Multicenter, Double-Blind, Randomized Trial of Emricasan in Subjects Post Liver Transplantation with Recurrent Hepatitis C Virus and Liver Fibrosis or Cirrhosis Despite Achieving Sustained Virologic Response: POLT

K. Rajender Reddy[1], Michael P. Curry[2], Catherine T. Frenette[3], Fredric G. Regenstein[4], Eugene R. Schiff[5], Zachary D. Goodman[6], James M. Robinson[7], Jean L. Chan[7], Alfred P. Spada[7], Joanne C. Imperial[7] and David Hagerty[7]
[1]University of Pennsylvania Medical Center, [2]Beth Israel Deaconess Medical Center, Boston, MA, [3]Scripps Clinic, [4]Tulane Medical Center, [5]University of Miami, [6]Inova Fairfax Hospital, [7]Conatus Pharmaceuticals

Background:

Before the use of direct-acting antiviral agents (DAAs), recurrent HCV post liver transplantation (LT) was common, often leading to progressive fibrosis and liver failure.

Newer DAA agents have high sustained virologic response (SVR) [1-3] rates in post LT HCV patients, but many transplanted prior to their use have residual fibrosis.

Caspases mediate apoptosis and inflammation, contributing to chronic liver disease (CLD) progression[4]. Emricasan (EMR), an oral pan-caspase inhibitor, reduces hepatic inflammation/fibrosis and decreases mechanism-specific (caspase3/7) and inflammatory (ALT) biomarkers in CLD patients[5,6] (**Fig. 1**). This exploratory study assessed EMR's effect on Ishak fibrosis stage at month 24 in HCV subjects post LT achieving SVR[7].

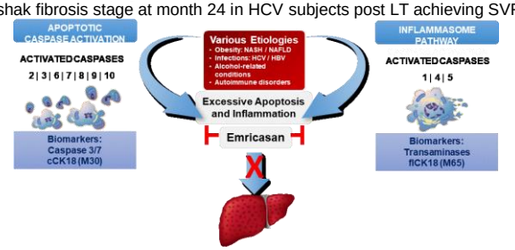

Figure 1: Caspase activation pathways in Liver Disease

Objectives:

Primary

- To assess the effect of oral EMR upon Ishak fibrosis stage in subjects with HCV reinfection and liver fibrosis or cirrhosis following LT for chronic HCV who subsequently achieved a SVR following anti-HCV therapy.

Secondary

- To determine the effects of oral EMR on markers of mechanism of action and inflammation
- To assess the safety and tolerability of oral EMR in subjects status post orthotopic liver transplantation

Study Design, Methods & Endpoints:

A total of 64 LT subjects (Ishak fibrosis stage F2-F6) were randomized 2:1 to 25 mg BID EMR or PBO for 24 months treatment. Baseline, M12, and M24 biopsies were reviewed by a central pathologist (**Fig. 2**).

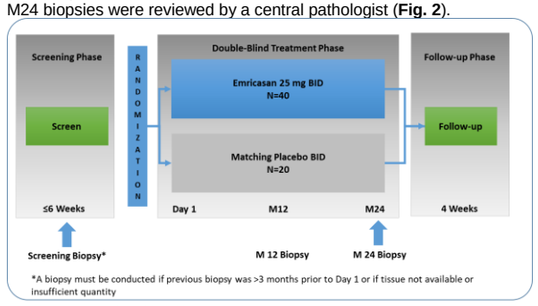

Figure 2: Study design scheme

- Primary endpoint: improvement or stability in Ishak fibrosis stage between EMR compared to PBO at M24
  - ❖ Improvement defined as ≥1-stage decrease in fibrosis stage (all subjects)
  - ❖ Stability defined as no change in fibrosis stage (in baseline F2-F5 subjects)
- Secondary endpoints included:
  - ❖ Change from baseline in caspases 3/7 and ALT
  - ❖ Long-term assessment of safety and tolerability of EMR over 24 months in subjects post liver transplantation
- Statistical considerations:
  - ❖ Primary endpoint was assessed using multiple imputation approach for subjects with missing data.
  - ❖ All other analyses were done on observed data

Key Inclusion Criteria:

- History of liver transplant for HCV-induced liver disease and diagnosis of HCV infection post liver transplantation
- SVR with anti-viral therapy within 18 months prior to Day 1
- Confirmed liver fibrosis or cirrhosis (Ishak F2 to F6) on biopsy, as read by central histopathologist within three months of Day 1

Key Exclusion Criteria:

- Active HIV and/or HBV infection
- Autoimmune diseases
- Chronic liver disease of any other etiology
- Evidence of allograft rejection within three months of Day 1
- Decompensated liver disease
- HCC at entry into the study
- Renal transplant or severe renal impairment with eGFR <30mL/min/1.73m^2

Demographics:

N=64 subjects included 50 M and 14 F, mean age 61. Median time from LT was 7.1 yrs. N=52 (81%) received DAAs alone; median time from SVR 230 days. N=54 (84%) subjects received tacrolimus-based immune suppression; none mTOR. Baseline characteristics were equally distributed among the treatment groups (**Table 1**).

Results:

- The overall response by multiple imputation at M24 was 77% EMR vs. 74% PBO (p=NS) (**Fig. 3**)
- EMR had greater response vs. PBO in the pre-specified F2-F5 (ad hoc p=0.082) and F3-F5 (ad hoc p=0.011) subgroups (**Table 2**; **Fig. 4**)
- Median baseline and Month 24 ALT were 18 IU/L and 16 IU/L in EMR and 21 IU/L and 17 IU/L in PBO, respectively
- Baseline caspase 3/7 values were modestly elevated with a clear treatment effect between baseline and month 12 but no effect observed at month 24 (**Fig. 5**) comparing EMR vs. PBO
- No observable safety profile differences with EMR and PBO (**Table 5**)

Table 1: Baseline Characteristics

	Emricasan (N=41)	Placebo (N=23)
Ishak Fibrosis Stage (n%)		
F2	9 (22.0)	6 (26.1)
F3	20 (48.8)	7 (30.4)
F4	5 (12.2)	5 (21.7)
F5	2 (4.9)	2 (8.7)
F6	5 (12.2)	3 (13.0)
Median		
ALT (U/L)	18.0	21.0
Caspase 3/7 (raw RLU)*	1808.5	2057.0
Liver Transplant History		
Median number of years since transplant	5.87	6.55
Median time since SVR (days)	227.0	233.0
Immunosuppressant Therapy		
tacrolimus +/-steroids cyclosporine +/- steroids	35 (85.5) 5 (12.2)	19 (82.6) 4 (17.4)
Previous HCV treatement		
antiviral antiviral-immunotherapy	33 (80.5) 8 (19.5)	19 (82.6) 4 (17.4)

Table 2: Month 24 Ishak Fibrosis Stage Result`s

Observed Cases	Improved n (%)	Stable n (%)	Worsened n (%)
Emricasan (N=32)	18 (56.3)	12 (37.5)	2 (6.3)
F2 (N=6)	5 (83.3)	0 (0.0)	1 (16.7)
F3-F5 (N=21)	13 (61.9)	7 (33.3)	1 (4.8)
F6 (N=5)	0 (0.0)	5 (100.0)	N/A
Placebo (N=19)	12(63.1)	2 (10.5)	5 (26.3)
F2 (N=5)	4 (80.0)	1 (20.0)	0 (0.0)
F3-F5 (N=11)	5 (45.5)	1 (9.1)	5 (45.5)
F6 (N=3)	3 (100.0)	0 (0.0)	N/A

Figure 3. Primary Endpoint: Response Rate F2-F6 Ishak Fibrosis Stages at Month 24*

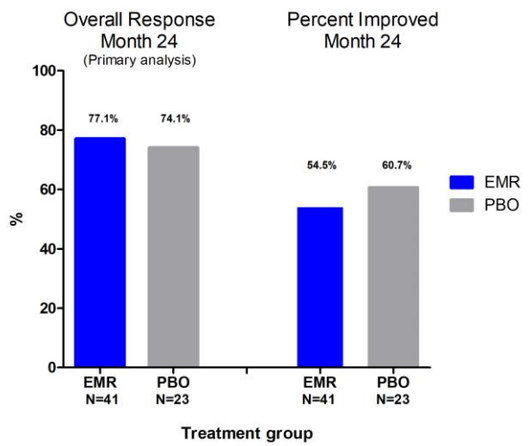

Figure 4: Prespecified F3-F5 Subgroup: Ishak Fibrosis Stage Response at Month 24

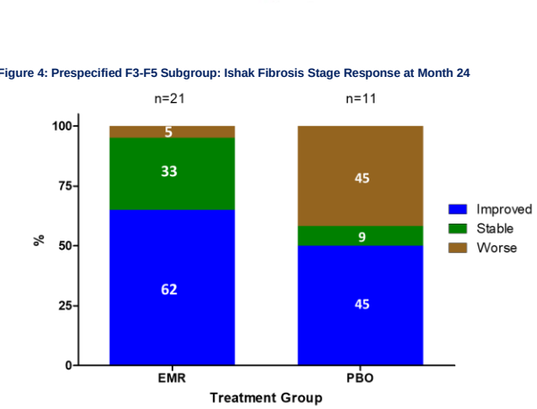

Figure 5: Caspase 3/7 Activity

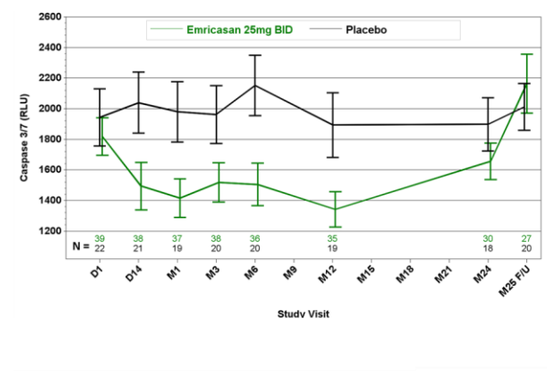

Table 3: Safety Overview

	Emricasan (N=41)	Placebo (N=23)
Treatment Emergent Adverse Events (TEAEs): Balanced Between Groups		
Subjects with TEAE – n (%)	37 (90.2)	20 (87.0)
Subjects with serious TEAE – n (%)	14 (34.1)	7 (30.4)
Subjects with moderate TEAE – n (%)	26 (63.4)	16 (69.6)
Subjects with severe TEAE – n (%)	13 (31.7)	7 (30.4)
Subjects with TEAE leading to study discontinuation – n (%)	3 (7.3)	3 (13.0)
Adverse Events with Preferred Term Incidence of ≥10% in Either Treatment Group		
Diarrhea	9 (22)	5 (21.7)
Nausea	7 (17.1)	4 (17.4)
Fatigue	7 (17.1)	6 (26.1)
Arthralgia	6 (14.6)	2 (8.7)
Upper respiratory tract infection	1 (2.4)	4 (17.4)
Muscle spasms	0 (0.0)	3 (13.0)
Treatment Emergent Adverse Events of Interest: System Organ Class-Preferred term		
Infections & infestations	13 (31.7)	9 (39.1)
Neoplasms, malignant		
Hepatocellular CA*	2 (4.9)	0 (0)
Pancreatic CA	0 (0)	1 (4.3)
Prostate CA	1 (2.4)	0 (0)
Squamous cell CA, skin	0 (0)	1 (4.3)

*10 subjects in EMR group vs 2 subjects in PBO underwent liver transplantation for HCC; one recurrence in EMR group was within 4 years of liver transplantation; the other was at 11 years post transplant in an F3 subject.

Summary:

- In liver transplant recipients with recurrent HCV, fibrosis, and despite SVR:
  - ❖ The primary endpoint, subjects with improvement or stability in Ishak fibrosis stage, was similar between groups at 24 months (p=NS)
  - ❖ The high placebo response rate in the F6 subgroup may have obscured a treatment response
  - ❖ However, there was both significant improvement & stability in fibrosis stage in the F3-F5 subgroup vs. placebo (p=0.011)
  - ❖ Tolerability and safety profiles were similar in emricasan and placebo subjects
  - ❖ Emricasan safety profile was encouraging given use for 24 months in combination with immunosuppression

Special thanks to the study coordinators, the patients, and their families

References

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