Emricasan (IDN-6556) Orally for 6 Months in Patients with Non-alcoholic Steatohepatitis (NASH) Cirrhosis Decreases the Progression of MELD Score and Improves Liver Function

#2099

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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) in cirrhosis patients with baseline MELD ≥15. Results from a pre-specified subgroup with NASH cirrhosis (independent of baseline MELD) are reported.

Methods: In this 6-mo Phase 2 study at 26 U.S. sites, 86 subjects with cirrhosis (N=20 [23%] with NASH etiology) and MELD 11-18 were randomized to EMR 25 mg or placebo (pbo) orally twice daily for 3 mo, followed by open-label EMR for 3 mo in both groups. 3 analyses were conducted: 3-mo EMR vs. pbo, 6-mo EMR, and 3-mo pbo to 3-mo EMR.

Results: 20 subjects were randomized (11 EMR, 9 pbo); 16 completed 3-mo randomized phase (8 EMR, 8 pbo); 15 completed 6 mo (7 EMR-EMR, 8 pbo-EMR). Mean age was 61 yrs, with 55% male, 90% Caucasian with mean (SD) MELD 12.9 (2.1) and CP 7.1 (1.1). After 3 mo, there was a significant treatment effect (p<0.05) of EMR vs. pbo on MELD (-1.63 least squares adjusted mean difference), CP (-0.96), INR (-0.13), and caspase 3/7 (-52%), and directional improvement for bilirubin (-0.40, p=0.27). ALT and AST were reduced (median -2.0, -3.0). In subjects treated initially with 3-mo pbo, mean MELD score increased (+1.0, N=9) but decreased (-0.8) after 3-mo EMR (Figure 1). In subjects receiving 6-mo EMR, less progression of MELD occurred with EMR (+0.3 at 3 mo vs. Day 1) compared to the increase in MELD on pbo, with improvement between 3 and 6 mo (+0.1 at 6 mo vs. Day 1). CP improved with EMR (-0.3 at 3 mo, -0.1 at 6 mo). EMR was well tolerated, with no clinically relevant difference vs. pbo in AEs, SAEs, routine labs, vitals, ECGs.

Conclusions: Emricasan had beneficial effects in decreasing the progression of MELD and improving CP scores in subjects with NASH cirrhosis after 3 and 6 mo and was well tolerated. The current data support the further study of emricasan in patients with NASH cirrhosis and mild to moderate hepatic impairment.

Background

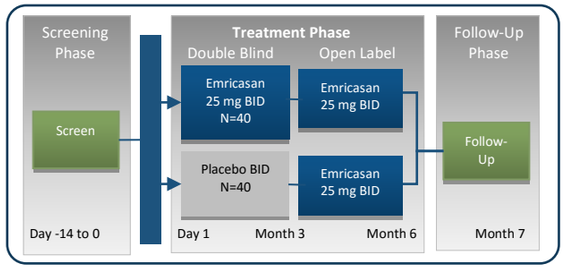
- Caspases are enzymes responsible for executing apoptosis (programmed cell death) and inflammation
- Excessive caspase-mediated apoptosis and inflammation are key drivers of pathology in chronic liver diseases[1]
- Emricasan (IDN-6556): orally active pan-caspase inhibitor
  - Suppresses apoptosis and inflammation
  - Preferential uptake by liver via active transport
  - Shown to decrease ALT, AST, and mechanism-specific biomarkers (cCK18, caspase 3/7) in patients with chronic liver disease due to different etiologies[2,3] and varying levels of hepatic impairment[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 or 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)



Results

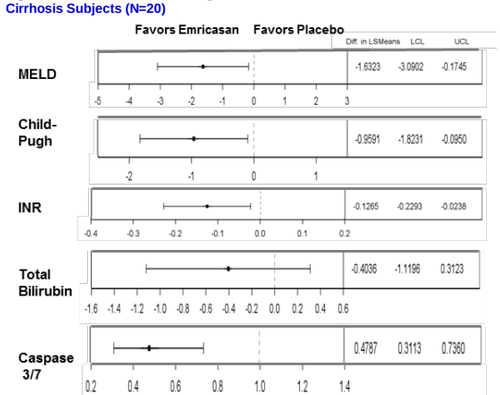
Patient Population and Disposition

- N= 86 randomized & received ≥1 dose study drug
- N=20 (23%) with NASH etiology of cirrhosis randomized
  - N=11 emricasan, N=9 placebo
  - Mean age: 61 yrs
  - Sex: 55% male
  - Race: 90% Caucasian
  - Baseline MELD: mean (SD) 12.9 (2.1)
  - Baseline Child Pugh: mean (SD) 7.1 (1.1)
- N=16 completed 3-mo double blind
  - N=8 emricasan, N=8 placebo
- N=15 completed 6-mo study
  - N=7 emricasan-emricasan, N=8 placebo-emricasan

Efficacy

- Significant improvement in MELD, Child-Pugh, INR, caspase 3/7 (all p<0.05) and favorable trend for total bilirubin with emricasan vs. placebo at Month 3 (**Figure 1**)

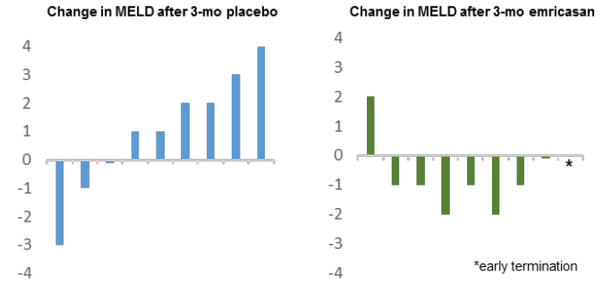
Figure 1. Forest Plot for Change from Baseline in MELD Score at Month 3 in NASH Cirrhosis Subjects (N=20)



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

- In group randomized to placebo (N=9), MELD increased at Month 3 (mean change +1.0), but decreased with emricasan at Month 6 (mean change -0.8 vs. Month 3) (**Figure 2**)

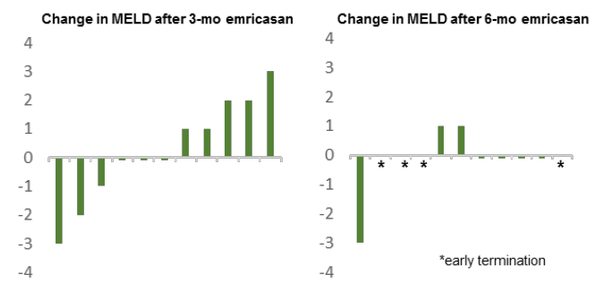
Figure 2. Change in MELD Score after 3-mo Placebo followed by 3-mo Emricasan in NASH Cirrhosis Subjects (N=9)



Mean Change: +1.0 (vs. Day 1) Mean Change: -0.8 (vs. Month 3)

- In group randomized to emricasan (N=11), there was less MELD progression (mean change +0.3 vs. Day 1) vs. placebo (mean change +1.0) at Month 3, and further improvement at Month 6 (mean change +0.1 vs. Day 1, N=7) (**Figure 3**). Similar results observed for CP with emricasan: (-0.3 at Month 3, -0.1 at Month 6).

Figure 3. Change in MELD Score after 6-mo Emricasan in NASH Cirrhosis Subjects (N=11 at Month 3, N=7 at Month 6)



Mean Change: +0.3 (vs. Day 1) Mean Change: +0.1 (vs. Day 1)

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 (**Table 1**), including SAEs, severe AEs, AEs leading to discontinuation
- No safety signal or concerns based on other routine clinical labs, vital signs, ECG parameters, or physical exam

Table 1. Adverse Events Overall and Occurring in >5% of Subjects Treated with Emricasan or Placebo for 3 Months (N=86)

	Placebo (N=42)	Emricasan (N=44)
Any adverse event	30 (71%)	34 (77%)
Headache	3 (7%)	7 (16%)
Nausea	4 (10%)	7 (16%)
Hepatic encephalopathy	2 (5%)	5 (11%)
Vomiting	1 (2%)	5 (11%)
Fatigue	6 (14%)	4 (9%)
Abdominal pain	3 (7%)	3 (7%)
Arthralgia	0	3 (7%)
Urinary tract infection	1 (2%)	3 (7%)
Ascites	3 (7%)	1 (2%)
Muscle spasms	3 (7%)	0
Peripheral edema	4 (10%)	1 (2%)

Conclusions

- Emricasan decreased progression of MELD and improved Child Pugh scores in subjects with NASH cirrhosis
- Emricasan was overall well tolerated in patients with cirrhosis and mild to moderate hepatic impairment
- These results support further study of emricasan in patients with NASH cirrhosis and hepatic impairment

References

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