Treatment Efficacy and Safety of Seladelpar, a Selective Peroxisome Proliferator-Activated Receptor Delta agonist, in Primary Biliary Cholangitis Patients: 12- and 26-Week Analyses of an Ongoing, International, Randomized, Dose Ranging Phase 2 Study

LBP-2

Hirschfield Gideon[1], Boudes Pol[2], Bowlus Christopher[3], Gitlin Norman[4], Galambos Michael[5], Harrison Stephen[6], Gordon Stuart[7], Aspinall Richard[8], Dörffel Yvonne[9], Kremer Andreas E.[10], Sheridan David[11], Bacon Bruce[12], Berg Christoph[13], Borg Brian[14], Hassanein Tarek[15], Odin Joseph[16], Shiffman Mitchell[17], Thuluvath Paul[18], Thorburn Douglas[19], Bernstein David[20], Buggisch Peter[21], Corless Lynsey[22], Levy Cynthia[23], Mayo Marlyn J.[24], Swain Mark[25], Vierling John[26], Wörns Marcus-Alexander[27], Steinberg Sasha[2], Bergheanu Sandrin[28], Choi Yun-Jung[2], Varga Monika[2], Martin Robert[2], McWherter Charles[2], Jones David[29]

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BACKGROUND AND AIMS

Seladelpar is a potent and selective PPAR-delta agonist with potential as a new therapeutic approach for patients with inflammatory liver diseases, including NASH and Primary Biliary Cholangitis (PBC).

Seladelpar's initial proof of concept in PBC was established in a previous Phase 2 clinical study in patients with an inadequate response to ursodeoxycholic acid (UDCA) (Lancet Gastroenterol Hepatol. 2017;2(10):716-726).

The current study (EudraCT: 2016-002996-91) is an ongoing one year open-label Phase 2 study in patients with primary biliary cholangitis (PBC). A first planned interim analysis indicated that seladelpar appeared safe and efficacious at 5 and 10 mg/day for up to 12 weeks (J Hepatol 2017;66: S357).

We now report additional safety data, biochemical responses, and disease symptom evaluation in a larger number of patients and with a longer duration of treatment (up to 26 weeks) across three doses (2, 5, and 10 mg/day) of seladelpar.

METHODS

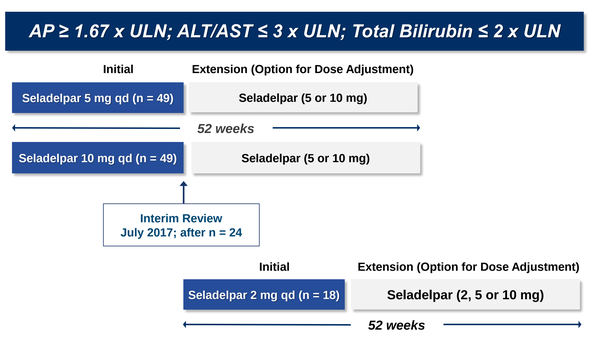
- Phase 2 ongoing, randomized, open-label study
- PBC subjects either inadequately responding to UDCA or intolerant of UDCA (alkaline phosphatase (AP) ≥ 1.67 x upper limit of normal)
- Seladelpar doses of 2, 5 and 10 mg/day with an optional dose escalation for 2 and 5 mg/day if the AP treatment goal was not achieved after 12 weeks of treatment
- Data analyses by Week 12 cohort (subjects completing 12 weeks of treatment), Week 26 cohort (subjects completing 26 weeks of treatment) and the safety population (all subjects enrolled as of January 8, 2018)

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

- Primary efficacy outcome: AP % change from baseline
- Secondary outcomes: AP responder analyses and changes in other liver, metabolic, and inflammatory markers.
- Safety analyses: Adverse events (AEs) and serious AEs, discontinuations, and laboratory abnormalities.
- Pruritus: Visual analogue scale (VAS, 0-100) and PBC-40 questionnaire This is a patient-derived, disease specific quality of life (QoL) measure developed and validated for use in PBC. It comprises 40 distinct questions grouped by different dimensions with fatigue being the most prominent.

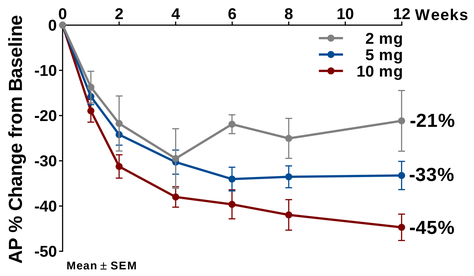
Study Design



RESULTS

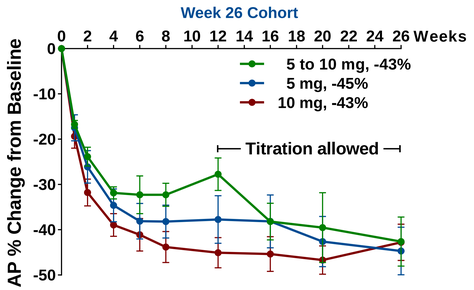
AP: Dose Response

Week 12 Cohort



AP: Dose Titration

Week 26 Cohort



Responder Rate

At Week 26 n (%)	Seladelpar Titration 5 mg or 5 to 10 mg	Seladelpar 10 mg
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 12	2 (8%)	9 (41%)
AP ≤ ULN at Week 26	5 (26%)	6 (32%)

Other Biochemical Parameters

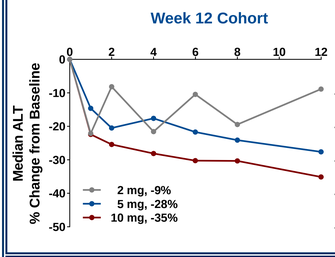
% Change from Baseline	Seladelpar 2 mg	Seladelpar 5 mg	Seladelpar 10 mg
GGT	-12 (-28, 4)	-40 (-48, -10)	-46 (-55, -34)
LDL-C	10 (5, 23)	-8 (-19, -1)	-13 (-19, 1)
hs-CRP	14 (-6, 36)	-7 (-45, 27)	-28 (-47, 25)

Week 12 Cohort

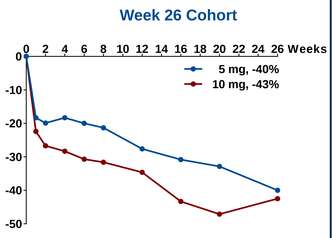
Median (Quartiles: 25, 75)

ALT

Week 12 Cohort

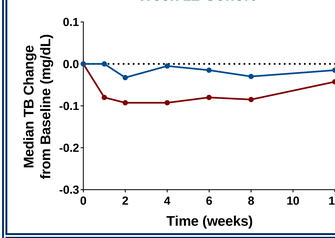


Week 26 Cohort

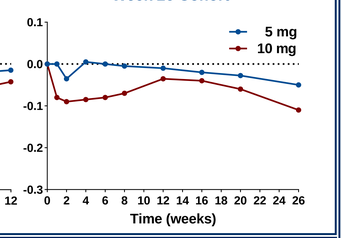


Total Bilirubin

Week 12 Cohort



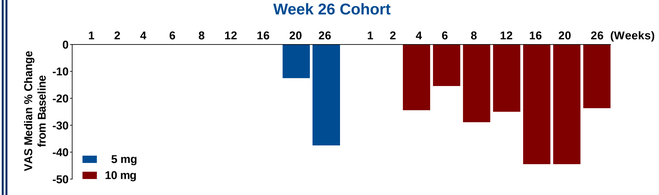
Week 26 Cohort



Changes in Self-Reported Symptom Scores

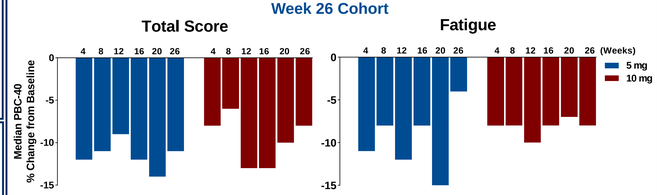
Pruritus VAS

Week 26 Cohort



PBC-40 QoL

Week 26 Cohort



Baseline	Seladelpar Titration 5 mg or 5 to 10 mg	Seladelpar 10 mg
VAS (0-100)	19	37
PBC-40, Total (34-200)	108	97
PBC-40, Fatigue (11-55)	31	29

Baseline Demographics

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/m²*	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)

Mean (SD)

Safety

- Six Serious Adverse Events (SAE), all deemed unrelated to seladelpar
  - Pyonephrosis in a patient with a non-functional saccular kidney; traumatic rib fractures; femoral neck fracture in an osteoporotic woman; epistaxis following sinus surgery; metabolic acidosis; pneumonia/pleurisy in a patient with chronic obstructive pulmonary disease
- No transaminase safety signal
- No signal for drug-induced pruritus

Adverse Event (AE) Safety Population n (%)	Seladelpar 2 to 5 mg (n = 11)	Seladelpar 5 mg (n = 17)	Seladelpar 5 to 10 mg (n = 13)	Seladelpar 10 mg (n = 30)
Any AE	11 (100)	7 (41)	12 (92)	22 (73)
Any AE ≥ Grade 3	2 (18)	2 (12)	1 (8)	2 (7)
Any treatment-related AE	5 (45)	2 (12)	5 (38)	9 (30)
Any treatment-related AE ≥ Grade 3	0	0	0	0
Any AE with outcome of death	0	0	0	0
Any SAE	1 (9)	2 (12)	1 (8)	2 (7)
Any treatment-related SAE	0	0	0	0
Any AE leading to discontinuation from Seladelpar	0	1 (6)	0	1 (3)
Most Common AEs				
Pruritus	4 (36)	2 (12)	4 (31)	7 (23)
Fatigue	2 (18)	2 (12)	1 (8)	3 (10)
Nasopharyngitis	2 (18)	1 (6)	1 (8)	4 (13)
Urinary tract infection	1 (9)	0	3 (23)	4 (13)

CONCLUSION: Seladelpar for PBC

- Seladelpar demonstrates sustained anti-cholestatic and anti-inflammatory effects in subjects with PBC at doses of 2, 5 and 10 mg, without inducing pruritus
  - Composite responder rate (AP < 1.67 x ULN, ≥ 15% AP decrease and Total Bilirubin ≤ ULN) was 68-79% at 26 weeks
  - At 10 mg, 32-41% of subjects normalized their AP
  - The potential of seladelpar to decrease pruritus in PBC patients should be further explored
- A phase 3 pivotal PBC study will be initiated in 2018

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[1] University of Birmingham, UK; [2] CymaBay Therapeutics, USA; [3] University of California Davis, USA; [4] Atlanta Gastroenterology Associates, USA; [5] Digestive Healthcare of Georgia, USA; [6] Pinnacle Clinical Research, USA; [7] Henri Ford Health System, USA; [8] Queen Alexandra Hospital, UK; [9] Charité Hospital, Germany; [10] Friedrich-Alexander-University Erlangen-Nürnberg, Germany; [11] Plymouth Hospitals NHS Trust & Plymouth University, UK; [12] Saint Louis University School of Medicine, USA; [13] Universitätsklinik Tübingen, Germany; [14] Southern Therapy and Advanced Research, USA; [15] Southern California Research Center, USA; [16] Icahn School of Medicine at Mount Sinai, USA; [17] Liver Institute of Virginia, USA; [18] The Institute for Digestive Health & Liver Disease at Mercy, USA; [19] Royal Free London, UK; [20] Hofstra Northwell School of Medicine, USA; [21] IFI at the Asklepiosklinik St. Georg, Germany; [22] Hull Royal Infirmary, UK; [23] Division of Hepatology, University of Miami, USA; [24] University of Texas, Southwestern Medical center, USA; [25] University of Calgary, Canada; [26] Advanced Liver Therapies, Baylor College of Medicine, USA; [27] Universitätsmedizin der Johannes Gutenberg-Universität Mainz, Germany; [28] Saberg Clinical Research BV, The Netherlands; [29] University of Newcastle, UK