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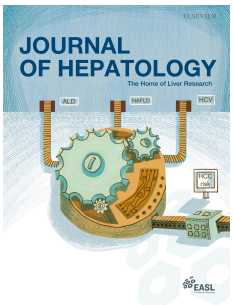

Randomized Placebo-Controlled Trial of Emricasan in Non-alcoholic Steatohepatitis (NASH) Cirrhosis with Severe Portal Hypertension

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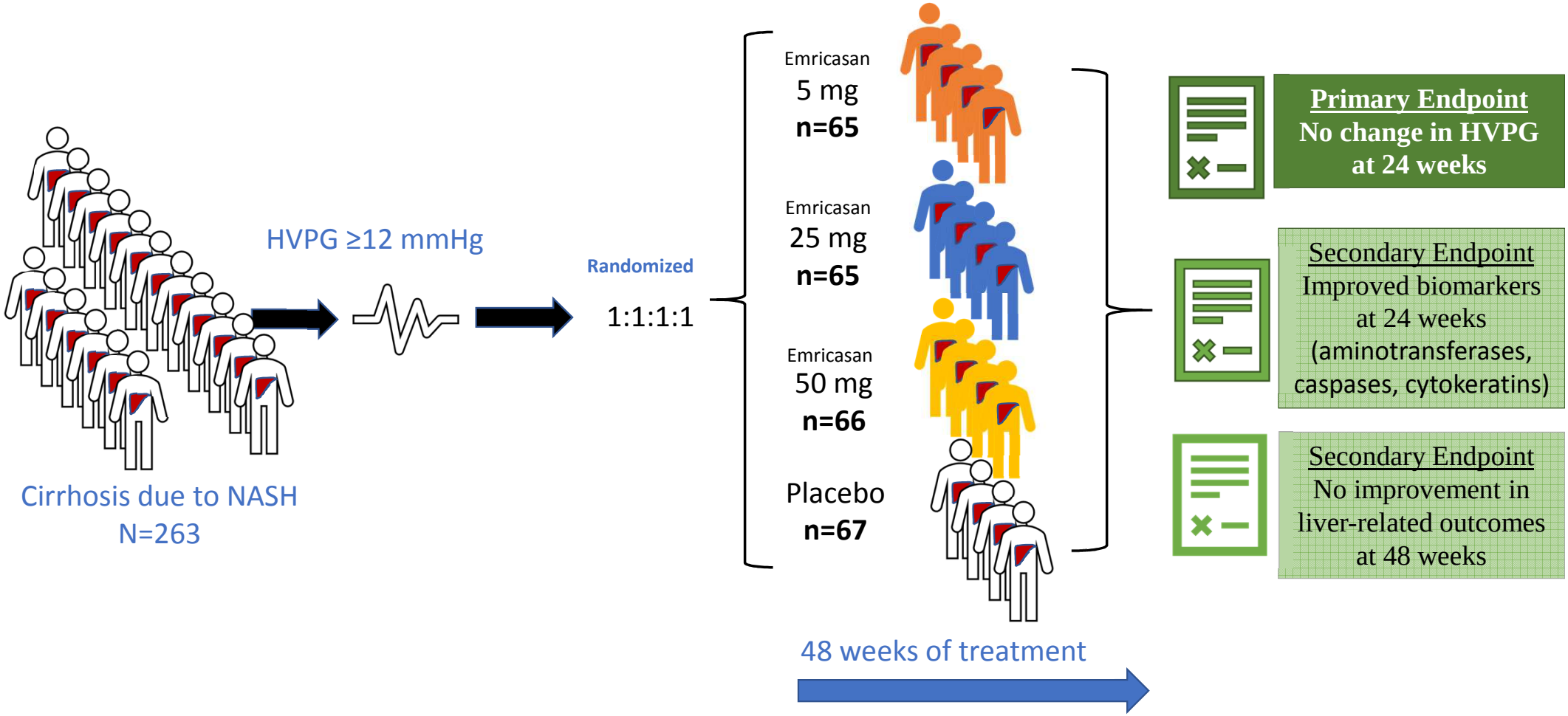
Conatus 14: Multicenter randomized controlled study comparing emricasan, (a caspase inhibitor) at 3 different doses vs. placebo in patients with NASH cirrhosis and severe portal hypertension



Title: Randomized Placebo-Controlled Trial of Emricasan in Non-alcoholic Steatohepatitis (NASH) Cirrhosis with Severe Portal Hypertension

Short title: Emricasan in NASH cirrhosis with severe portal hypertension

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Abstract

Background and Aim: Emricasan, an oral pan-caspase inhibitor, decreased portal pressure in experimental cirrhosis and in patients with cirrhosis and portal pressure (assessed by the hepatic venous pressure gradient [HVPG]) ≥12 mmHg. We aimed to confirm these results in a randomized, placebo-controlled, double blind study.

Methods: Multicenter study including 263 patients with cirrhosis due to non-alcoholic steatohepatitis (NASH) and baseline HVPG ≥12 mmHg randomized 1:1:1:1 to emricasan 5 (n=65), 25 (n=65), 50 (n=66) mg or placebo (n=67) orally twice daily for up to 48 weeks. Primary endpoint was change in HVPG (ΔHVPG) at week 24. Secondary endpoints were changes in biomarkers (aminotransferases, caspases, cytokeratins) and development of liver-related outcomes.

Results: There were no significant differences in ΔHVPG for any emricasan dose vs. placebo (-0.21, -0.45, -0.58 mmHg, respectively) adjusted by baseline HVPG, compensation status, and non-selective beta-blocker use. Compensated subjects (n=201 [76%]) tended to have a greater decrease in HVPG (emricasan all vs. placebo, p=0.06), the decrease being greater in those with higher baseline HVPG (p=0.018), with a significant interaction between baseline HVPG (continuous, p=0.024; dichotomous at 16 mmHg [median], p=0.013) and treatment. Biomarkers decreased significantly with emricasan at week 24 but returned to baseline levels by week 48. New or worsening decompensating events (~10% over median exposure of 337 days), progression in MELD and Child Pugh scores, and treatment-emergent adverse events were similar among treatment groups.

Conclusions: Despite reduction in biomarkers indicating target engagement, emricasan was not associated with improvement in HVPG or clinical outcomes in patients with NASH cirrhosis and

severe portal hypertension. Compensated subjects with higher baseline HVPG had evidence of a small treatment effect. Emricasan treatment appeared safe and well-tolerated.

Lay Summary:

Cirrhosis (scarring of the liver) is the main consequence of non-alcoholic steatohepatitis (NASH) Cirrhosis leads to high pressure in the portal vein and this accounts for most of the complications of cirrhosis. Reducing portal pressure is beneficial in patients with cirrhosis. We studied the possibility that emricasan, a drug that improves inflammation and scarring in the liver, would reduce portal pressure in patients with NASH cirrhosis and severe portal hypertension. Our results in a large, prospective, double-blind study could not demonstrate a beneficial effect of emricasan in these patients.

Introduction

Cirrhosis due to non-alcoholic fatty liver disease is fast becoming a major disease burden worldwide (1). In fact, non-alcoholic steatohepatitis (NASH) is a leading indication for liver transplantation in the U.S. (2). Portal hypertension is a key driver of the major complications of cirrhosis that define decompensation, the latter being the main predictor of death in cirrhosis. (3, 4) A portal pressure (determined by the hepatic venous pressure gradient [HVPG]) ≥10 or ≥12 mmHg is the strongest predictor of decompensation in patients with mostly viral-induced cirrhosis (4), but also in patients with NASH cirrhosis (5). Importantly, decreases in HVPG are associated with lower rates of decompensation and death in compensated and decompensated patients (6). There are currently no approved therapies that can ameliorate the abnormalities leading to significant portal hypertension in NASH cirrhosis patients.

Emricasan is an oral pan-caspase inhibitor that decreased excessive apoptosis, inflammation, and fibrosis in animal models of NASH and decreased portal pressure and/or improved survival in rodent models of cirrhosis (7, 8). A 28-day open-label study of emricasan (25 mg orally twice daily) in 22 patients with compensated cirrhosis (primarily due to NASH or HCV) demonstrated clinically meaningful decrease in mean HVPG of -3.7 mmHg in a subgroup with baseline HVPG ≥12 mmHg, with concomitant decreases in aminotransferases that suggested an intrahepatic anti-inflammatory effect (9).

We now report the results of a randomized, double-blind, placebo-controlled multicenter trial of emricasan in NASH cirrhosis patients with severe portal hypertension (HVPG ≥12 mmHg). This study focused on patients with compensated cirrhosis but also enrolled ~25%

decompensated patients (with no more than one decompensating event) to determine if similar efficacy would be observed.

Patients and Methods

Study Oversight

The study was designed by expert clinicians who had experience in cirrhosis and portal hypertension in collaboration with representatives from the Sponsor. The study protocol was approved by the institutional review boards and ethics committees at each participating site prior to study initiation. The study was conducted in accordance with standards that met applicable regulations, including the International Conference on Harmonization Guideline for Good Clinical Practice. All patients provided written informed consent prior to participation in the study. Data were collected by investigators. An independent Data Monitoring Committee regularly reviewed unblinded safety data from the study. A separate independent Hepatic Adjudication Committee reviewed in a blinded fashion cases that met protocol-specified criteria for closer monitoring of elevated liver tests. Authors from the Sponsor had access to all data and vouch for the integrity of the data analyses. All authors participated in the drafting and/or review of the manuscript and provided final approval to submit. No medical writer was involved in the manuscript development.

Study Design

Across 59 sites in the US, Spain, France, Germany, and Switzerland, NASH cirrhosis patients with screening HVPG ≥12mmHg were randomized 1:1:1:1 to emricasan 5 mg, 25 mg, or 50 mg or matching placebo orally twice daily for 24 weeks with HVPG performed again at week 24. Patients were stratified by baseline compensated vs. decompensated status and by use of non-

selective beta-blockers (NSBB) or not. The Sponsor used a validated Interactive Web Response System with strict quality control procedures for central coordination and random assignment of subjects to emricasan or placebo. Study participants, site personnel, and the Sponsor were all blinded to treatment group assignment. After completing week 24, subjects were eligible to continue the same randomized blinded treatment for an additional 24 weeks. Emricasan doses selected were based on dose-response modelling using biomarkers (ALT, AST, cCK18, caspase 3/7) in earlier Phase 1 and 2 studies (primarily patients with chronic liver disease due to HCV infection) and based on the dose (25 mg) used in the prior open-label study (9).

The primary endpoint of the study was to compare the change in HVPG from baseline to week 24 between emricasan and placebo. Secondary endpoints were a) to assess the safety and tolerability of emricasan, b) to characterize the dose-response of emricasan on portal pressure as assessed by HVPG at Week 24, c) to assess whether emricasan compared to placebo improves HVPG response at Week 24 using a 20% reduction from baseline response definition, and d) to assess whether emricasan compared to placebo decreases mechanism specific (caspase 3/7) and non-specific alanine aminotransferase (ALT) biomarkers at Weeks 24 and 48. Exploratory endpoints were to assess whether emricasan compared to placebo decreases development of decompensation or worsening of decompensation and to assess whether emricasan compared to placebo improves liver function and prognosis at Weeks 24 and 48 as assessed by model for end-stage liver disease (MELD) and Child-Pugh (C-P) scores.

Patient Population

Key inclusion criteria were: cirrhosis due to NASH with exclusion of other causes of cirrhosis, compensated or decompensated (no more than one decompensating event), HVPG ≥12

mmHg, on stable medications (NSBB, nitrates, diuretics, lactulose, rifaximin, statins) at least 3 months. At least 60% subjects but no more than 75% were to have compensated cirrhosis. The presence or absence of varices was not a selection criterion. A complete list of inclusion and exclusion criteria, including criteria for decompensating events, is provided (**Table S1**). All versions of the protocol are published online as supplementary information (Supplementary CTAT table).

Study Procedures

After a 6-week screening period, eligible subjects were randomized and seen at study visits in an outpatient setting every 4 weeks during the initial 24-week phase and every 8 weeks during the second 24-week phase, with a follow-up visit off study drug ~2 weeks after the last visit. At each study visit, vital signs, MELD, and Child-Pugh status were assessed, and blood samples obtained for routine chemistries, hematology, coagulation, and biomarkers (including caspase 3/7, cCK18, flCK18). Transient elastography to assess liver stiffness was performed at screening, week 24, and week 48 at a subset of sites. Subjects were assessed for the occurrence of clinical outcome events (new or worsening decompensation) throughout the study. Worsening decompensation was defined as worsening ascites requiring paracentesis (in subjects with prior history of ascites), recurrent variceal hemorrhage (VH) (in subjects with prior history of VH) or worsening hepatic encephalopathy (HE) requiring hospitalization (in subjects with prior history of HE).

HVPG was done at the end of screening (baseline) and again at week 24. All HVPG measurements were performed and pressure tracings recorded according to standard operating procedure outlined in a study manual provided to sites and following didactic training. Each study site provided an acceptable sample HVPG tracing prior to patient enrollment. Portal

pressure was determined indirectly by the HVPG, as previously described (10). Using the transjugular approach, a balloon-tipped catheter was advanced into a hepatic vein under fluoroscopic guidance. The free hepatic venous pressure (FHVP) was measured with the balloon deflated, and the wedged hepatic venous pressure (WHVP) with the balloon inflated until the branch of hepatic vein was completely occluded. HVPG was obtained by subtracting FHVP from WHVP. Measurements were performed in triplicate. Tracings were read independently by a single experienced investigator (GGT) who provided a subjective assessment of the overall quality (excellent, very good to good, or fair) and if significant variability was present. Only subjects with screening HVPG assessed at least fair in quality were eligible for randomization.

Clinical laboratory tests and biomarker measurements were performed by PPD Labs (Highland Heights, KY, USA; Zaventem, Belgium). Keratin-18 is a major cytoplasmic intermediate filament protein cleaved by executioner caspases during apoptosis and cell death. Full□length keratin-18 (flCK18) and caspase cleaved keratin-18 (cCK18) were quantified using ELISA detecting the M65 (VLVbio, reference range: 115□413 U/L) and M30 (VLVbio, reference range: <260 U/L) epitopes, respectively. Caspase-3/7 activity (Promega, reference range: 1429□3908 relative light units) detects activity of the executioner caspases-3 and -7.

Statistical Analyses

The primary analysis was performed after the collection of all week 24 HVPG data. A final analysis was performed after the study was completed. Data (mean [SD] or N [%]) are summarized by treatment group (emricasan 5 mg, 25 mg, 50 mg, placebo) as well as for all 3 emricasan doses together (referred to as “emricasan all”).

The primary endpoint (mean change in HVPG from baseline to week 24) was analyzed using a fixed effects analysis of covariance (ANCOVA) model in the full analysis set, which

included all randomized subjects receiving at least 1 dose of study drug, comparing the change from baseline in HVPG for each emricasan dose vs. placebo, adjusting for baseline HVPG, baseline compensated vs. decompensated status, and baseline NSBB use. A one-step Dunnett's test adjusted for multiple comparisons of emricasan doses vs. placebo. Using multiple imputation, missing data for HVPG was imputed a priori based on demographic and baseline clinical factors (i.e. age, gender, compensated status, MELD, Child-Pugh). A per-protocol analysis (for the primary endpoint only) was also performed excluding subjects with missing week 24 HVPG, significant non-compliance with study drug, or significant confounders such as initiation of NSBB after the screening HVPG. Pre-specified sub-group analyses were performed in compensated, decompensated, and treated or not with NSBB. Ad-hoc analyses were performed in compensated subjects according to baseline HVPG and presence or absence of varices. All subgroup analyses were performed with ANCOVA using observed data and adjusting only for baseline HVPG, with nominal p-values reported for informational purposes only. HVPG responder analyses were performed using a fixed effects logistic regression model using observed data and adjusting only for baseline HVPG. Three different published responder criteria were used: 1) decrease ≥20% or to <12 mmHg (6), 2) decrease ≥10% or to <12 mmHg (6), and 3) decrease ≥10% or to <10 mmHg (11). Ad-hoc analyses of mean change in HVPG according to biomarker (caspase 3/7, cCK18, flCK18, ALT) response was performed, where the biomarker response was defined (arbitrarily) as ≥20% decrease from baseline at 1) all visits from weeks 4 to 24, or 2) at least 4 of 6 visits from week 4 to 24) were performed.

Continuous secondary endpoints were analyzed using ANCOVA adjusting for baseline value with log-transformation (e.g. biomarkers) as appropriate. Binary secondary endpoints (e.g. clinical outcome events, MELD progression) were analyzed using a logistic regression model,

adjusting for baseline value. No multiplicity adjustment or imputation methods were used for analysis of secondary endpoints. Clinical outcome events included new or recurrent VH, new onset ascites requiring chronic diuretics, worsening ascites requiring paracentesis, new onset or worsening HE requiring hospitalization. For compensated subjects who experienced a new decompensation event that subsequently met criteria for worsening, both new and worsening events were included in the analysis. The occurrence of clinical outcome events was analyzed based on subject incidence by the end of the study as well as based on an ad hoc time-to-event analysis. Pre-specified analyses of MELD and Child-Pugh evaluated the number of subjects having 4-point MELD or 2-point Child-Pugh progression. Ad-hoc analyses evaluated the number of compensated subjects with baseline MELD score ≤12 reaching MELD ≥15 and the number of baseline Child-Pugh A subjects progressing to Child-Pugh B.

A sample size of 192 (48 per group) subjects was estimated to provide 80% power to detect a statistically significant difference between at least one emricasan dose vs. placebo in the mean change from baseline in HVPG, assuming a difference of 3 mmHg and standard deviation of 4.5 mmHg, at the conventional alpha=0.05. Assuming an attrition rate of 20%, the sample needed would be 240 (60 subjects per group)

Results

Subject Disposition

A total of 564 subjects signed informed consent and were screened between October 2016 and March 2018, with 263 randomized and treated with study drug, with the last subject follow-up visit occurring in April 2019 (**Fig. S1**). The most common reason for screen failure was not meeting HVPG ≥12 mmHg (N=137 [45.5%]). Of the 263 randomized, 250 completed the initial 24-week phase, 236 consented to the second 24-week phase, and 219 completed week

48. Evaluable HVPG data was available for 243 subjects (N=13 not done due to subject not completing week 24, N=4 not done for other reasons, N=3 HVPG tracing not evaluable) (**Fig. S1**). Of the 263 patients randomized, 124 (47.1%) subjects reported a biopsy showing NASH features (of these, 52 had biopsy only, whereas 72 had both biopsy and at least 2 metabolic features), 126 (47.9%) had >=2 metabolic features alone (without biopsy) and 13 (4.9%) had biopsy showing some but not all NASH features with fatty liver or at least 1 metabolic feature.

Subject Demographics and Baseline Characteristics

Demographics and baseline characteristics were generally balanced across treatment groups (**Table 1)**. Overall, mean age was 61 years, with 57% female and 91% Caucasian. The majority (76%) had compensated cirrhosis and 24% had decompensation (28% prior VH, 40% diuretic-responsive ascites, 32% history of ≥grade 2 HE). Mean MELD score was 9, and 88% were CP A at baseline. Most subjects had varices (71% compensated, 76% decompensated) with 41% treated with NSBB. Mean liver stiffness (assessed by transient elastography) was 38.8 kPa, and mean platelet count was 98 K/mm^3. The majority (75%) had at least 2 metabolic risk factors for NASH for at least 5 years preceding cirrhosis, including diabetes (79%), hypertension (76%), and obesity (82%) with mean BMI of 35.3 kg/m^2. Mean cCK18 and flCK18 were moderately elevated, and mean caspase 3/7 was mildly elevated. Mean (SD) HVPG for all subjects was 17 (3.6) mmHg (range 12.0 to 27.5 mmHg).

Primary Efficacy Endpoint: HVPG

In the overall patient population, there was no statistically significant change in HVPG at week 24 for any emricasan dose compared to placebo, with least squares mean (LSM) difference and 95% confidence intervals of -0.21 (-1.4, 0.95), -0.45 (-1.6, 0.72), -0.58 (-1.7, 0.59) mmHg for emricasan 5 mg, 25 mg, and 50 mg, respectively (**Table 2, Fig. 1**). The change in HVPG

ranged from approximately -5 mmHg to +5 mmHg in placebo subjects **(Fig. 2A)**. Similar results were obtained in the per-protocol analysis. In addition, sensitivity analyses excluding HVPGs assessed as "fair" quality and excluding HVPGs with significant variability showed similar results as the primary analysis (data not shown).

Compensated subjects tended to have a greater decrease in HVPG (LSM difference of -0.94 mmHg vs. placebo, p=0.06) when all emricasan doses were combined (**Table 2, Fig. 1**). This trend to greater decrease in HVPG with emricasan was more prominent in those with varices (**Table 2**). In decompensated patients, there appeared to be a dose response with greater decrease from baseline in HVPG with emricasan 50 mg, but the placebo group had an unexpectedly large mean decrease in HVPG (2.6 mmHg) that rendered the LSM differences in HVPG between emricasan and placebo non-significant. There were no significant differences in HVPG between emricasan and placebo according to NSBB use. HVPG responder analyses showed similar findings for all subjects and compensated and decompensated subgroups with a non-significant trend for more responders with emricasan, especially in compensated subjects (**Table S2**).

Given the trend for a greater decrease in HVPG with emricasan in compensated subjects, we evaluated if there were factors that predicted likelihood of better response (i.e. greater decrease in HVPG) and found that baseline HVPG was the strongest predictor. In compensated subjects, baseline HVPG (as a continuous variable) was a significant covariate for HVPG change at week 24 (p=0.0002) using a model that included all 4 treatment groups. In a model combining the 3 emricasan doses, baseline HVPG remained a significant covariate (p=0.018). In addition, there was a significant interaction between treatment and baseline HVPG, whether baseline HVPG was treated as a continuous variable (p=0.024) or dichotomized by the median value of

16 mmHg (p=0.013). Compensated subjects with baseline HVPG ≥16 mmHg had LSM difference in HVPG of -2.2 mmHg (95% CI: -3.5, -0.8) with emricasan all vs. placebo (**Table 2, Fig. 1**). In contrast, a model that assessed the interaction between treatment and baseline HVPG in compensated subjects did not find a significant interaction between treatment and presence of varices (p=0.21).

Since baseline HVPG was a significant covariate, we evaluated the correlation between change in HVPG at week 24 vs. baseline HVPG (**Fig. 2**). In placebo subjects, change in HVPG at week 24 was not correlated with baseline HVPG (r=-0.12), but for all three emricasan doses, there was a greater decrease in HVPG at week 24 with higher baseline HVPG, particularly at 50 mg (r=-0.42) (**Fig. 2A**). A similar pattern was observed in compensated subjects (**Fig. 2B**). However, the strongest correlation was only -0.43.

Secondary and Exploratory Endpoints

The rate of clinical outcome events (occurring at any time during the study) was not different between emricasan and placebo (**Table 3**). Similar results were obtained when analyzed according to a time-to-event analysis (data not shown). The overall subject incidence of events was low at ~10% (median exposure of 337 days), with a lower rate of new events in compensated (7%) compared to new or worsening events in decompensated subjects (21%). In the latter group, occurrence of a new type of decompensation was slightly higher numerically than worsening of an existing decompensation (13% vs. 8%). Further detail on the specific type of new or worsening event is provided in **Table S3**.

In addition, the incidence of subjects with a ≥4-point MELD progression, ≥2-point Child-Pugh progression, or progression from Child-Pugh A to B was similar between emricasan all vs.

placebo (**Table 3**). MELD progression to ≥15 (in compensated with baseline ≤12), which has been proposed as a transplant listing surrogate, was similar to the incidence of new or worse decompensation events (9.0% in emricasan all vs. 7.5% in placebo by week 48).

Liver function tests (bilirubin, albumin, INR) and creatinine remained stable without significant difference among treatments (**Table 4**). There were no meaningful treatment differences in other clinical and laboratory parameters including heart rate, weight, liver stiffness, and platelet count (**Table 4**), except for a difference in mean systolic blood pressure of 3 mmHg (-1.7 in emricasan all vs. -4.7 in placebo) due mainly to an increase (relative to placebo) in the emricasan 50 mg group.

Emricasan 25 and 50 mg treatment led to rapid and significant decreases in average caspase 3/7 values that were sustained to week 48, except for the 5 mg dose group that had an initial decrease at week 4 but not by week 24 **(Fig. 3A-B, S2A)**. cCK18, flCK18, ALT, and AST also generally showed significant average decreases at week 24 with emricasan vs. placebo, but these changes were generally no longer different from placebo by week 48 (**Fig. 3A-B, S2B-E**). Biomarker (caspase 3/7, ALT, CCK18, flCK18) "responders" (defined arbitrarily as those who maintained levels ≥20% from baseline for all or most of visits through week 24) tended to have a greater decrease in HVPG compared to biomarker non-responders (**Table S4**).

Safety

Table 5 presents a summary of treatment-emergent adverse events (TEAEs). In the emricasan all and placebo groups, 91% of subjects reported at least one TEAE, with most (~80%) being mild or moderate in severity. The incidence of TEAEs leading to study discontinuation was slightly higher with emricasan all vs. placebo (without any dose response or

specific system clustering or pattern), but similar between emricasan all and placebo for TEAEs leading to discontinuation of study drug. The incidence of serious TEAEs was slightly higher in emricasan 25 mg (33.8%) and 50 mg (30.3%) vs. placebo (22.4%) whereas emricasan 5 mg was similar (21.5%) to placebo. Of serious TEAEs that occurred in more than 1 subject, VH was reported in 9 (4.6%) emricasan subjects (N=4 [5 mg], N=5 [25 mg]), pneumonia in 5 (2.6%) emricasan subjects (N=2 [5 mg], N=3 [50 mg]), and cellulitis in 4 (2.0%) emricasan (N=1 [5 mg], N=2 [25 mg], N=1 [50 mg]). For all other serious TEAEs, there was no difference more than 3 between emricasan all vs. placebo. There were 4 deaths during the study (1 in emricasan 5 mg, 2 in 25 mg, 1 in 50 mg), all assessed as unrelated to study drug.

TEAEs were generally balanced between treatment groups across different system organ classes. No imbalance for serious TEAEs in other systems of interest, e.g. gastrointestinal and malignancies, was observed. More infection serious TEAEs were observed with emricasan but these were generally single cases (except pneumonia and cellulitis as noted) without any unusual types of infections. When considering all infection TEAEs (not only serious events), there was no imbalance between treatment groups. For frequent TEAEs (occurring in >5% of all subjects), peripheral edema, upper abdominal pain, and muscle spasms were more frequent with emricasan, while diarrhea, HE, anemia, and back pain were more frequent with placebo.

Finally, there was no imbalance in liver test elevations that triggered additional monitoring (with or without interruption of study drug). Two subjects on emricasan (1 on 25 mg, 1 on 50 mg) had increases in aminotransferases and total bilirubin meeting criteria for possible Hy's law. Both cases were reviewed by an independent adjudication committee (blinded to study drug assignment) and assessed as more likely due to autoimmune hepatitis or progression of

underlying NASH, but a possible contribution of study drug could not be entirely excluded. There was no safety concern based on review of routine lab tests, vital signs, and ECG.

Discussion

The main strategy in treating cirrhosis is to control/eliminate the etiologic agent and ameliorate portal hypertension, the main driver of cirrhosis decompensation. In addition to treating etiological therapy, portal pressure-reducing therapies such as NSBB, decrease the risk of developing complications of cirrhosis (6, 11, 12) and are recommended in subjects with high-risk varices (13). Portal pressure-reducing therapies are particularly relevant in NASH cirrhosis, where etiological therapies are as yet unavailable. Because a significant reduction in portal pressure is only achieved in ~50% of patients on NSBB (6), therapies that would enhance this effect are necessary.

Emricasan, a pan-caspase inhibitor, had previously been shown (in an uncontrolled study) to result in clinically meaningful reductions in portal pressure in patients with compensated cirrhosis and severe portal hypertension (HVPG ≥ 12 mmHg) (9). However, in the current larger placebo-controlled study in patients with NASH cirrhosis and baseline HVPG ≥12 mmHg, emricasan failed to meet the primary endpoint of reduction in HVPG in the overall patient population. The significant decrease in caspase and other relevant biomarkers indicated target engagement, and ad-hoc analyses suggested that those with better caspase-related biomarker responses may have a greater decrease in HVPG (**Table S4**).

Although the change in HVPG was not significant overall, there was evidence of a small treatment effect in the compensated subgroup (planned analysis) in whom a trend for a greater reduction in HVPG with emricasan was observed, and baseline HVPG appeared to be the main

variable predicting response. In these subjects, ad-hoc analyses demonstrated that higher baseline HVPG (at a cut-off of 16 mmHg which represented the median value) was associated with greater reduction in HVPG. An HVPG greater than 16 mmHg has clinical relevance as it has been shown to predict decompensation in cirrhosis patients who already have clinically significant portal hypertension (11, 14, 15). In this study, the adjusted mean reduction in HVPG observed in compensated patients with HVPG ≥16 mmHg was -2.2 mmHg compared to placebo. This degree of reduction in HVPG might be important as reductions in HVPG as small as 1 mmHg have recently been shown to be associated with lower decompensation/death rates (16). However, it is also important to note that these ad-hoc subgroup analyses must be interpreted with caution, given the possibility of false positives by chance alone from multiple comparisons.

In patients with severe portal hypertension, increased portal blood flow plays a major role in maintaining and aggravating the portal hypertensive state (15, 17). Therefore, one could speculate that the mechanism by which emricasan could have a portal pressure-reducing effect would be through a decrease in portal blood flow. In fact, a previous study in patients with cirrhosis (due to alcohol or hepatitis C) had shown that increased caspase activation and apoptosis resulted in vasoactive particles that decreased blood pressure and increased portal blood flow thereby worsening portal hypertension (18). Although emricasan treated-groups tended to have a smaller reduction in blood pressure compared to placebo, the significant improvement in aminotransferases suggests an intrahepatic rather than an extrahepatic effect. This would be consistent with a study in rats with CCl_4-induced cirrhosis and ascites in which emricasan (for 7 days) was associated with improved liver function, reduced hepatic inflammation, and reduced fibrosis (through improvement of hepatocyte phenotype and modification of the hepatocyte secretome) without changes in portal blood flow (8).

Furthermore, another study in mice with bile duct ligation-induced cirrhosis showed that long-term (20 days) treatment with emricasan reduced portal pressure and improved survival, with decrease in hepatocellular cell death and circulating microparticles, consistent with a decrease in liver injury (7).

Because there may be a mechanistic explanation for a portal-pressure lowering effect of emricasan and because there was a trend for a small treatment effect in compensated patients, the lack of a significant effect of emricasan on HVPG in the overall patient population may have been due to an unexpected high placebo response rate in decompensated patients, for which there is no clear explanation. Although itt could be hypothesized that the presence of shunting (more prominent in decompensated patients) or down-regulation of organic anion-transporting polypeptide transporters (19) decreased emricasan to target cells, this would not be consistent with a seemingly larger effect in compensated patients with varices or with higher baseline HVPG. The fact that reductions in caspases and aminotransferases were transient (despite continuation of emricasan) may suggest that effects on portal hypertension could also be transient, which could explain the differences between the initial exploratory study (with only 28 days of emricasan) (9) and the current study.

From a safety and tolerability perspective, emricasan appeared to be generally safe and well-tolerated with no specific safety signal identified. More definitive conclusions on the presence (or absence) of a concerning safety issue generally require substantially more subjects than the number enrolled in this study as well as evaluation over a longer time frame. However, no TEAE was clearly attributable to emricasan, and although there was a trend towards more serious and severe TEAEs, the absolute numerical difference was small. The incidence of all frequent TEAEs (occurring in >5% of subjects) was relatively low (generally <15-20%) in this

study and within the range expected in clinical trials and considering the patient population under evaluation (with cirrhosis and severe portal hypertension).

Independent of the lack of a significant overall effect of emricasan on HVPG, this study provides invaluable data regarding the natural history of compensated (and decompensated) NASH cirrhosis, including the relatively low rate of clinical events over a median follow-up of almost a year in this patient population. Emricasan did not have an effect on the development of clinically relevant decompensation events; however, the study was very underpowered to detect any potential difference in decompensation events. This underscores the challenge of using a clinical outcome endpoint in patients with compensated NASH cirrhosis. Because of this, we used HVPG as the primary endpoint for this study, since HVPG could be a strong surrogate of clinical outcomes in patients with compensated cirrhosis, and the large numbers of patients and long duration of follow-up that would be needed in trials with a primary endpoint of clinical outcomes could be impractical to conduct for initial regulatory approval. Including MELD or Child-Pugh progression as part of a composite clinical endpoint could increase the event rate. Finally, the data in the placebo group highlights the challenges of large placebo effects that have been previously observed in patients with compensated NASH cirrhosis (e.g. simtuzumab) (20), which could impact sample sizes required for future studies in this patient population.

In summary, this randomized, multicenter, double-blind, placebo-controlled study of patients with NASH cirrhosis (primarily compensated) and severe portal hypertension demonstrated that emricasan was not associated with a significant reduction in HVPG or the incidence of decompensation, despite evidence of target engagement (decrease in caspases). However, it appeared to have a small effect in reducing HVPG in compensated patients,

especially those with higher baseline HVPG (threshold 16 mmHg), although the exact mechanism (if a true effect) is unclear.

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Table 1. Subject demographics and baseline characteristics

Mean (SD) or N (%)*	**Emricasan 5 mg (n=65)**	**Emricasan 25 mg (n=65)**	**Emricasan 50 mg (n=66)**	**Emricasan All (N=196)**	**Placebo (N=67)**
Age (years)	60.2 (8.8)	62.0 (8.8)	59.5 (9.5)	60.6 (9.0)	61.4 (7.9)
Female	37 (56.9%)	35 (53.8%)	33 (50.0%)	105 (53.6%)	45 (67.2%)
Race (Caucasian)	58 (89.2%)	58 (89.2%)	60 (90.9%)	176 (89.8%)	64 (95.5%)
BMI (kg/m^2)	35.3 (7.3)	34.4 (6.2)	35.6 (5.9)	35.1 (6.5)	35.9 (7.9)
Diabetes mellitus	52 (80.0%)	52 (80.0%)	47 (71.2%)	151 (77.0%)	56 (83.6%)
Hypertension	50 (76.9%)	49 (75.4%)	51 (77.3%)	150 (76.5%)	50 (74.6%)
Compensated	49 (75.4%)	49 (75.4%)	48 (72.7%)	146 (74.5%)	55 (82.1%)
Varices Absent	16 (32.7%)	12 (24.5%)	14 (29.2%)	42 (28.8%)	16 (29.1%)
Varices Present	33 (67.3%)	37 (75.5%)	34 (70.8%)	104 (71.2%)	39 (70.9%)
Decompensated	16 (24.6%)	16 (24.6%)	18 (27.3%)	50 (25.5%)	12 (17.9%)
Varices Present	13 (81.3%)	13 (81.3%)	13 (72.2%)	39 (78.0%)	8 (66.7%)
Prior VH	7 (43.8%)	5 (31.3%)	3 (16.7%)	15 (30.0%)	2 (16.7%)
Ascites (treated)	7 (43.8%)	4 (25.0%)	9 (50.0%)	20 (40.0%)	5 (41.7%)
HE (history≥grade2)	2 (12.5%)	7 (43.8%)	6 (33.3%)	15 (30.0%)	5 (41.7%)
NSBB use	28 (43.1%)	26 (40.0%)	26 (39.4%)	80 (40.8%)	27 (40.3%)
Statin use	25 (38.5%)	26 (40.0%)	22 (33.3%)	73 (37.2%)	23 (34.3%)
AST (U/L)	46 (22)	48 (18)	46 (20)	47 (20)	47 (18)
ALT (U/L)	34 (17)	35 (13)	36 (16)	35 (15)	34 (17)
Platelet (K/mm^3)	102 (39)	107 (48)	91 (31)	100 (41)	95 (34)
Child Pugh score	5.5 (1.0)	5.4 (0.7)	5.6 (0.9)	5.5 (0.8)	5.4 (0.8)
MELD score	9.2 (2.7)	9.1 (2.2)	9.2 (2.5)	9.2 (2.5)	8.4 (2.5)
Liver stiffness (kPa)	39.1 (18.1)	44.7 (21.1)	34.2 (17.3)	39.4 (19.3)	36.8 (18.9)
Caspase 3/7 (RLU)	3195 (1143)	3243 (1339)	3355 (1553)	3265 (1351)	3558 (1601)
cCK18 (U/L)	408 (311)	394 (197)	395 (214)	399 (245)	366 (194)
flCK18 (U/L)	792 (389)	814 (416)	851 (489)	819 (432)	817 (479)
HVPG (mmHg)	16.9 (3.6)	17.3 (3.3)	16.9 (3.8)	17.0 (3.5)	16.8 (3.7)
%Excellent/very good/good	60 (92.3%)	60 (92.3%)	61 (92.4%)	181 (92.3%)	61 (91.0%)

BMI = body mass index, VH = variceal hemorrhage, HE = hepatic encephalopathy, NSBB = non-selective beta-blocker

*Continuous variables are expressed as mean (standard deviation) and categorical variables are expressed as the number of patients (percentage from total).

Table 2. Change in HVPG (mmHg) from baseline to Week 24 in all subjects and subgroups

	Emricasan 5 mg	Emricasan 25 mg	Emricasan 50 mg	Emricasan All	Placebo
All Subjects (N=263)	n=65	n=65	n=66	N=196	N=67
Baseline	16.9 (3.6)	17.3 (3.3)	16.9 (3.8)	17.0 (3.5)	16.8 (3.7)
Mean (SD) CFB	-0.48 (3.4)	-0.81 (3.7)	-0.70 (3.4)	-0.66 (3.5)	-0.18 (3.0)
Difference in LSM (CI)	-0.21 (-1.4,0.95)	-0.45 (-1.6,0.72)	-0.58 (-1.7,0.59)	-0.44 (-1.37,0.49)	
*p-value**	*0.97*	*0.79*	*0.65*	*0.35*	
Compensated	n=46	n=47	n=42	N=135	N=53
Baseline	16.8 (3.7)	17.2 (3.1)	16.8 (3.6)	17.0 (3.5)	16.5 (3.6)
Mean CFB	-0.79 (3.5)	-0.91 (3.2)	-0.44 (3.7)	-0.73 (3.4)	+0.33 (2.3)
Difference in LSM (CI)	-1.0 (-2.3,0.19)	-1.1 (-2.3,0.16)	-0.70 (-2.0,0.56)	-0.94 (-1.9,0.04)	
p-value[ʃ]	*0.10*	*0.09*	*0.28*	*0.06*	
Compensated, no varices	n=15	n=12	n=12	N=39	N=16
Baseline	16.9 (4.6)	16.2 (2.7)	14.5 (2.9)	15.9 (3.6)	15.8 (2.6)
Mean CFB	-0.83 (3.5)	-1.4 (3.1)	+0.95 (4.6)	-0.46 (3.8)	-0.44 (2.4)
Difference in LSM (CI)	-0.31 (-2.8,2.2)	-0.95 (-3.6,1.7)	+1.3 (-1.4,4.0)	0.00 (-2.1,2.1)	
p-value[ʃ]	*0.80*	*0.48*	*0.33*	*1.0*	
Compensated, varices	n=31	n=35	n=30	N=96	N=37
Baseline	16.8 (3.3)	17.6 (3.2)	17.7 (3.6)	17.4 (3.4)	16.8 (3.9)
Mean CFB	-0.77 (3.6)	-0.74 (3.2)	-1.0 (3.3)	-0.83 (3.3)	+0.66 (2.2)
Difference in LSM (CI)	-1.4 (-2.8,0)	-1.2 (-2.5,0.19)	-1.4 (-2.8,0.02)	-1.3 (-2.4,-0.21)	
p-value[ʃ]	*0.05*	*0.09*	*0.05*	*0.02*	
Compensated HVPG≥16	n=26	n=30	n=21	N=77	N=26
Baseline	19.2 (3.0)	19.1 (2.4)	19.8 (2.5)	19.4 (2.6)	19.4 (2.8)
Mean CFB	-1.63 (3.9)	-1.67 (2.8)	-1.59 (3.2)	-1.64 (3.2)	+0.52 (2.1)
Difference in LSM (CI)	-2.2 (-3.8,-0.5)	-2.3 (-3.8,-0.7)	-2.0 (-3.8,-0.3)	-2.2 (-3.5,-0.8)	
p-value[ʃ]	*0.01*	*0.006*	*0.02*	*0.002*	
Decompensated	n=15	n=15	n=14	N=44	N=11
Baseline	17.3 (3.4)	18.0 (3.7)	15.8 (3.2)	17.1 (3.5)	18.2 (2.7)
Mean CFB	+0.50 (2.7)	-0.50 (5.1)	-1.5 (2.0)	-0.47 (3.5)	-2.6 (4.6)
Difference in LSM (CI)	+2.9 (-0.10,5.9)	+2.1 (-0.88,5.0)	+0.52 (-2.6,3.6)	+1.9 (-0.64,4.5)	
p-value[ʃ]	*0.06*	*0.16*	*0.74*	*0.14*	
NSBB use	n=27	n=25	n=22	n=74	N=26
Baseline	16.8 (3.9)	17.9 (3.6)	17.2 (3.1)	17.3 (3.6)	16.7 (4.1)
Mean CFB	-1.0 (3.0)	-0.68 (4.0)	-1.2 (2.7)	-1.0 (3.3)	+0.10 (2.8)
Difference in LSM (CI)	-1.1 (-2.7,0.61)	-0.46 (-2.2,1.3)	-1.2 (-2.9,0.60)	-0.90 (-2.3,0.50)	
p-value[ʃ]	*0.21*	*0.60*	*0.19*	*0.20*	
No NSBB use	n=34	n=37	n=34	N=105	N=38
Baseline	17.0 (3.4)	17.1 (3.0)	16.1 (3.8)	16.7 (3.4)	16.8 (3.1)
Mean CFB	-0.04 (3.6)	-0.91 (3.4)	-0.35 (3.8)	-0.45 (3.6)	-0.37 (3.2)
Difference in LSM (CI)	+0.37 (-1.2,2.0)	-0.48 (-2.0,1.1)	-0.16 (-1.8,1.4)	-0.10 (-1.4,1.2)	
p-value[ʃ]	*0.65*	*0.55*	*0.84*	*0.88*	

CFB = change from baseline (unadjusted mean), LSM = least squares mean, CI = 95% confidence intervals.
NSBB = non-selective beta-blocker. Difference in LSM is based on adjusted means
*p-value vs. placebo based on ANCOVA adjusting for baseline compensation status, baseline NSBB use, and baseline HVPG, using multiple imputation for missing Week 24 data[ʃ]p-value vs. placebo based on ANCOVA adjusting for baseline HVPG (observed data)

Table 3. Clinical outcome events and MELD and Child-Pugh progression. Clinical outcome events during the study in all subjects and compensated and decompensated subgroups. MELD progression in all subjects and in compensated subjects with MELD ≤12. Child-Pugh progression in all subjects and in subjects with baseline Child-Pugh class A.

	Emricasan 5 mg	**Emricasan 25 mg**	**Emricasan 50 mg**	**Emricasan All**	**Placebo**
All Subjects	n=65	n=65	n=66	N=196	N=67
Total Events	**7 (10.8%)**	**9 (13.8%)**	**4 (6.1%)**	**20 (10.2%)**	**7 (10.4%)**
				p=0.95	
Compensated*	n=49	n=49	n=48	N=146	N=55
Any new event	**5 (10.2%)**	**4 (8.2%)**	**1 (2.1%)**	**10 (6.8%)**	**4 (7.3%)**
				p=0.92	
New VH	2 (4.1%)	3 (6.1%)	0	5 (3.4%)	0
New ascites	1 (2.0%)	2 (4.1%)	1 (2.1%)	4 (2.7%)	4 (7.3%)
New HE	2 (4.1%)	1 (2.0%)	0	3 (2.1%)	1 (1.8) %
Decompensated[§]	n=16	n=16	n=18	N=50	N=12
Any new or worsening event	**2 (12.5%)**	**5 (31.3%)**	**3 (16.7%)**	**10 (20.0%)**	**3 (25.0%)**
				p=0.70	
- New event	1 (6.3%)	3 (18.8%)	2 (11.1%)	6 (12.0%)	2 (16.7%)
- Worsening of existing event[ʃ]	1 (6.3%)	2 (12.5%)	1 (5.6%)	4 (8.0%)	1 (13.9%)
≥4-point MELD progression in All Subjects	n=65	n=65	n=66	N=196	N=67
Week 24	15 (23.1)	8 (12.3)	8 (12.1)	31 (15.8)	10 (14.9)
				p=0.86	
Week 48	15 (23.1)	10 (15.4)	14 (21.2)	39 (19.9)	16 (23.9)
				p=0.49	
Progress to MELD ≥15 in Compensated MELD ≤12	n=43	n=45	n=45	N=133	N=53
Week 24	7 (16.3)	2 (4.4)	1 (2.2)	10 (7.5)	2 (3.8)
				p=0.35	
Week 48	7 (16.3)	2 (4.4)	3 (6.7)	12 (9.0)	4 (7.5)
				p=0.75	
≥2-point CP progression in All Subjects	n=65	n=65	n=66	N=196	N=67
Week 24	8 (12.3)	2 (3.1)	3 (4.5)	13 (6.6)	4 (6.0)
				p=0.85	

Week 48	9 (13.8)	7 (10.8)	6 (9.1)	22 (11.2)	12 (17.9)
				p=0.16	
Progression to CP B in baseline CP A	n=56	n=59	n=54	N=169	N=61
Week 24	13 (23.2)	5 (8.5)	7 (13.0)	25 (14.8)	10 (16.4)
				p=0.77	
Week 48	13 (23.2)	13 (22.0)	12 (22.2)	38 (22.5)	15 (24.6)
				p=0.74	

VH = variceal hemorrhage, HE = hepatic encephalopathy

*1 subject (25 mg) had new ascites, HE, and VH, and 1 subject (placebo) had new ascites and HE.

§1 subject (50 mg) with prior VH had new and worsening ascites.

ʃIncludes recurrent VH for subjects with prior VH

Table 4. Baseline and change from baseline at Week 24 in clinical and laboratory parameters.

Mean (SD)	**Emricasan 5 mg (n=65)**	**Emricasan 25 mg (n=65)**	**Emricasan 50 mg (n=66)**	**Emricasan All (N=196)**	**Placebo (N=67)**	**p-value for All EMR v PBO**
Systolic BP (mmHg)	**128.9 (16.2)**	**128.8 (12.9)**	**126.8 (13.6)**	**128.1 (14.3)**	**132.8 (17.2)**	
Change at Week 24 (N=243)	-2.8 (15.8)	-3.1 (14.3)	+0.7 (13.7)	-1.7 (14.6)	-4.7 (15.6)	<0.001
Mean arterial pressure (mmHg)	**90.8 (10.7)**	**91.1 (8.2)**	**88.8 (8.4)**	**90.2 (9.1)**	**92.9 (10.8)**	
Change at Week 24 (N=243)	-2.3 (11.0)	-2.4 (9.1)	-0.01 (9.6)	-1.6 (9.9)	-3.3 (10.9)	0.001
Heart rate (bpm)	**69.8 (9.4)**	**72.4 (12.5)**	**69.4 (9.4)**	**70.6 (10.6)**	**71.7 (10.1)**	
Change at Week 24 (N=243)	+0.1 (8.9)	-1.0 (8.5)	+0.7 (9.0)	-0.1 (8.8)	-1.5 (8.9)	0.002
Body weight (kg)	**98.5 (23.9)**	**99.4 (23.4)**	**104.6 (22.7)**	**100.8 (23.3)**	**98.7 (23.4)**	
Change at Week 24 (N=242)	+0.11 (4.4)	-0.04 (3.9)	-0.04 (4.2)	+0.01 (4.1)	+0.02 (4.4)	0.399
Liver stiffness (kPa)	**40.9 (18.8)**	**47.2 (20.8)**	**32.2 (16.5)**	**40.4 (19.7)**	**34.5 (17.5)**	
Change at Week 24 (N=176)	-3.1 (18.7)	-6.7 (22.9)	-0.9 (14.5)	-3.6 (19.1)	-0.3 (14.3)	<0.001
Platelet (K/mm^3)	**105 (41)**	**108 (49)**	**92 (32)**	**102 (42)**	**95 (35)**	
Change at Week 24 (N=229)	-3.5 (19.8)	-7.3 (22.8)	-4.6 (17.4)	-5.2 (20.1)	-4.6 (13.7)	0.235
MELD score	**9.1 (2.8)**	**9.0 (2.2)**	**9.1 (2.0)**	**9.1 (2.3)**	**8.5 (2.6)**	
Change at Week 24 (N=234)	+0.1 (2.1)	+0.0 (1.7)	+0.2 (1.4)	+0.1 (1.8)	+0.4 (2.2)	0.148
Child Pugh score	**5.5 (1.0)**	**5.4 (0.7)**	**5.6 (0.9)**	**5.5 (0.8)**	**5.4 (0.8)**	
Change at Week 24 (N=236)	+0.14 (0.55)	+0.15 (0.58)	+0.05 (0.48)	+0.12 (0.54)	+0.31 (0.56)	0.087
Total bilirubin (µmol/L)	**20.5 (12.0)**	**18.8 (10.3)**	**20.5 (17.1)**	**20.5 (13.7)**	**17.1 (12.0)**	
Change at Week 24 (N=243)	-0.51 (6.7)	-0.51 (6.3)	-0.17 (5.3)	-0.34 (6.2)	+0.34 (6.0)	0.002
Albumin (g/L)	**40.0 (5.0)**	**40.0 (4.0)**	**40.0 (5.0)**	**40.0 (4.0)**	**39.0 (4.0)**	
Change at Week 24 (N=243)	-1.0 (2.0)	-1.0 (3.0)	-1.0 (2.0)	-1.0 (2.0)	-1.0 (3.0)	0.399
INR	**1.2 (0.2)**	**1.2 (0.1)**	**1.2 (0.1)**	**1.2 (0.1)**	**1.2 (0.1)**	
Change at Week 24 (N=240)	0.00 (0.10)	+0.04 (0.11)	+0.02 (0.07)	+0.02 (0.10)	+0.02 (0.07)	0.399
Creatinine (µmol/L)	**61.9 (17.7)**	**61.9 (17.7)**	**61.9 (17.7)**	**61.9 (17.7)**	**61.9 (17.7)**	
Change at Week 24 (N=242)	-0.88 (9.7)	0.00 (8.0)	+2.7 (11.5)	+0.88 (9.7)	+1.8 (15.9)	0.097

Table 5. Summary of treatment-emergent adverse events (TEAEs) in all subjects

Subject incidence N (%)	**Emricasan 5 mg (n=65)**	**Emricasan 25 mg (n=65)**	**Emricasan 50 mg (n=66)**	**Emricasan All (N=196)**	**Placebo (N=67)**
All TEAEs	59 (90.8)	62 (95.4)	57 (86.4)	178 (90.8)	61 (91.0)
Serious TEAEs	14 (21.5)	22 (33.8)	20 (30.3)	56 (28.6)	15 (22.4)
Severe TEAEs	13 (20.0)	16 (24.6)	16 (24.2)	45 (23.0)	13 (19.4)
Related to study drug	14 (21.5)	18 (27.7)	23 (34.8)	55 (28.1)	18 (26.9)
Study discontinuation	6 (9.2)	4 (6.2)	7 (10.6)	17 (8.7)	3 (4.5)
Study drug stopped	4 (6.2)	3 (4.6)	5 (7.6)	12 (6.1)	4 (6.0)
Frequent TEAEs (>5%*)					
Edema peripheral	9 (13.8)	14 (21.5)	8 (12.1)	31 (15.8)	8 (11.9)
Urinary tract infection	9 (13.8)	11 (16.9)	6 (9.1)	26 (13.3)	10 (14.9)
Diarrhea	10 (15.4)	7 (10.8)	6 (9.1)	23 (11.7)	13 (19.4)
Nausea	6 (9.2)	9 (13.8)	8 (12.1)	23 (11.7)	11 (16.4)
Abdominal pain upper	4 (6.2)	7 (10.8)	8 (12.1)	19 (9.7)	3 (4.5)
Muscle spasms	7 (10.8)	6 (9.2)	5 (7.6)	18 (9.2)	2 (3.0)
Ascites	4 (6.2)	9 (13.8)	4 (6.1)	17 (8.7)	8 (11.9)
Headache	3 (4.6)	7 (10.8)	7 (10.6)	17 (8.7)	5 (7.5)
Bronchitis	6 (9.2)	2 (3.1)	7 (10.6)	15 (7.7)	3 (4.5)
Fatigue	3 (4.6)	6 (9.2)	6 (9.1)	15 (7.7)	6 (9.0)
Hepatic encephalopathy	5 (7.7)	5 (7.7)	5 (7.6)	15 (7.7)	12 (17.9)
Abdominal pain	7 (10.8)	2 (3.1)	5 (7.6)	14 (7.1)	7 (10.4)
Upper resp tract infection	4 (6.2)	4 (6.2)	4 (6.1)	12 (6.1)	5 (7.5)
Asthenia	6 (9.2)	1 (1.5)	4 (6.1)	11 (5.6)	3 (4.5)
Cellulitis	3 (4.6)	4 (6.2)	4 (6.1)	11 (5.6)	4 (6.0)
Anemia	4 (6.2)	2 (3.1)	4 (6.1)	10 (5.1)	10 (14.9)
Dizziness	4 (6.2)	2 (3.1)	4 (6.1)	10 (5.1)	6 (9.0)
Vomiting	3 (4.6)	4 (6.2)	3 (4.5)	10 (5.1)	4 (6.0)
Back pain	3 (4.6)	4 (6.2)	2 (3.0)	9 (4.6)	8 (11.9)
Fall	2 (3.1)	4 (6.2)	3 (4.5)	9 (4.6)	6 (9.0)
Nasopharyngitis	1 (1.5)	4 (6.2)	4 (6.1)	9 (4.6)	5 (7.5)
Constipation	3 (4.6)	4 (6.2)	1 (1.5)	8 (4.1)	6 (9.0)

*Occurring in >5% of all subjects

Figure Legends:

Fig. 1. Forest plot of change in HVPG at week 24 in all subjects and subgroups. Small solid rectangular boxes reflect point estimate of least squares mean difference between emricasan dose group compared to placebo and bars represent 95% confidence intervals.

Fig. 2. Change in HVPG at week 24 vs. baseline HVPG by treatment group in all subjects and compensated subjects. Line represents regression line, shaded area shows 95% confidence interval, and r value indicates correlation coefficient. (A) All subjects and (B) Compensated subjects.

Fig. 3. Forest plot of change in caspase 3/7, cCK18, flCK18, ALT, and AST at week 24 and week 48 in all subjects. Small solid rectangular boxes reflect point estimate of least squares mean difference between emricasan dose group compared to placebo and bars represent 95% confidence intervals. (A) Week 24 and (B) Week 48.

Fig. 1.

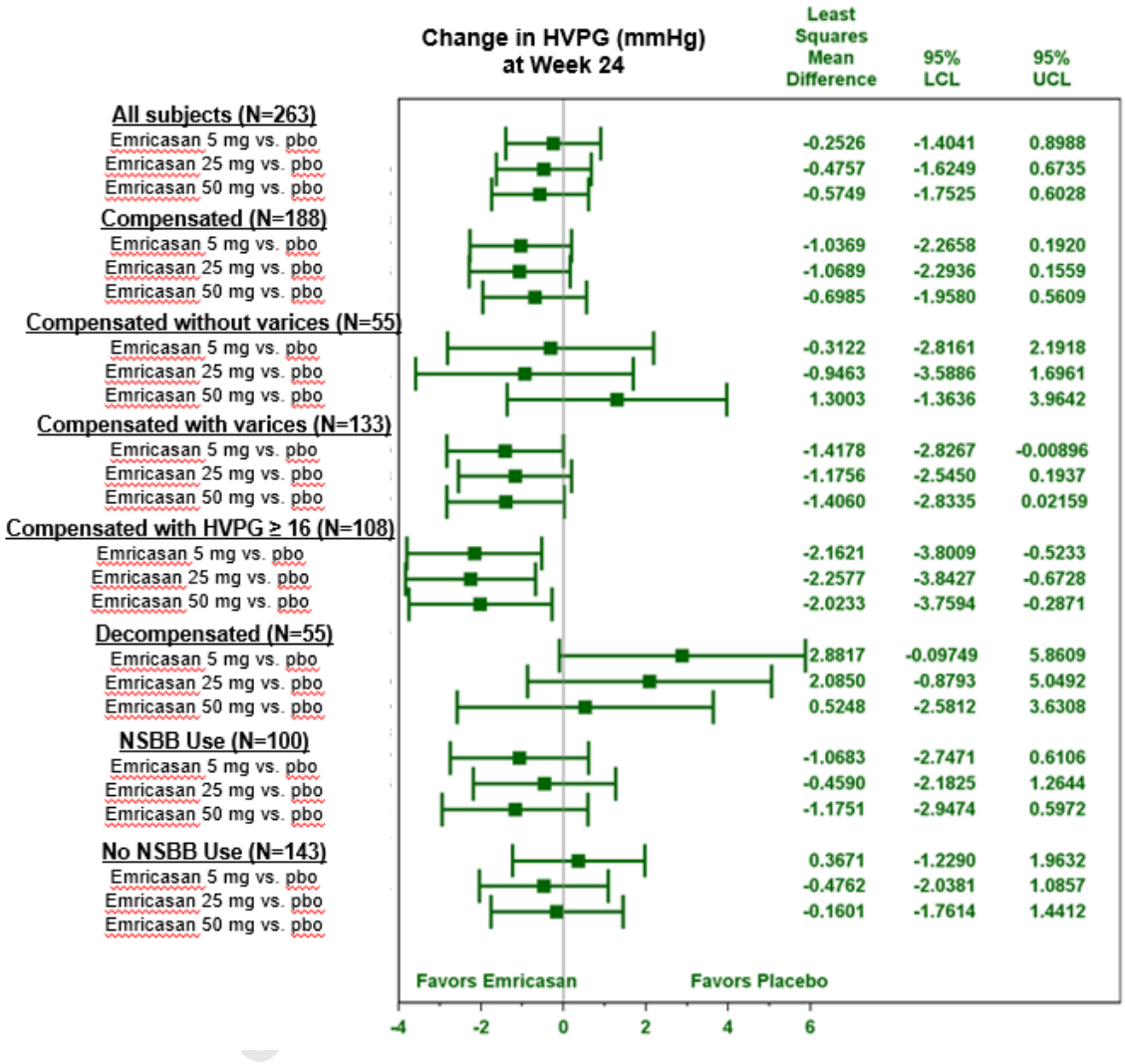
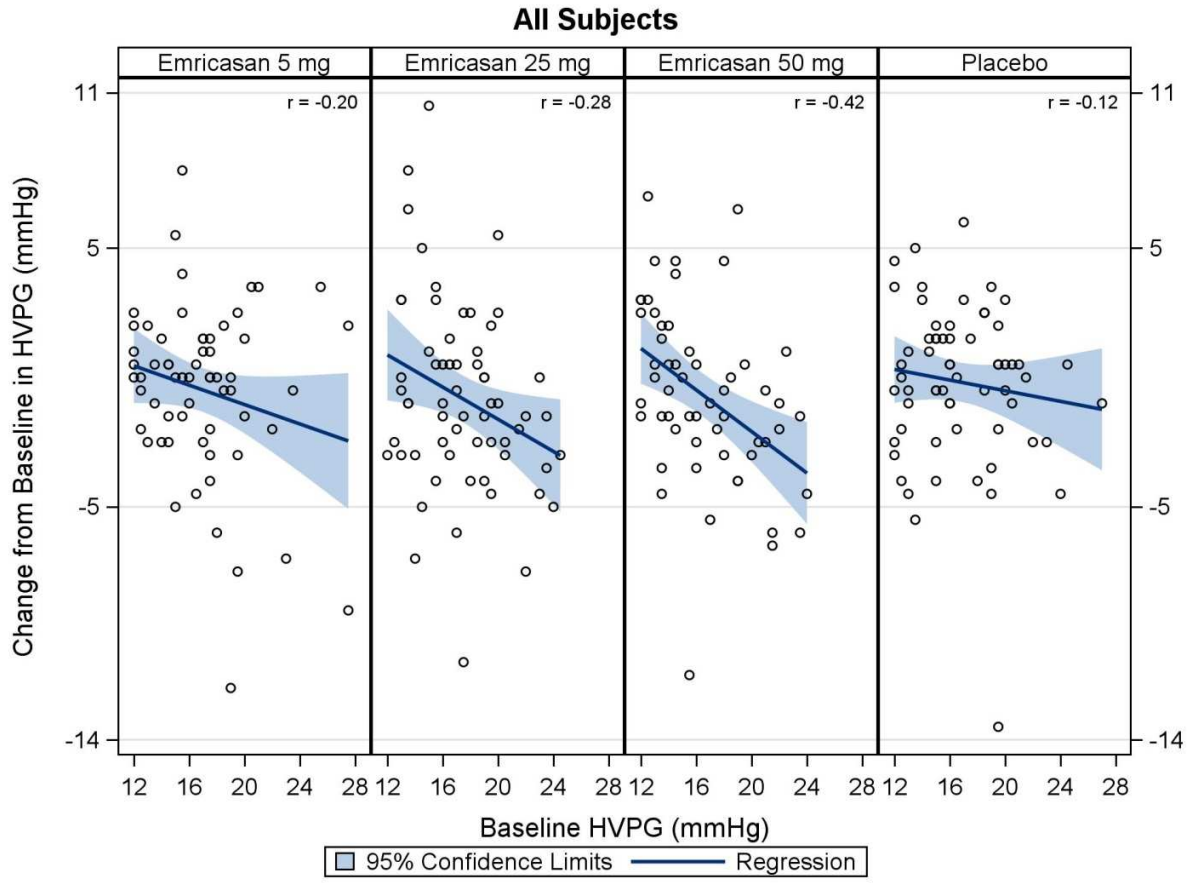

Change in HVPG (mmHg) at Week 24
Least Squares Mean Difference
95% LCL
95% UCL
All subjects (N=263)
Emricasan 5 mg vs. pbo -0.2526 -1.4041 0.8988
Emricasan 25 mg vs. pbo -0.4757 -1.6249 0.6735
Emricasan 50 mg vs. pbo -0.5749 -1.7525 0.6028
Compensated (N=188)
Emricasan 5 mg vs. pbo -1.0369 -2.2658 0.1920
Emricasan 25 mg vs. pbo -1.0689 -2.2936 0.1559
Emricasan 50 mg vs. pbo -0.6985 -1.9580 0.5609
Compensated without varices (N=55)
Emricasan 5 mg vs. pbo -0.3122 -2.8161 2.1918
Emricasan 25 mg vs. pbo -0.9463 -3.5886 1.6961
Emricasan 50 mg vs. pbo 1.3003 -1.3636 3.9642
Compensated with varices (N=133)
Emricasan 5 mg vs. pbo -1.4178 -2.8267 -0.00896
Emricasan 25 mg vs. pbo -1.1756 -2.5450 0.1937
Emricasan 50 mg vs. pbo -1.4060 -2.8335 0.02159
Compensated with HVPG ≥ 16 (N=108)
Emricasan 5 mg vs. pbo -2.1621 -3.8009 -0.5233
Emricasan 25 mg vs. pbo -2.2577 -3.8427 -0.6728
Emricasan 50 mg vs. pbo -2.0233 -3.7594 -0.2871
Decompensated (N=55)
Emricasan 5 mg vs. pbo 2.8817 -0.09749 5.8609
Emricasan 25 mg vs. pbo 2.0850 -0.8793 5.0492
Emricasan 50 mg vs. pbo 0.5248 -2.5812 3.6308
NSBB Use (N=100)
Emricasan 5 mg vs. pbo -1.0683 -2.7471 0.6106
Emricasan 25 mg vs. pbo -0.4590 -2.1825 1.2644
Emricasan 50 mg vs. pbo -1.1751 -2.9474 0.5972
No NSBB Use (N=143)
Emricasan 5 mg vs. pbo 0.3671 -1.2290 1.9632
Emricasan 25 mg vs. pbo -0.4762 -2.0381 1.0857
Emricasan 50 mg vs. pbo -0.1601 -1.7614 1.4412
Favors Emricasan
Favors Placebo
-4
-2
0
2
4
6

Fig. 2.

(A)


All Subjects
Emricasan 5 mg
Emricasan 25 mg
Emricasan 50 mg
Placebo
r = -0.20
r = -0.28
r = -0.42
r = -0.12
Change from Baseline in HVPG (mmHg)
11
5
-5
-14
12
16
20
24
28
Baseline HVPG (mmHg)
95% Confidence Limits
Regression

(B)

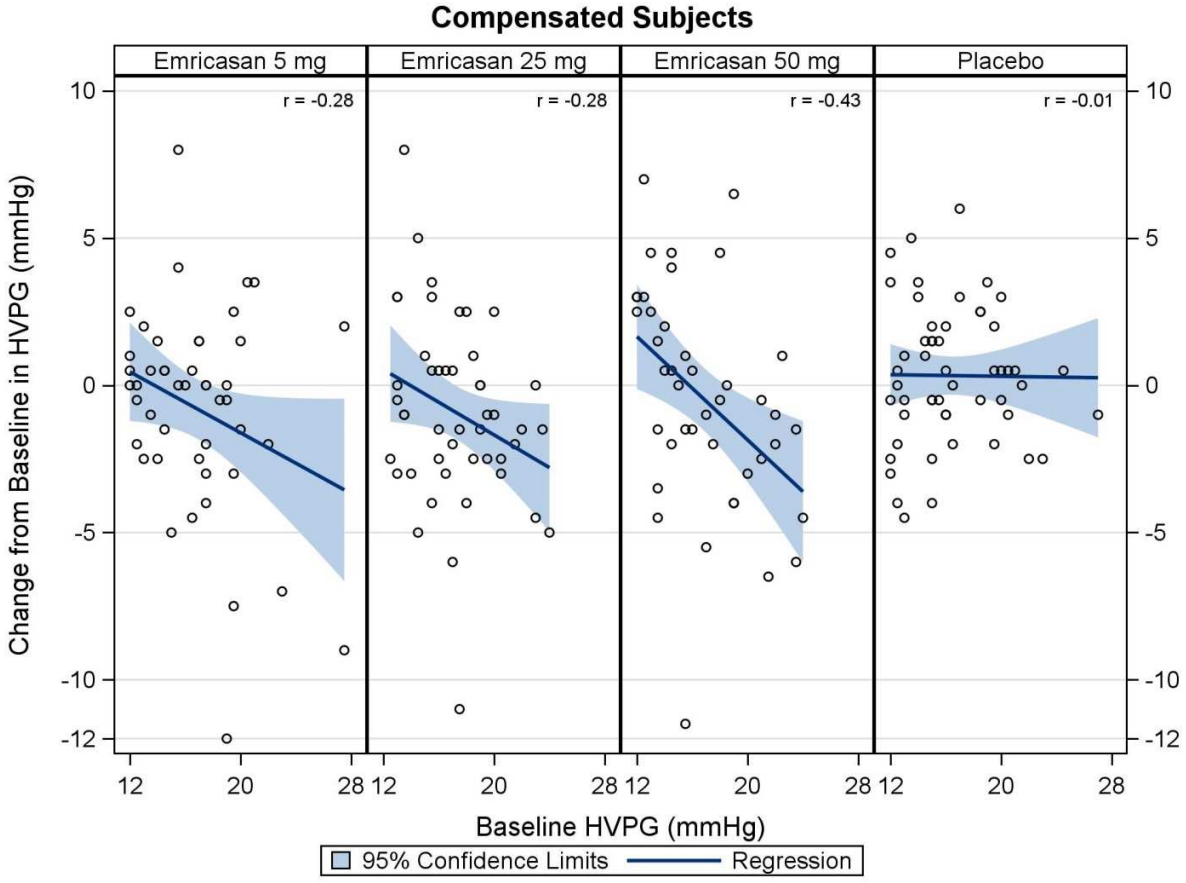
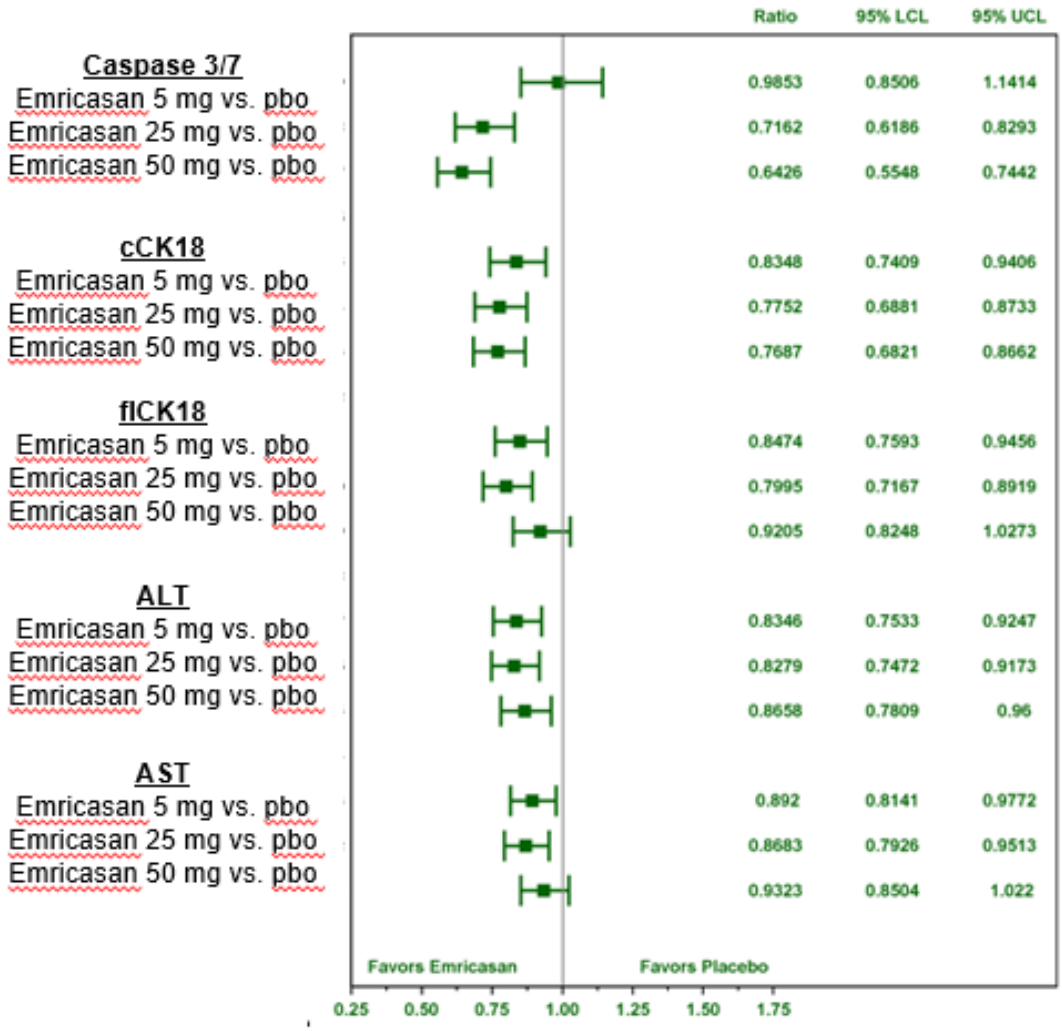
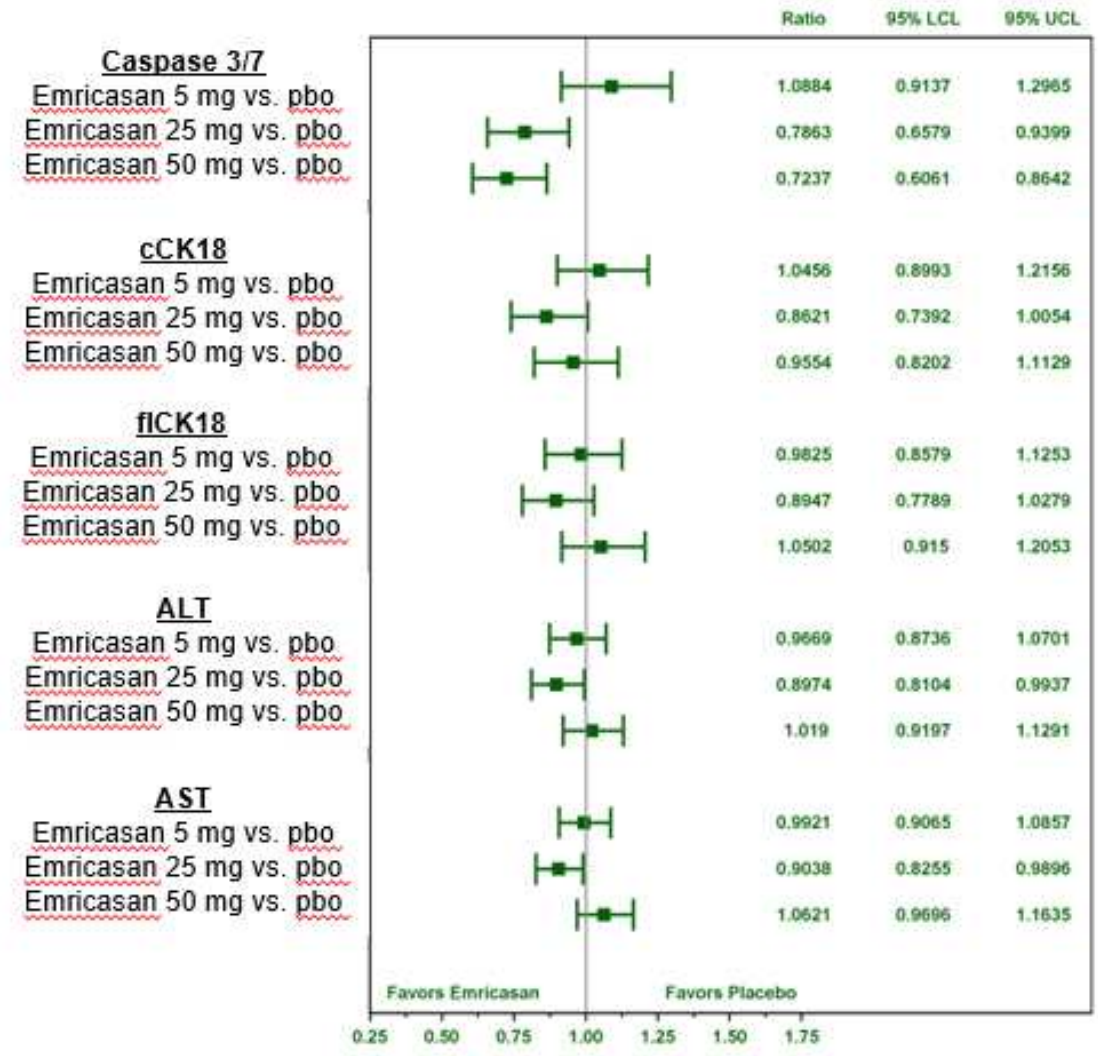

Compensated Subjects
Emricasan 5 mg
Emricasan 25 mg
Emricasan 50 mg
Placebo
r = -0.28
r = -0.28
r = -0.43
r = -0.01
Change from Baseline in HVPG (mmHg)
10
5
0
-5
-10
-12
12
20
28
Baseline HVPG (mmHg)
95% Confidence Limits
Regression

Fig. 3.

(A) Week 24



(B) Week 48


Ratio
95% LCL
95% UCL
Caspase 3/7
Emricasan 5 mg vs. pbo
1.0884
0.9137
1.2965
Emricasan 25 mg vs. pbo
0.7863
0.6579
0.9399
Emricasan 50 mg vs. pbo
0.7237
0.6061
0.8642
cCK18
Emricasan 5 mg vs. pbo
1.0456
0.8993
1.2156
Emricasan 25 mg vs. pbo
0.8621
0.7392
1.0054
Emricasan 50 mg vs. pbo
0.9554
0.8202
1.1129
fICK18
Emricasan 5 mg vs. pbo
0.9825
0.8579
1.1253
Emricasan 25 mg vs. pbo
0.8947
0.7789
1.0279
Emricasan 50 mg vs. pbo
1.0502
0.915
1.2053
ALT
Emricasan 5 mg vs. pbo
0.9669
0.8736
1.0701
Emricasan 25 mg vs. pbo
0.8974
0.8104
0.9937
Emricasan 50 mg vs. pbo
1.019
0.9197
1.1291
AST
Emricasan 5 mg vs. pbo
0.9921
0.9065
1.0857
Emricasan 25 mg vs. pbo
0.9038
0.8255
0.9896
Emricasan 50 mg vs. pbo
1.0621
0.9696
1.1635
Favors Emricasan
Favors Placebo
0.25
0.50
0.75
1.00
1.25
1.50
1.75

Highlights

- Phase III, multicenter study, comparing emricasan, (a caspase inhibitor) at 3 different doses vs. placebo in patients with NASH cirrhosis and severe portal hypertension
- Despite evidence of target engagement, emricasan did not reduce portal hypertension in the overall study population
- The portal pressure-reducing effect may be more evident in latter stages of portal hypertension
- Treatment-emergent adverse events were similar between emricasan and placebo