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

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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 cell death and inflammation in patients with 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 cirrhosis (independent of baseline MELD) are reported.

Methods: In a 6-mo Em (placebo) study (26 US 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 3 mo for both groups. 2 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); 13 completed 6 mo (7 EMR-EMR, 6 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 in MELD (-1.63 least square adjusted mean change, CP (-0.67), 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 compared to pbo (-0.4 at 3 mo, -0.6 at 6 mo). EMR was well tolerated, with no clinically relevant difference in labs, vital signs, ECG parameters, or physical exam.

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, with no clinically relevant difference vs pbo in AEs, SAEs, routine labs, vital, ECGs.

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.

Emricasan (IDN-6556): orally active pan-caspase inhibitor
• Suppresses apoptosis and inflammation
• Preferential uptake by liver via active transport

Shown to decrease AEs, ALT, AST, and mechanism-specific biomarkers (cCK18, caspase 3/7) in patients with chronic liver disease due to different etiologies and varying levels of hepatic impairment.

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
  • Variecal hemorrhage within 3 mo of Screening
  • Ascolates inadecuate 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)

• 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)

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 Child Pugh: mean (SD) 7.1 (1.1)
  • N=16 completed 3-mo double blind study
  • 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 <0.05) and favorable trend for total bilirubin with emricasan vs. placebo at Month 3 (Figure 1).

Safety
• No deaths during 6-month study
• No related serious AEs (SAEs) in emricasan group
  • 1 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

References

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Table 1. Adverse Events Occurred in ≥5% of Subjects Treated with Emricasan or Placebo for 3 Months (N=44)

Poster #2095
See related Poster #2095