Emricasan (IDN-6556) Orally for 6 Months in Patients with Cirrhosis and Elevated MELD Score Improves Liver Function

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#2095

Abstract

Background: Caspases play a central role in apoptosis and inflammation, contributing to progression of chronic liver disease. Emricasan (EMR), an oral caspase inhibitor, decreases apoptotic and inflammatory markers in patients with chronic liver disease and improved MELD and Child-Pugh (CP) scores after 3 months (mo) vs. placebo (pbo) in cirrhosis patients with baseline MELD ≥15. Final results from the 3-mo open-label EMR phase are reported here.

Methods: In this 6-mo Phase 2 study at 26 U.S. sites, 86 subjects with cirrhosis (alcohol [N=33], HCV [N=25], NASH [N=20], other [N=8]) and MELD 11-18 were randomized to EMR 25 mg or pbo orally twice daily for 3 mo, followed by open-label EMR 25 mg for 3 mo.

Results: 86 subjects were randomized (44 EMR, 42 pbo); 74 completed 3-mo randomized phase (40 EMR, 34 pbo); 69 completed 6 mo (36 EMR-EMR, 33 pbo-EMR). Mean age was 58 yrs, with 63% male, 88% Caucasian, mean (SD) MELD 12.8 (2.4) and CP 6.9 (1.2). EMR for 3 mo led to non-significant decreases vs. placebo in MELD (-0.1 vs. +0.1) and CP (-0.2 vs. +0.1). Further improvement in MELD and CP occurred after 6 mo EMR (both -0.3 vs. Day 1). In the pre-specified subgroup with MELD ≥15, there was a significant treatment effect of EMR vs. pbo on MELD (least squares [LS] adjusted mean difference -2.2) and CP (-1.3) with sustained improvements after 6-mo EMR (MELD -2.8 [Figure 1] and CP -0.7 vs. Day 1). Improvement was observed across etiologies (LS adjusted mean difference for MELD: -1.63 NASH [p<0.05], -0.60 HCV, -0.77 alcohol, -0.74 other; for CP: -0.96 NASH [p<0.05], -0.31 HCV, -0.78 alcohol [p<0.05], -0.95 other). EMR was well tolerated, with no clinically relevant difference vs. pbo in AEs, SAEs, routine labs, vitals, ECGs.

Conclusions: Emricasan had beneficial effects in improving MELD and CP scores in subjects with cirrhosis of various etiologies and mildly to moderately elevated MELD scores after 6 mo and was well tolerated. Baseline MELD ≥15 and NASH etiology were the strongest predictors of response. The current data support the further study of emricasan in patients with cirrhosis and mild to moderate hepatic impairment.

Background

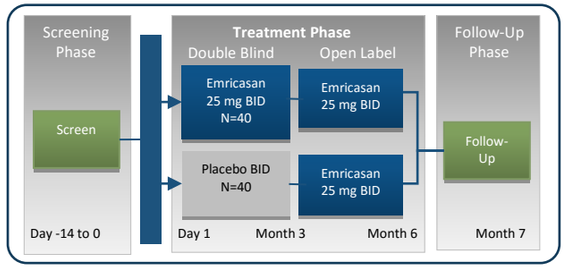
- Caspases are enzymes responsible for executing apoptosis (programmed cell death) and inflammation
- Excessive caspase-mediated apoptosis and inflammation are key drivers of pathology in chronic liver diseases[1]
- Emricasan (IDN-6556): orally active pan-caspase inhibitor
  - Suppresses apoptosis and inflammation
  - Preferential uptake by liver via active transport
  - Decreased ALT, AST, & mechanism-specific biomarkers (cCK18, caspase 3/7) in patients with chronic liver disease due to different etiologies[2,3]
  - Improved MELD and Child Pugh scores (vs. placebo) at 3 months in cirrhosis patients with MELD ≥ 15[4]

Methods

Patient Population

- Key inclusion criteria
  - Clinical, radiological, biochemical evidence of cirrhosis
  - Model for End-Stage Liver Disease (MELD): 11 to 18 [MELD=3.78(Ln bili)+11.2(Ln INR)+9.57(Ln Cr)+6.43]
- Key exclusion criteria
  - Hepatitis C subjects receiving therapy during the study
  - Hepatitis B subjects on stable anti-HBV therapy < 3 mo
  - HIV infection
  - Uncontrolled infection
  - Autoimmune hepatitis
  - Advanced liver disease
    - Variceal hemorrhage within 3 mo of Screening
    - Ascites inadequately controlled on stable meds (at least 3 months prior to Screening)
    - Encephalopathy grade III or IV
    - Child-Pugh (CP) score of 10-15 (Child-Pugh C)

- Phase 2 randomized, double-blind, placebo-controlled study; 26 US sites; 6-month (3-mo placebo-controlled, 3-mo open-label)



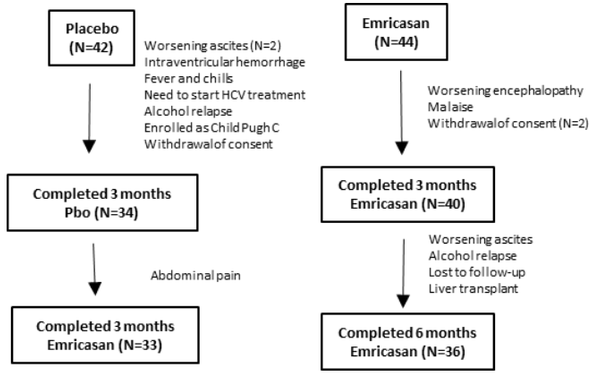
- 3-mo data: placebo vs. emricasan ("treatment effect")
- 6-mo data:
  - Emricasan to emricasan group – 6-mo open-label
    - Day 1 vs. Month 3, and Day 1 vs. Month 6
  - Placebo to emricasan group
    - Day 1 vs. Month 3 for placebo ("natural history"), Month 3 vs. Month 6 for emricasan (open-label)

Results

Patient Population

- N= 86 randomized & received ≥1 dose study drug
  - N=44 emricasan, N=42 placebo
  - Mean age: 58 yrs
  - Sex: 63% male
  - Race: 88% Caucasian
  - Etiology: alcohol (38%), HCV (29%), NASH (23%), other (9%: cryptogenic, PSC, PBC, HCV/ alcohol)
  - Baseline MELD: mean (SD) 12.8 (2.4)
  - Baseline Child Pugh (CP): mean (SD) 6.9 (1.2)

Subject Disposition



Efficacy

- Non-significant decreases in MELD and CP with emricasan vs. placebo at Month 3 in overall population (**Table 1**)
- Further decreases in MELD & CP with emricasan at Month 6

Table 1. MELD, Child Pugh, Total bilirubin, INR, Albumin Change in Overall Group (N=86)

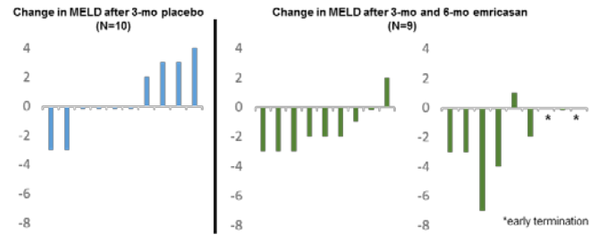
	Placebo (N=42)		Emricasan (N=44)			Adjusted Model p-value
	Baseline	M3 Change	Baseline	M3 Change	M6 Change	
MELD	12.9	+0.1	12.8	–0.1	-0.3	0.466
CP	6.9	+0.1	6.9	–0.2	-0.3	0.124
T. bili	2.59	+0.07	2.25	–0.05	-0.05	0.209
INR	1.31	+0.02	1.33	–0.02	-0.04	0.117
Alb	3.48	+0.06	3.46	+0.02	+0.06	0.440

- Pre-specified sub-group with MELD ≥ 15 had significant improvement in MELD and CP with emricasan vs. placebo (**Figure 1**), due to decreases in total bilirubin and INR (**Table 2**), with improvements sustained at Month 6

Table 2. MELD, Child Pugh, Total bilirubin, INR Change in Subjects with Baseline MELD Score ≥15 (N=20)

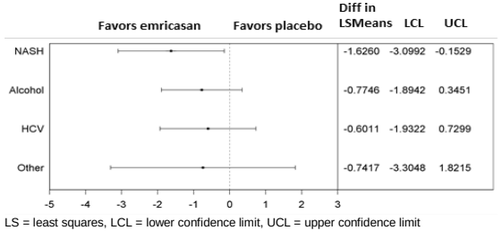
	Placebo (N=10)		Emricasan (N=9)			Adjusted Model p-value
	Baseline	M3 Change	Baseline	M3 Change	M6 Change	
MELD	16.3	+0.6	16.0	–1.6	–2.8	0.003
CP	8.2	+0.6	7.8	–0.6	–0.7	0.003
T. bili	4.30	–0.06	3.17	–0.55	–0.65	0.029
INR	1.45	+0.06	1.54	–0.14	–0.21	<0.001

Figure 1. Change in MELD Score after 3-mo Placebo (N=10) and after 3-mo and 6-mo Emricasan (N=9) in Subjects with Baseline MELD Score ≥15



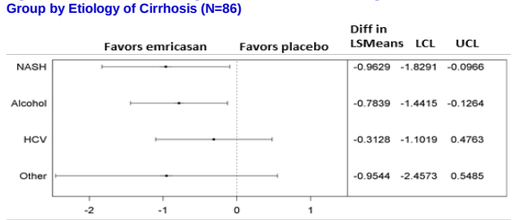
- Improvements in MELD (**Figure 2**) and CP (**Figure 3**) were observed across etiologies (greatest magnitude in NASH)

Figure 2. Forest Plot for Change from Baseline in MELD Score at Month 3 in Overall Group by Etiology of Cirrhosis (N=86)



LS = least squares, LCL = lower confidence limit, UCL = upper confidence limit

Figure 3. Forest Plot for Change from Baseline in Child Pugh Score at Month 3 in Overall Group by Etiology of Cirrhosis (N=86)



Safety

- No deaths during 6-month study
- No related serious AEs (SAEs) in emricasan group
  - 1 related SAE (intraventricular hemorrhage) in placebo
- AE frequencies similar between emricasan vs. placebo, including SAEs, severe AEs, AEs leading to discontinuation
  - Most common AEs included headache (pbo 7% vs. emr 16%), nausea (10% vs. 16%), hepatic encephalopathy (5% vs. 11%), fatigue (14% vs. 9%) [**Poster #2099**]
- No safety signal or concerns based on other routine clinical labs, vital signs, ECG parameters, or physical exam

Conclusions

- Emricasan improved MELD and CP in higher MELD (≥15) and across different etiologies (greatest effect in NASH)
- Emricasan was overall well tolerated in cirrhosis patients with cirrhosis and mild to moderate hepatic impairment
- These results support further study of emricasan in patients with cirrhosis and hepatic impairment

References

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