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Efficacy, Safety, and Tolerability of Seladelpar in Patients With Compensated Liver Cirrhosis Due to Primary Biliary Cholangitis (PBC): A Pooled Analysis of Phase 2 and Phase 3 Studies

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BACKGROUND AND AIMS

- Patients with PBC and compensated cirrhosis can progress to decompensation with its associated complications, liver transplantation or death
- PBC patients with an incomplete response or intolerance to UDCA have an unmet need to slow disease progression
- Seladelpar, a selective peroxisome proliferator-activated receptor (PPAR)-delta agonist, has shown potent anti-cholestatic and anti-pruritic activity in PBC studies
- We now report a pooled analysis from two studies assessing the efficacy, safety, and tolerability of seladelpar in PBC patients with or without compensated cirrhosis

METHODS

- A pooled analysis of an open-label phase 2 study (EudraCT 2016-002996-91) and a double-blinded, randomized, placebo-controlled phase 3 study (ENHANCE, EudraCT 2018-001171-20)
- 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
- Diagnosis of cirrhosis by liver biopsy, liver elastography or imaging
- Efficacy and safety analyses at Month 3
- Efficacy endpoints:
  - Composite endpoint:
    ALP < 1.67 x ULN, ALP decrease of ≥ 15% and TB ≤ ULN
  - ALP % change, ALP ≤ ULN
  - Changes in liver biochemistry

RESULTS

Cirrhosis Determination

- Diagnosis based on medical history (N = 53)
  - Liver biopsy: n = 19
  - Liver elastography (FibroScan®, MRE): n = 14
  - Imaging (Ultrasound, CT or MRI): n = 20
- All cirrhotic patients were Child-Pugh A
- One patient had a medical history of hepatic encephalopathy

Phase 2 (N = 101)*	Cirrhotic (n = 24)	Seladelpar 5 mg or 10 mg
	Non-Cirrhotic (n = 77)	Seladelpar 5 mg or 10 mg
Phase 3 (N = 265)	Cirrhotic (n = 29)	Placebo, Seladelpar 5 mg or 10 mg
	Non-Cirrhotic (n = 236)	Placebo, Seladelpar 5 mg or 10 mg
		3 Month Treatment

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

RESULTS

Demographic and Baseline Characteristics

Parameters Mean (SD) (Normal range)	Cirrhotic (N = 53)			Non-Cirrhotic (N = 313)		
	Placebo n = 7	5 mg n = 22	10 mg n = 24	Placebo n = 80	5 mg n = 116	10 mg n = 117
Female/Male	7/0	21/1	21/3	78/2	109/7	110/7
Age, *years*	56 (12)	57 (8)	59 (9)	56 (8)	56 (9)	56 (9)
Age at PBC diagnosis, *years*	47 (10)	46 (9)	49 (9)	47 (8)	47 (9)	47 (8)
Duration of PBC, *years*	9 (9)	10 (8)	10 (5)	8 (6)	9 (6)	9 (7)
AMA positive, *n (%)*	6 (86)	21 (96)	23 (96)	69 (86)	104 (90)	104 (89)
BMI, *kg/m²*	26 (5)	26 (5)	27 (5)	28 (6)	27 (6)	28 (6)
History of Pruritus, *n (%)*	6 (86)	19 (86)	20 (83)	51 (64)	83 (72)	81 (69)
MELD Score	7.0 (1.2)	7.6 (1.6)	7.6 (1.6)	6.6 (0.7)	6.7 (0.8)	6.7 (0.8)
UDCA Dose, *mg/kg/day*	15 (4)	15 (5)	17 (4)	15 (2)	16 (4)	15 (4)
UDCA intolerant, *n (%)*	0 (0)	1 (5)	2 (8)	2 (3)	9 (8)	9 (8)
ALP *(37-116 U/L)*	278 (68)	278 (121)	299 (103)	295 (109)	319 (148)	294 (124)
ALT *(6-41 U/L)*	46 (18)	43 (25)	57 (24)	44 (21)	48 (22)	44 (20)
Total bilirubin *(0.1-1.1 mg/dL)*	0.9 (0.6)	0.9 (0.4)	0.9 (0.4)	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)
Direct bilirubin *(0-0.2 mg/dL)*	0.3 (0.3)	0.3 (0.2)	0.3 (0.2)	0.2 (0.1)	0.2 (0.2)	0.2 (0.1)
GGT *(7-38 U/L)*	219 (165)	232 (238)	226 (134)	230 (196)	236 (183)	245 (229)
AST *(9-34 U/L)*	41 (12)	44 (20)	55 (20)	37 (17)	40 (16)	39 (14)
Platelet count *(140-400 x 10^9/L)*	279 (72)	161 (90)	206 (73)	265 (77)	243 (70)	258 (73)
INR *(0.8-1.2)*	1.0 (0.1)	1.1 (0.1)	1.1 (0.1)	1.0 (0.1)	1.0 (0.1)	1.0 (0.1)
Albumin *(3.5-5.5 g/dL)*	4.1 (0.2)	3.9 (0.4)	4.0 (0.4)	4.2 (0.2)	4.1 (0.3)	4.1 (0.3)

Safety

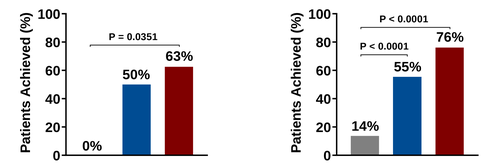
Adverse Event (AE), n (%)	Cirrhotic (N = 53)			Non-Cirrhotic (N = 313)		
	Placebo n = 7	5 mg n = 22	10 mg n = 24	Placebo n = 80	5 mg n = 116	10 mg n = 117
Patients with at least 1 AE	6 (86%)	17 (77%)	15 (63%)	48 (60%)	75 (65%)	76 (65%)
Any treatment-related AE	3 (43%)	8 (36%)	3 (13%)	6 (8%)	27 (23%)	22 (19%)
Any treatment-related AE ≥ Grade 3 (CTCAE)	0	0	0	0	0	0
Any AE with outcome of death	0	0	0	0	0	0
Any SAE†	0	2 (9%)	1 (4%)	2 (3%)	2 (2%)	2 (2%)
Any treatment-related SAE	0	0	0	0	0	0
Any AE leading to discontinuation from Seladelpar‡		0	1 (4%)		2 (2%)	1 (1%)
Most Common AEs						
Pruritus	0	2 (9%)	3 (13%)	6 (8%)	7 (6%)	12 (10%)
Fatigue	1 (14%)	0	3 (13%)	2 (3%)	6 (5%)	4 (3%)
Nausea	0	1 (5%)	3 (13%)	2 (3%)	8 (7%)	4 (3%)
Dry mouth	0	1 (5%)	4 (17%)	0	6 (5%)	0
Headache	0	1 (5%)	3 (13%)	0	7 (6%)	6 (5%)

† SAE:
- Cirrhotic patients: 2 on 5 mg (febrile neutropenia, procedural pain) and 1 on 10 mg (angina pectoris)
- Non-Cirrhotic patients: 2 on Placebo (rectal polyp, pyelonephritis acute), 2 on 5 mg (atrial fibrillation, cognitive disorder), and 2 on 10 mg (supraventricular tachycardia, cellulitis)

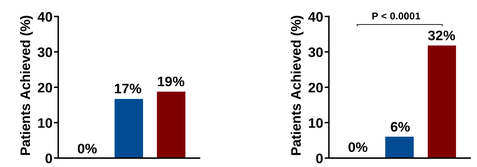
‡ Discontinuation:
- Cirrhotic patient: 1 on 10 mg (pruritus)
- Non-Cirrhotic patients: 2 on 5 mg (gastroesophageal reflux disease, pruritus) and 1 on 10 mg (insomnia and pruritus)

Cirrhotic | Non-Cirrhotic

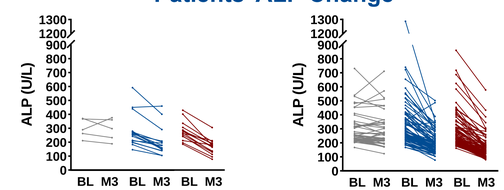
Composite Endpoint



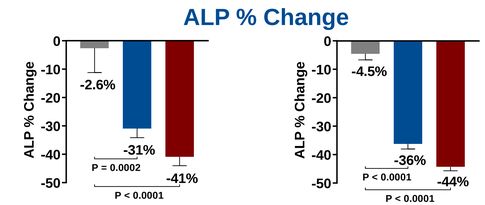
ALP Normalization



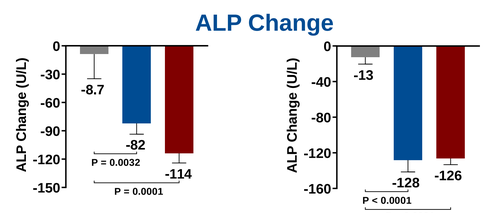
Patients' ALP Change



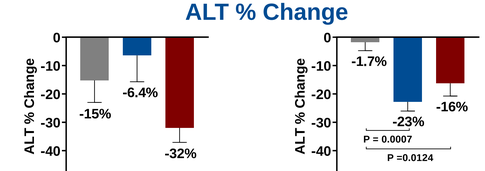
ALP % Change



ALP Change



ALT % Change

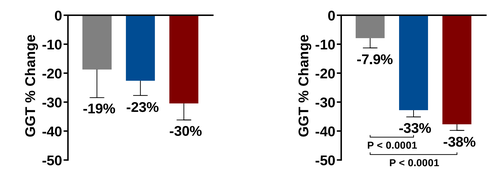


Mean (SE) Placebo 5 mg 10 mg

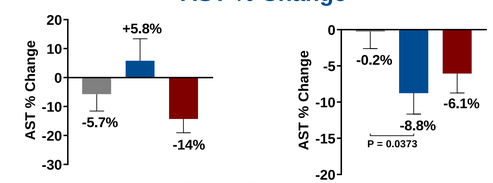
P-values are presented only when significant at P < 0.05 compared to placebo.

Cirrhotic | Non-Cirrhotic

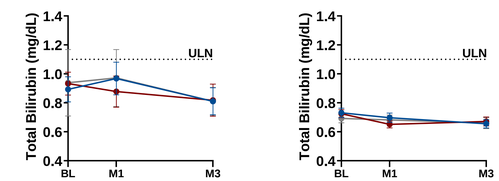
GGT % Change



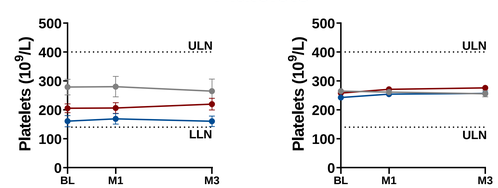
AST % Change



Total Bilirubin



Platelets



- Albumin and INR were stable throughout 3 months in all groups

CONCLUSIONS

- Seladelpar appeared safe and was well tolerated
- Seladelpar treatment of more than 50 patients with compensated cirrhosis for 3 months led to stable or improved liver biochemistry
- Efficacy appeared comparable in these studies in both compensated cirrhotic and non-cirrhotic patients with PBC
- Seladelpar may potentially offer an effective treatment option for patients with compensated liver cirrhosis due to PBC
- RESPONSE, a global 52-week phase 3 study is currently enrolling patients with non-cirrhotic and compensated cirrhotic PBC

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