Efficacy and Safety of Seladelpar in Patients With Compensated Cirrhosis and Evidence of Portal Hypertension Due to Primary Biliary Cholangitis (PBC)

Cynthia Levy[1], Joseph A. Odin[2], Guy Neff[3], Palak Trivedi[4], Liliana-Simona Gheorghe[5], Christopher L. Bowlus[6], John M. Vierling[7], Aliya F. Gulamhusein[8], Sook-Hyang Jeong[9], Emily Xu[10], Ke Yang[10], Yun-Jung Choi[10], Elaine Watkins[10] and Charles McWherter[10]

1. University of Miami, 2. Icahn School of Medicine at Mount Sinai, 3. Covenant Research and Clinics, LLC, 4. National Institute for Health Research Birmingham Biomedical Research Centre and Centre for Liver and Gastrointestinal Research, Institute of Immunology and Immunotherapy, University of Birmingham, United Kingdom, 5. Digestive Diseases and Liver Transplantation Center, Fundeni Clinical Institute, 6. Division of Gastroenterology and Hepatology, University of California Davis School of Medicine, 7. Departments of Medicine and Surgery, Baylor College of Medicine, 8. Institute of Health Policy, Management and Evaluation, University of Toronto, 9. Department of Internal Medicine, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Korea, 10. CymaBay Therapeutics, Inc.

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BACKGROUND AND AIMS

- Patients with PBC and compensated cirrhosis can develop portal hypertension (PHT) which may precede decompensation and increase the risk of liver transplantation or death
- Seladelpar, a selective peroxisome proliferator-activated receptor (PPAR)-delta agonist, has shown potent anti-cholestatic and anti-pruritic activity in PBC studies
- We report a pooled analysis from two studies assessing the efficacy, safety, and tolerability of seladelpar in PBC patients with compensated cirrhosis and evidence of portal hypertension

METHODS

A pooled analysis of an open-label phase 2 study (NCT02955602) and a double-blinded, randomized, placebo-controlled phase 3 study (ENHANCE, NCT03602560)

- Key Inclusion Criteria:
  - Diagnosis of PBC
  - ALP ≥ 1.67 × ULN (Upper Limit of Normal)
  - UDCA for the past 12 months or intolerant to UDCA
- Key Exclusion Criteria:
  - Total bilirubin (TB) > 2 mg/dL (phase 2) or 2 x ULN (phase 3)
  - Advanced PBC (albumin < LLN and TB > ULN)
  - Prothrombin Time International Normalized Ratio (INR) > ULN
  - Platelet count < 100 x 10^9/L (phase 3)
  - Presence of clinically significant hepatic decompensation
- Patients received oral, once daily placebo, seladelpar 5 mg or 10 mg + UDCA if tolerated
- Efficacy analyses at Month 3 and safety analyses for 1 year
- Efficacy endpoints:
  - Composite endpoint:
    ALP < 1.67 x ULN, ALP decrease of ≥ 15% and TB ≤ ULN
  - ALP % change, ALP ≤ ULN
  - Changes in liver biochemistry
- Cirrhosis diagnosis
  - By investigator's clinical judgement based on liver biopsy, liver elastography (FibroScan®, MRE), Imaging (Ultrasound, CT or MRI)
- Portal hypertension (PHT) diagnosis
  - Based on thrombocytopenia, splenomegaly, gastroesophageal varices or medical record

RESULTS

- Patients with compensated cirrhosis: n = 53 (14%)
- Patients with compensated cirrhosis and PHT: n = 22 (6%)
- Non-cirrhotic patients: n = 313 (86%)

Phase 2 (N = 101)*	Seladelpar 5 mg or 10 mg	Cirrhotic (n = 24)	+ PHT (n = 15)
			- PHT (n = 9)
		Non-Cirrhotic (n = 77)	- PHT (n = 77)
Phase 3 (N = 265)	Placebo, Seladelpar 5 mg or 10 mg	Cirrhotic (n = 29)	+ PHT (n = 7)
			- PHT (n = 22)
		Non-Cirrhotic (n = 236)	- PHT (n = 236)

* mITT population with 5 mg and 10 mg patients
2 mg group had no cirrhotic patients and was not included for the analysis.

RESULTS

Table 1. Demographic and Baseline Characteristics

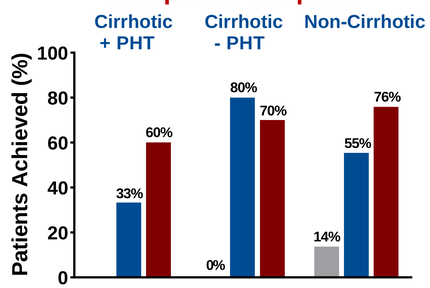
Parameters Mean (SD) (Normal range)	Cirrhotic N = 53: Portal Hypertension* n = 22		Cirrhotic N = 53: Without Portal Hypertension n = 31			Non-Cirrhotic N = 313		
	5 mg n = 13	10 mg n = 9	Placebo n = 7	5 mg n = 9	10 mg n = 15	Placebo n = 80	5 mg n = 116	10 mg n = 117
Female, *n (%)*	12 (92)	8 (89)	7 (100)	9 (100)	13 (87)	78 (98)	109 (94)	110 (94)
Age, *years*	55 (8)	57 (8)	56 (12)	60 (8)	60 (9)	56 (8)	56 (9)	56 (9)
Age at PBC diagnosis, *years*	44 (8)	48 (7)	47 (10)	49 (9)	50 (10)	47 (8)	47 (9)	47 (8)
AMA positive, *n (%)*	12 (92)	9 (100)	6 (86)	9 (100)	14 (93)	69 (86)	104 (90)	104 (89)
MELD Score	8 (1.8)	8 (1.3)	7 (1.2)	7 (0.7)	7 (1.7)	7 (0.7)	7 (0.8)	7 (0.8)
UDCA Dose, *mg/kg/day*	16 (6)	16 (2)	15 (4)	13 (3)	17 (4)	15 (2)	16 (4)	15 (4)
Concomitant UDCA, *n (%)*	12 (92)	8 (89)	7 (100)	9 (100)	13 (87)	78 (98)	107 (92)	108 (92)
ALP *(37-116 U/L)*	273 (117)	284 (77)	278 (68)	285 (134)	308 (118)	295 (109)	319 (148)	294 (124)
ALT *(6-41 U/L)*	46 (29)	47 (22)	46 (18)	40 (20)	62 (24)	44 (21)	48 (22)	44 (20)
Total bilirubin *(0.1-1.1 mg/dL)*	1.0 (0.45)	1.0 (0.45)	0.9 (0.61)	0.7 (0.28)	0.9 (0.35)	0.7 (0.28)	0.7 (0.34)	0.7 (0.30)
Direct bilirubin *(0-0.2 mg/dL)*	0.4 (0.23)	0.4 (0.27)	0.3 (0.29)	0.2 (0.13)	0.3 (0.17)	0.2 (0.13)	0.2 (0.17)	0.2 (0.15)
GGT *(7-38 U/L)*	196 (126)	207 (136)	219 (165)	285 (346)	237 (137)	230 (196)	236 (183)	245 (229)
AST *(9-34 U/L)*	46 (21)	61 (25)	41 (12)	42 (18)	51 (16)	37 (17)	40 (16)	39 (14)
Platelet count *(140-400 x 10^9/L)*	96 (27)	152 (72)	279 (72)	255 (57)	231 (60)	265 (77)	243 (70)	258 (73)
INR *(0.8-1.2)*	1.1 (0.1)	1.1 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)
Albumin *(3.5-5.5 g/dL)*	3.9 (0.35)	3.7 (0.43)	4.1 (0.16)	3.9 (0.38)	4.1 (0.22)	4.2 (0.23)	4.1 (0.27)	4.1 (0.25)

*There were no cirrhotic patients with PHT in the placebo group

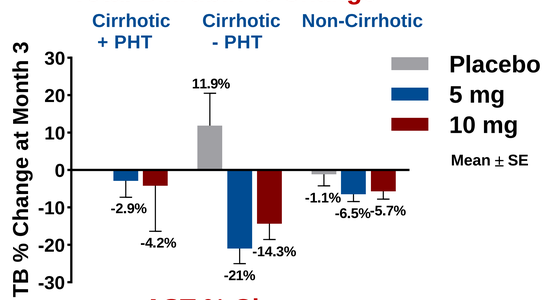
Table 2. Safety

Adverse Event (AE) within 1 Year, n (%)	Cirrhotic N = 53: Portal Hypertension n = 22		Cirrhotic N = 53: Without Portal Hypertension n = 31			Non-Cirrhotic N = 313		
	5 mg n = 13	10 mg n = 9	Placebo n = 7	5 mg n = 9	10 mg n = 15	Placebo n = 80	5 mg n = 116	10 mg n = 117
Patients with at least 1 AE	10 (77%)	7 (78%)	7 (100%)	7 (78%)	10 (67%)	57 (71%)	85 (73%)	86 (74%)
Treatment-related AE	6 (46%)	1 (11%)	4 (57%)	4 (44%)	2 (13%)	13 (16%)	36 (31%)	26 (22%)
Treatment-related AE ≥ Grade 3 (CTCAE)	0	0	0	0	0	0	0	0
AE leading to discontinuation	1 (8%)	2 (22%)	1 (14%)	1 (11%)	0	1 (1%)	3 (3%)	1 (1%)
SAE	3 (23%)	1 (11%)	0	2 (22%)	0	3 (4%)	6 (5%)	4 (3%)
Liver-related SAE	0	0	0	0	0	0	0	0
Treatment-related SAE	0	0	0	0	0	0	0	0
SAE with outcome of death	0	0	0	0	0	0	0	0
AE ≥ 8% In Seladelpar Groups Combined								
Pruritus	2 (15%)	1 (11%)	1 (14%)	0	3 (20%)	10 (13%)	12 (10%)	18 (15%)
Nausea	3 (23%)	1 (11%)	0	0	2 (13%)	4 (5%)	11 (9%)	10 (9%)
Abdominal pain upper	4 (31%)	0	0	1 (11%)	2 (13%)	3 (4%)	11 (9%)	9 (8%)
Diarrhea	2 (15%)	3 (33%)	1 (14%)	0	0	3 (4%)	9 (8%)	9 (8%)
Urinary tract infection	1 (8%)	2 (22%)	0	0	0	0	9 (8%)	11 (9%)

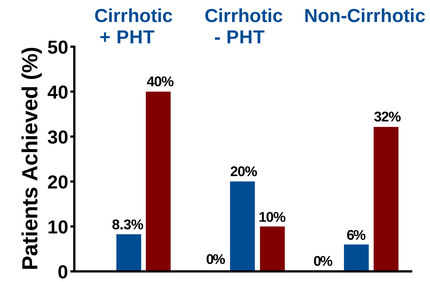
Composite Endpoint



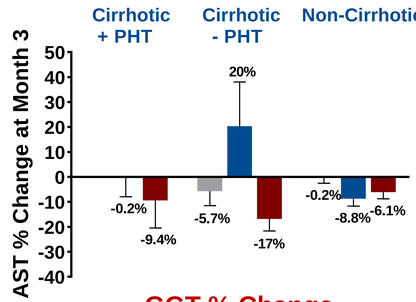
Total Bilirubin % Change



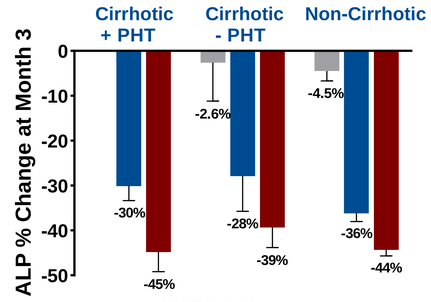
ALP Normalization



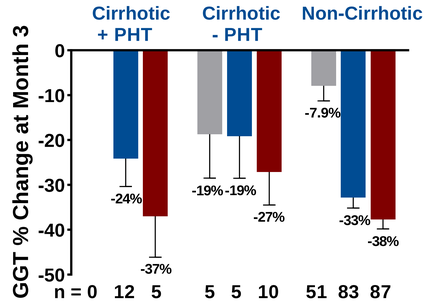
AST % Change



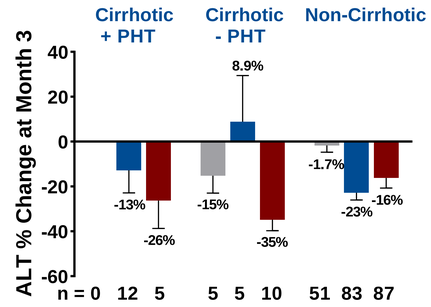
ALP % Change



GGT % Change



ALT % Change



- Albumin, INR and platelets were stable or improved throughout 3 months in cirrhotic and non-cirrhotic patients

CONCLUSIONS

- Seladelpar treatment for 3 months in patients with compensated cirrhosis and evidence of portal hypertension resulted in meaningful improvements in biomarkers of cholestasis and hepatocellular injury
- Seladelpar appeared safe and was well tolerated in cirrhotic patients with portal hypertension
- Efficacy appeared comparable in these studies in both cirrhotic or non-cirrhotic patients with PBC
- Seladelpar may potentially offer an effective treatment option for patients with compensated liver cirrhosis due to PBC