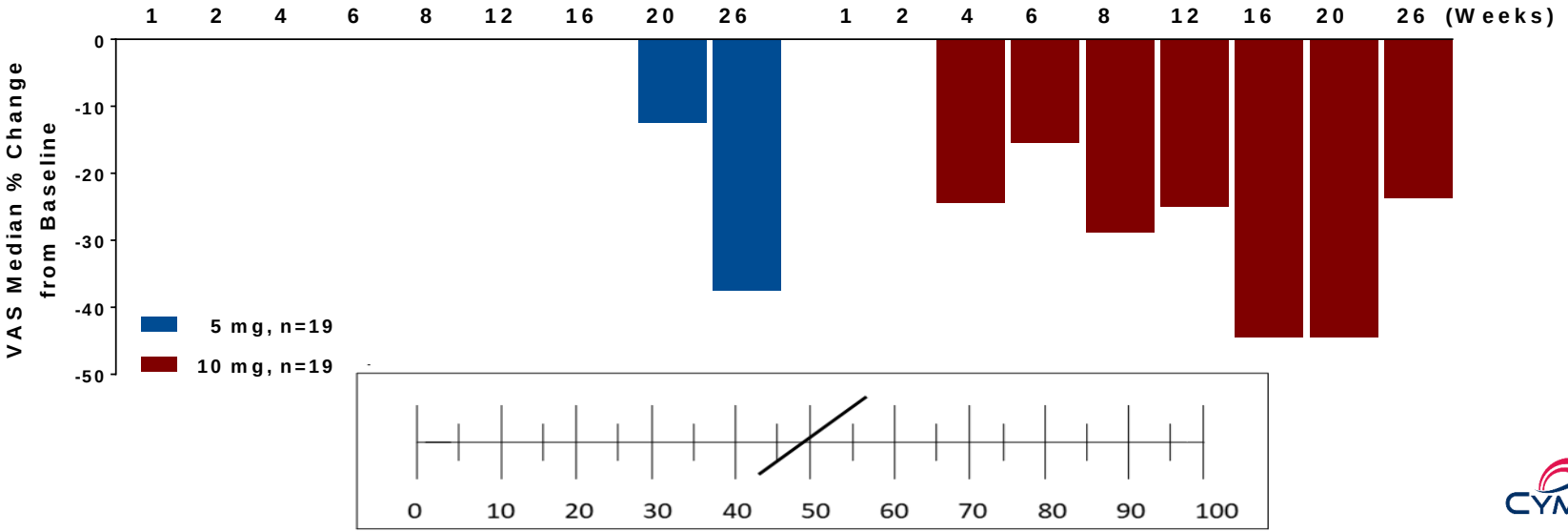
EASL 2018: Phase 2 Seladelpar '*Low Dose*' Study

Changes in self reported symptom scores: Pruritus

Baseline	Seladelpar Titration 5 mg or 5 to 10 mg	Seladelpar 10 mg
VAS (0-100)	19	37

Week 26 Cohort



Phase 2 Low Dose Study in PBC
Safety summary

- Six SAEs, all deemed unrelated to seladelpar
- No transaminase safety signal
- No signal for drug-induced pruritus
- Two AEs leading to seladelpar discontinuation, both unrelated to seladelpar
- Most frequent AEs: Pruritus (24%); fatigue, nasopharyngitis, and urinary tract infection (all 11%)

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Seladelpar for PBC
Next steps

Low dose study continues to recruit

New '*Long Term Extension*' study Initiated

Preparing for Phase 3 start in 2018

Objective: submit a New Drug Application

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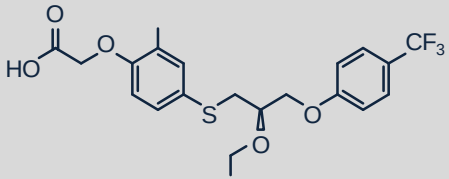
Back-up slides

Seladelpar

Once daily oral PPARδ agonist for inflammatory liver diseases



Human PPARδ EC_{50} = 2 nM
630-Fold Selective Over PPARα
Inactive Against PPARγ

Bile Acid Homeostasis

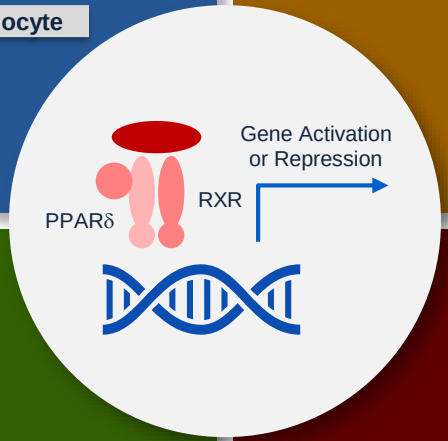
Hepatocyte
Cholangiocyte

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

Inflammation

Kupffer Cell
Macrophage

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



Fibrosis

Stellate Cell

- ↓ Connective Tissue Growth Factor
- ↓ Stellate cell activation
- ↓ Collagen deposition

Metabolic Effects

Hepatocyte
Myocyte
Adipocyte
Enterocyte

- ↓ Cholesterol/LDL-C
- ↓ Lipogenesis
- ↑ Fatty acid oxidation
- ↑ Insulin sensitivity

Current Therapies for PBC
Limited treatment alternatives

Ursodeoxycholic Acid (UDCA)
1st Line

- ▲First line therapy for PBC
- ▼~40% inadequate responders: AP >1.67x 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 biomarker for accelerated approval
- ▼~50% inadequate responders
- ▼Can cause or worsen pruritus

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

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Phase 2 Low Dose Study in PBC

Safety, Week 12 and Week 26 cohorts

Subjects (n)	Dose Through Week 12		
	2 mg	5 mg	10 mg
Safety Population	11	30	30
Week 12 Cohort	6	25	22

Subjects (n)	Dose Week 12 Through Week 26			
	2 or 2 to 5 mg	5 mg	5 to 10 mg	10 mg
Week 26 Cohort	4	13	6	19

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Phase 2 Low Dose Study in PBC
Baseline characteristics

CB8025-21629 Study	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg
N	11	30	30
Age, *years*	55 (10)	57 (8)	56 (9)
Female/Male	11/0	30/0	27/3
BMI, kg/m^2	29 (7)	27 (7)	26 (5)
History of Pruritus	7 (65%)	19 (63%)	22 (73%)
AP, *U/L*	300 (121)	310 (152)	265 (83)
GGT, *U/L*	255 (143)	201 (141)	254 (185)
ALT, *U/L*	54 (25)	40 (22)	49 (25)
Total Bilirubin, *mg/dL*	0.60 (0.12)	0.68 (0.35)	0.84 (0.34)
Albumin, *g/dL*	4.1 (0.2)	4.0 (0.4)	4.1 (0.3)
UDCA Dose, *mg/kg*	14 (4)	15 (3)	17 (6)

Safety population, Mean (SD), Baseline: mean of screening(s) and Day 1

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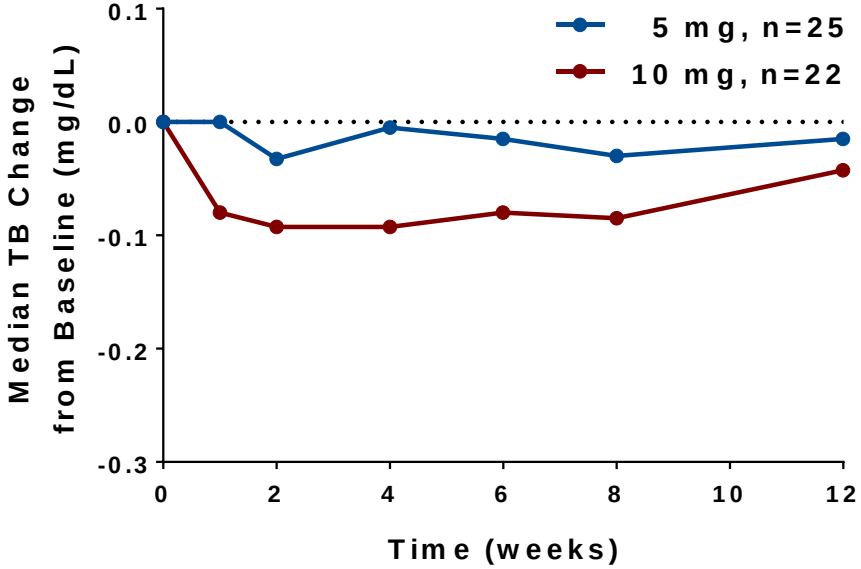
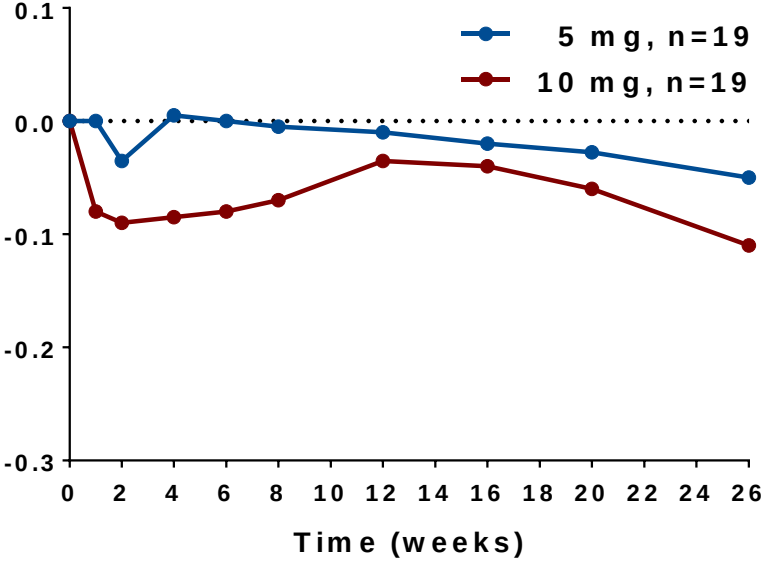
Phase 2 Low Dose Study in PBC

Total bilirubin

Week 12 Cohort



Week 26 Cohort



Phase 2 Low Dose Study in PBC

Percent change in other biochemical parameters of interest

Week 12 Cohort

% Change from Baseline	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg
GGT	-12 (-28, 4)	-40 (-48, -10)	-46 (-55, -34)
LDL-C	10 (5, 23)	-8 (-19, -1)	-13 (-19, 1)
hs-CRP	14 (-6, 36)	-7 (-45, 27)	-28 (-47, 25)

Median (Quartiles: 25, 75)

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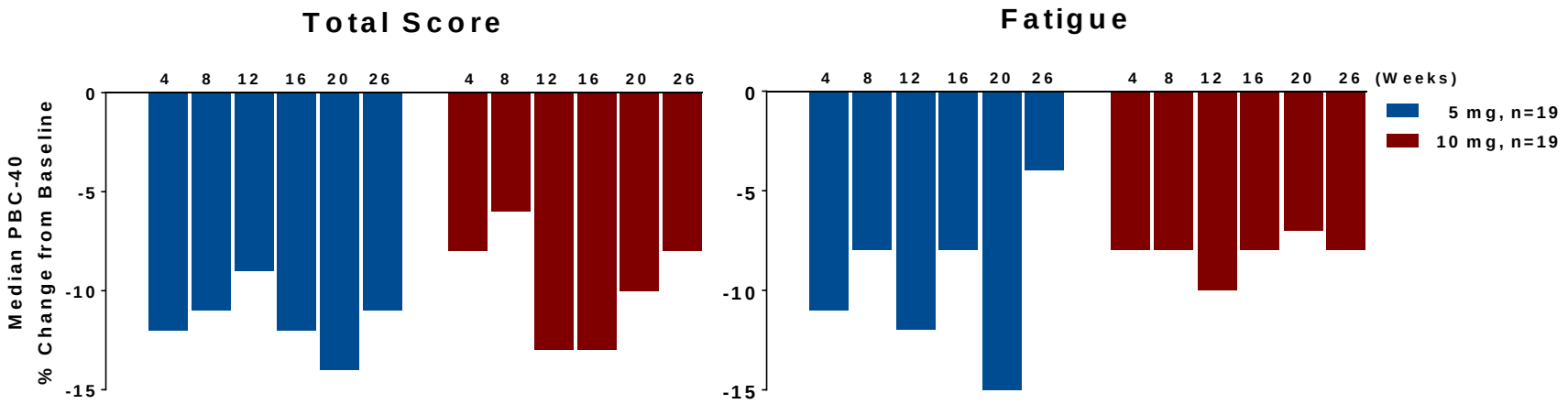
EASL 2018: Phase 2 '*Low Dose*' Study

Changes in self reported symptom scores: PBC-40 QoL

Baseline	Seladelpar Titration 5 mg or 5 to 10 mg	Seladelpar 10 mg
PBC-40, Total (34-200)	108	97
PBC-40, Fatigue (11-55)	31	29

Week 26 Cohort



Hirschfield et al, EASL, International Liver congress 2018

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