Emricasan (IDN-6556) Orally for Three Months in Patients with Cirrhosis and MELD Scores 11-18 Improves Clinical Parameters of Cirrhosis in Patients with Baseline MELD Score ≥15

CATHERINE FRENETTE[1], GIUSEPPE MORELLI[2], MITCHELL SHIFFMAN[3], R. TODD FREDERICK[4], RAYMOND A. RUBIN[5], MICHAEL FALLON[6], MASON YAMASHITA[7], ALFRED P. SPADA[7], JEAN L. CHAN[7], DAVID T. HAGERTY[7]

[1]Scripps Clinic, La Jolla, [2]University of Florida, Gainesville, [3]Liver Institute of Virginia, Richmond, [4]California Pacific Medical Center, San Francisco, [5]Piedmont Transplant Institute, Atlanta, [6]University of Texas Health Science Center, Houston, [7]Conatus Pharmaceuticals Inc., San Diego, United States

Background

Caspases are enzymes responsible for executing apoptosis (programmed cell death) and activating inflammatory cytokines (IL-1β, IL-18)

- Apoptotic pathway plays important role in chronic liver diseases[1]

Emricasan (IDN-6556): first-in-class, orally active, pan-caspase inhibitor

- Suppresses apoptosis and inflammation
- Preferential uptake by liver via active transport mechanism
- Demonstrated activity on mechanism-specific biomarkers (cleaved cytokeratin-18 [cCK18], caspase 3/7) and mechanism-independent inflammatory markers (ALT, AST) in patients with different etiologies of chronic liver disease[2] and varying levels of hepatic impairment[3]

[1]Guicciardi and Gores. Semin Liver Dis 2010; 30:402-10
[2]Shiffman et al. Aliment Pharmacol Ther 2010; 31:969-78
[3]Spada et al. Hepatology 2014; 60:1277A

Objectives

To assess the effects of emricasan in subjects with liver cirrhosis and MELD scores 11-18

To assess the safety and tolerability of emricasan in subjects with liver cirrhosis and MELD scores 11-18

Endpoints

The primary endpoint is change from baseline in cCK18 at week 12

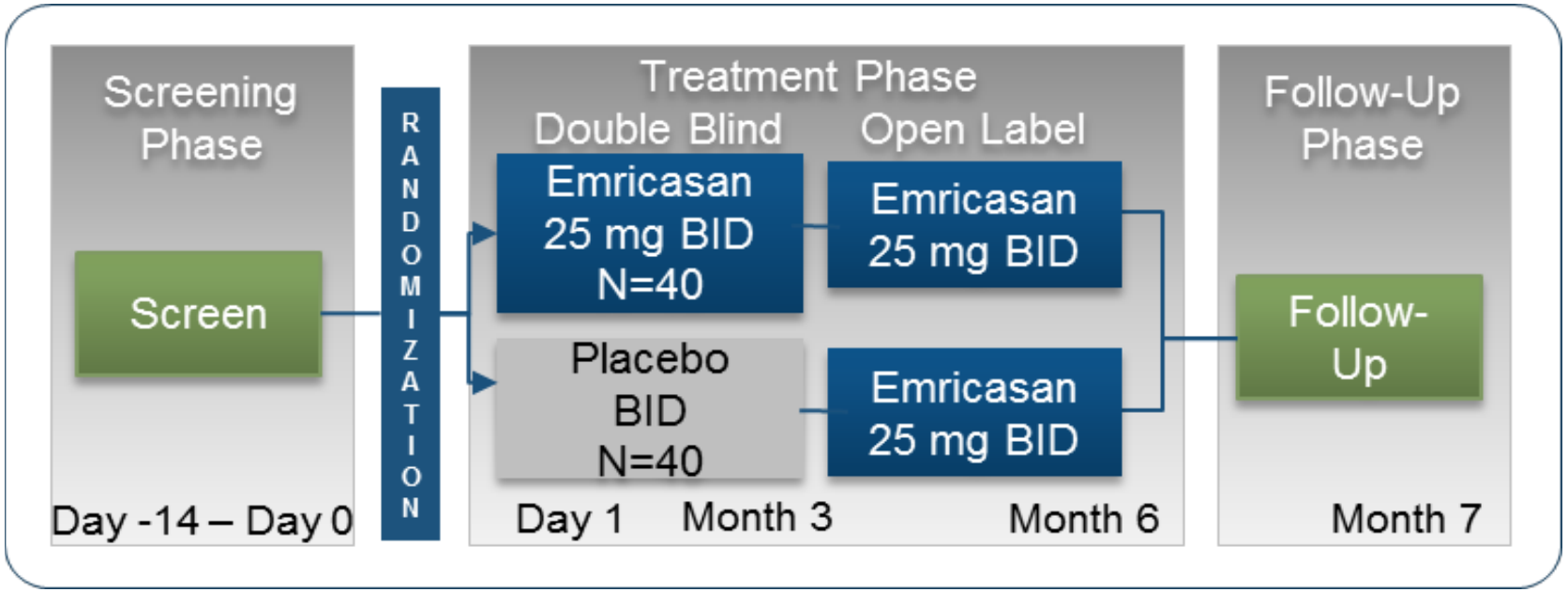
The secondary endpoints include

- Change from baseline in caspase 3/7, ALT, AST
- Change from baseline in MELD and Child-Pugh scores and components (serum bilirubin, INR, serum creatinine, albumin)

Pre-specified analysis of

- Subgroups by baseline MELD score (≤14 vs ≥15)
- Subgroups by disease etiology

Study Design



Results now reported

Key Inclusion/Exclusion Criteria

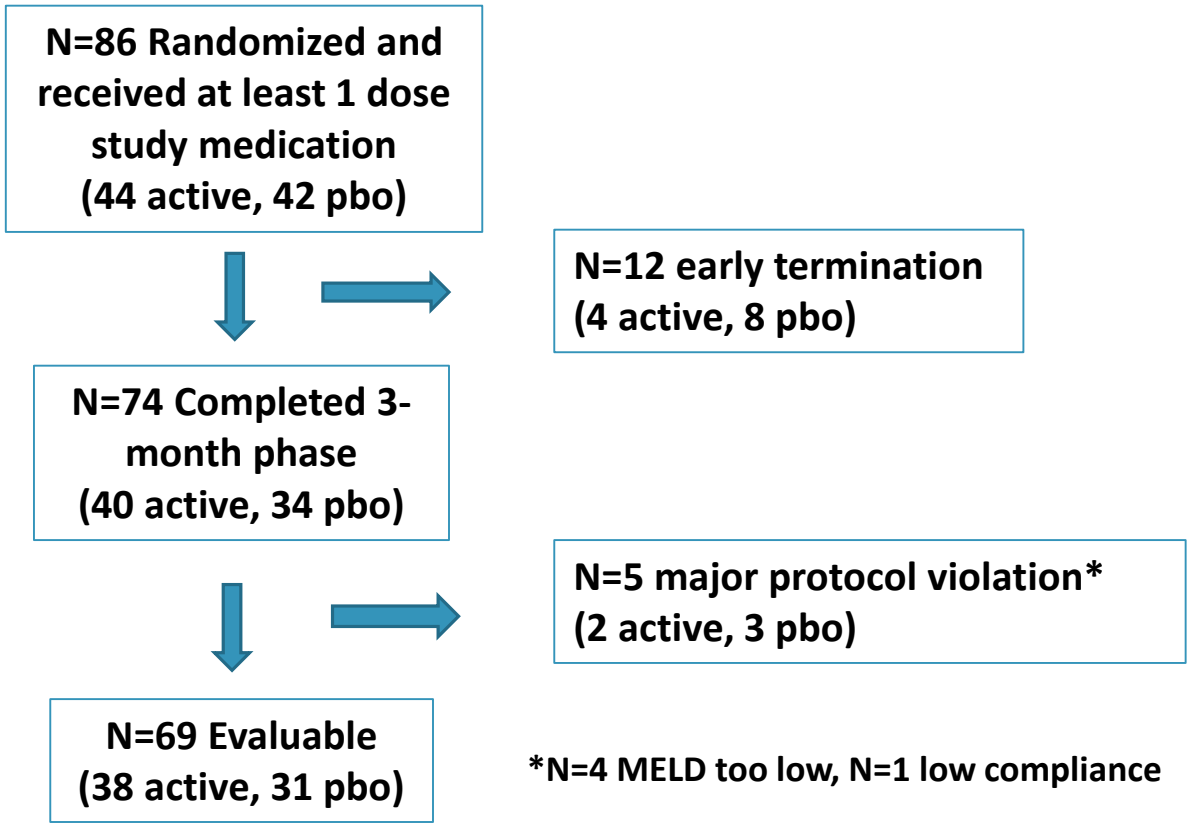
Inclusion

- Clinical, radiological, or biochemical evidence of liver cirrhosis
- Model for End-Stage Liver Disease (MELD) Score of 11 to 18

Exclusion

- HIV infection
- Autoimmune hepatitis
- Uncontrolled infection
- Hepatitis C subjects who are receiving or plan to receive therapy during the study
- Hepatitis B subjects who have been on stable anti-HBV therapy for less than 3 months
- Advanced liver disease
  - Variceal hemorrhage within 3 months of Screening
  - Ascites not adequately controlled on stable background medication
    - Stable dose of medications for at least 3 months prior to Screening
  - Encephalopathy grade III or IV
  - Child-Pugh score of 10-15 (Child-Pugh C)

Subject Disposition



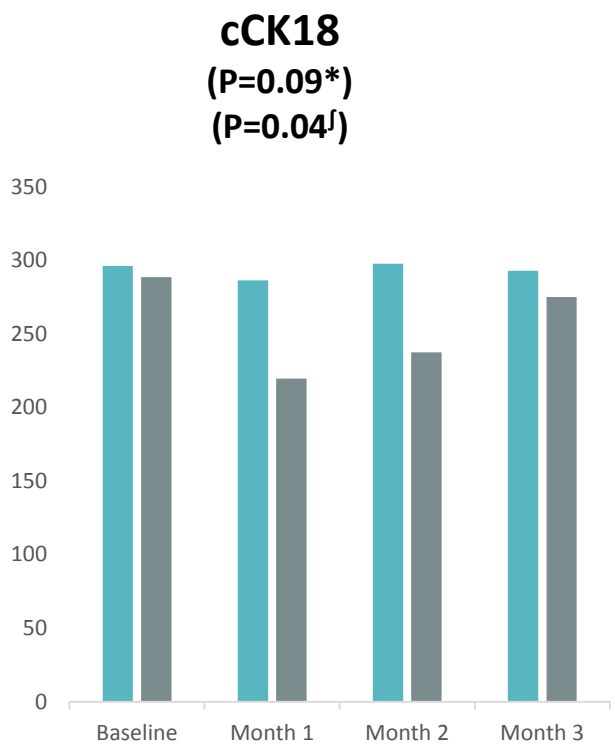
Subject Demographics

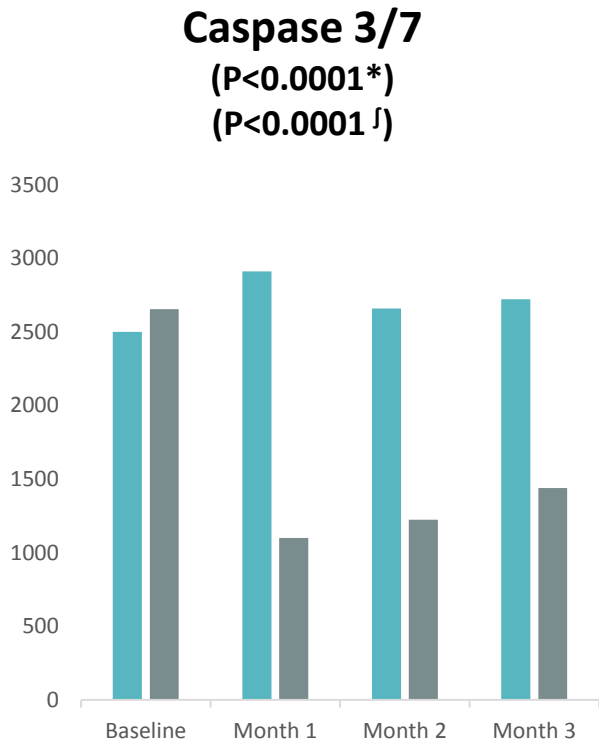
	Placebo (N=42)	Emricasan (N=44)	All Subjects (N=86)
	Number (%) of subjects	Number (%) of subjects	Number (%) of subjects
Gender			
Male	30 (71.4%)	24 (54.5%)	54 (62.8%)
Female	12 (28.6%)	20 (45.5%)	32 (37.2%)
Age Category (mean, SD)	57.5±8.8 (26-74)	58.5±8.2 (33-77)	58±8.4 (26-77)
18-40	2 (4.8%)	2 (4.5%)	4 (4.7%)
41-64	32 (76.2%)	33 (75.0%)	65 (75.6%)
≥65	8 (19.0%)	9 (20.5%)	17 (19.8%)
Race			
White	37 (88.1%)	39 (88.6%)	76 (88.4%)
Black/African American	2 (4.8%)	4 (9.1%)	6 (7.0%)
Asian	1 (2.4%)	0 (0%)	1 (1.2%)
More than 1 race	1 (2.4%)	0 (0%)	1 (1.2%)
Unknown / not reported	1 (2.4%)	1 (2.3%)	2 (2.3%)

Baseline Disease Characteristics and Labs

	Placebo (N=42)	Emricasan (N=44)	All Subjects (N=86)
MELD score (mean, SD)	12.9±2.6	12.8±2.1	12.8±2.4
MELD ≤ 14	32 (76.2%)	35 (79.5%)	67 (77.9%)
MELD ≥ 15	10 (23.8%)	9 (20.5%)	19 (22.1%)
Child-Pugh score (mean, SD)	6.9±1.2	6.9±1.3	6.9±1.2
Child-Pugh A	15 (35.7%)	22 (50.0%)	37 (43.0%)
Child-Pugh B	26 (61.9%)	22 (50.0%)	48 (55.8%)
Child-Pugh C	1 (2.4%)	0 (0%)	1 (1.2%)
Disease Etiology			
Alcohol	15 (35.7%)	18 (40.9%)	33 (38.4%)
HCV	16 (38.1%)	9 (20.5%)	25 (29.1%)
NASH	9 (21.4%)	11 (25.0%)	20 (23.3%)
Other	2 (4.8%)	6 (13.6%)	8 (9.3%)
ALT (U/L)	30.1 ± 17.5	31.7 ± 14.9	30.9 ± 16.1
AST (U/L)	50.0 ± 28.1	54.3 ± 22.0	52.2 ± 25.1
Total bilirubin (mg/dL)	2.59 ± 1.49	2.25 ± 1.12	2.41 ± 1.32
Albumin (g/dL)	3.48 ± 0.54	3.46 ± 0.41	3.47 ± 0.47
INR	1.31 ± 0.18	1.33 ± 0.17	1.32 ± 0.18
Creatinine (mg/dL)	0.74 ± 0.30	0.81 ± 0.31	0.77 ± 0.30

Consistent Improvements in Caspase-Related Biomarkers in Overall Emricasan Group





Placebo BID

Emricasan 25 mg BID

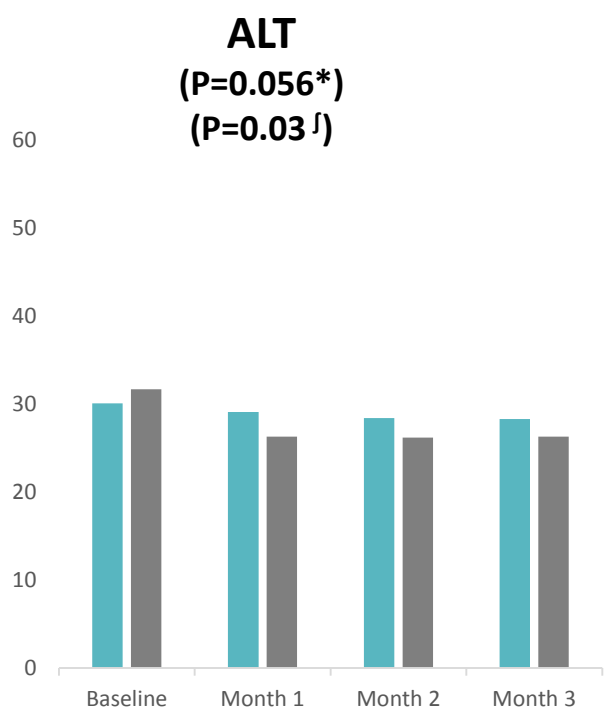
*P-value adjusting for baseline value

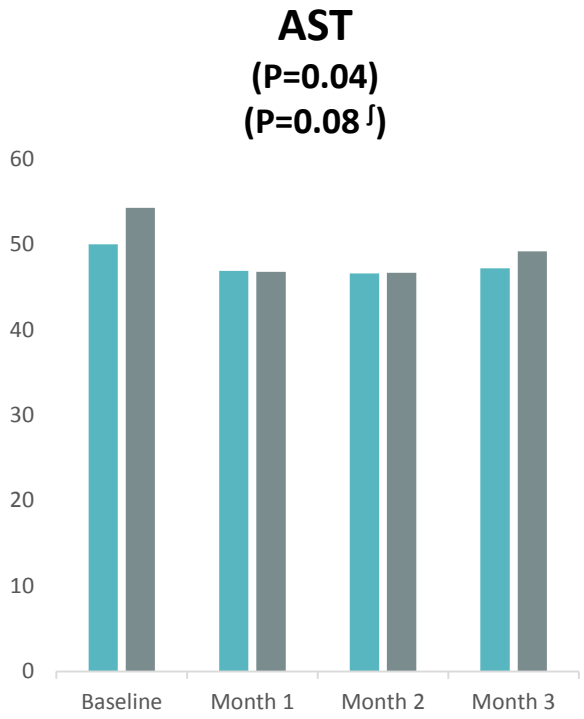
∫P-value adjusting for baseline value, MELD category, and etiology

Geometric mean presented for cCK18, caspase 3/7.

P-values for treatment effect at M3 time point based on last observation carried forward; not adjusted for multiple testing.

Consistent Improvements in Transaminase Levels in Overall Emricasan Group





Placebo BID

Emricasan 25 mg BID

***P-value adjusting for baseline value**
ʃP-value adjusting for baseline value, MELD category, and etiology

Mean presented for ALT and AST.
P-values for treatment effect at M3 time point based on last observation carried forward; not adjusted for multiple testing.

Non-significant Decreases in MELD and Child Pugh Scores in Overall Emricasan Group

Responses related to improvement in INR and bilirubin

Parameter	Placebo (N=42)		Emricasan (N=44)		P-value*
	Baseline	Change at Month 3†	Baseline	Change at Month 3†	
MELD Score	12.9	+0.1	12.8	-0.1	0.50
Child Pugh Score	6.9	+0.1	6.9	-0.2	0.10
Total Bilirubin (mg/dL)	2.59	+0.07	2.25	-0.05	0.19
INR	1.31	+0.02	1.33	-0.02	0.12
Albumin (g/dL)	3.48	+0.06	3.46	+0.02	0.38

*P-values for treatment effect at Month 3, adjusting for baseline, MELD category, etiology; not adjusted for multiple testing.
†Based on last observation carried forward.

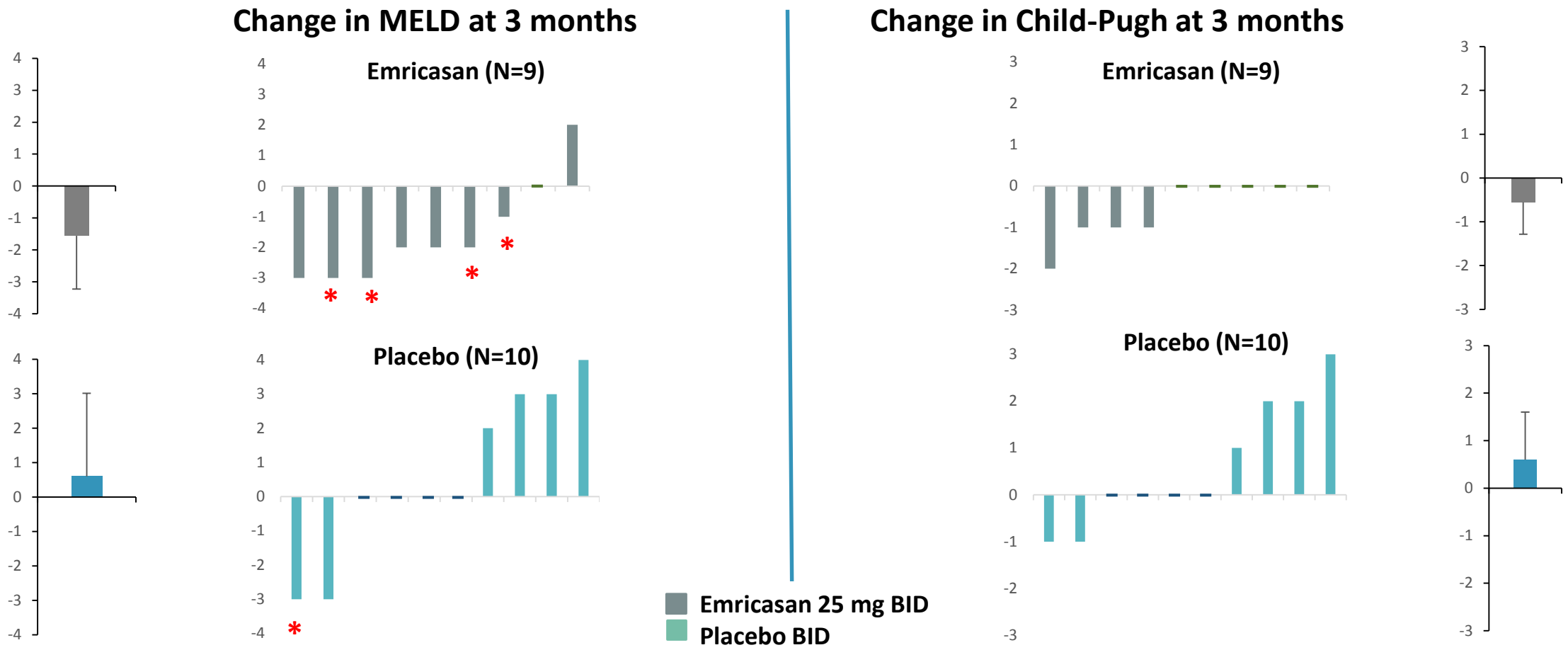
Emricasan Improves MELD and Child Pugh Scores in Patients with MELD ≥15

Responses related to improvement in INR and bilirubin

Parameter	Placebo (N=10)		Emricasan (N=9)		P-value*
	Baseline	Change at Month 3†	Baseline	Change at Month 3†	
MELD Score	16.3	+0.6	16.0	-1.6	0.003
Child Pugh Score	8.2	+0.6	7.8	-0.6	0.003
Total Bilirubin (mg/dL)	4.30	-0.06	3.17	-0.55	0.03
INR	1.45	+0.06	1.54	-0.14	0.0004
Albumin (g/dL)	3.19	+0.05	3.41	+0.07	0.78

*P-values for treatment effect at Month 3, adjusting for baseline, MELD category, etiology; not adjusted for multiple testing.
†Based on last observation carried forward.

Emricasan Improves MELD and Child Pugh Scores in Patients with MELD ≥15



*Also reached MELD ≤14 at Month 3

Subjects with Clinical Worsening Events Were Balanced across Treatment Groups

	Treatment Group	
	Placebo N=42 (%)	Emricasan 25 mg N=44 (%)
Subjects with any clinical worsening event	6 (14%)	6 (14%)
Subjects with development or worsening of ascites	3 (7%)	1 (2%)
Subjects with development or worsening of encephalopathy	2 (5%)	4 (9%)
Subjects with other worsening events*	2 (5%)	2 (5%)

*Including hepatocellular carcinoma recurrence, spontaneous bacterial peritonitis, hepatorenal syndrome, portal hypertensive bleeding

AEs Generally Balanced between Treatment Groups

	Treatment Group	
	Placebo (N=42)	Emricasan 25 mg (N=44)
Number of AEs	109	119
Number of AEs assessed as related	25 (23%)	21 (18%)
Subjects with AEs	30 (71%)	34 (77%)
Subjects with SAEs	6 (14%)	6 (14%)
Subjects with related SAEs	1 (2%)	0
Subjects with moderate AEs	12 (29%)	17 (39%)
Subjects with severe AEs	5 (12%)	5 (11%)
Subjects with AEs leading to discontinuation	2 (5%)	3 (7%)
System Organ Classes of Interest		
Neoplasm*	1 (2%)	1 (2%)
Infection	7 (17%)	7 (16%)
Hepatobiliary	4 (10%)	2 (5%)

*Case of treatment emergent hepatocellular carcinoma in placebo treatment group

Frequent AEs (≥5%) Generally Balanced between Treatment Groups

Adverse Event	Placebo N=42 (%)	Emricasan N=44 (%)
Fatigue	7 (16.7%)	4 (9.1%)
Headache	3 (7.1%)	7 (15.9%)
Nausea	4 (9.5%)	6 (13.6%)
Abdominal pain	3 (7.1%)	3 (6.8%)
Ascites	4 (9.5%)	1 (2.3%)
Hepatic encephalopathy	2 (4.8%)	3 (6.8%)
Edema peripheral	4 (9.5%)	1 (2.3%)
Vomiting	1 (2.4%)	4 (9.1%)

Conclusions

- Confirmed mechanism of action with consistent treatment effect of emricasan on mechanism-specific and clinical biomarkers
  - Favorable trend for primary endpoint cCK18 ($p=0.09$) with significant difference when also adjusting for differences between groups in baseline MELD and disease etiology ($p=0.04$)
- Emricasan improves measures of liver function in patients with baseline MELD ≥15
- Reassuring safety profile
- These results support further study of emricasan in patients with cirrhosis and liver impairment

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