# Multicenter, Double-Blind, Placebo-controlled, Randomized Trial of Emricasan in Subjects with NASH Cirrhosis and Severe Portal Hypertension

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# Background

- **NASH is a leading cause of cirrhosis and liver transplant**
- **Severe portal hypertension, defined as an hepatic venous pressure gradient (HVPG) >10-12 mmHg, is a key driver of decompensation and worse clinical outcomes**
  - Decreases in HVPG as small as 1 mmHg have been associated with a reduction in the risk of decompensation/death
    - *Abraldes, Garcia-Tsao et al. AASLD 2018 abstract*
- **Caspases play a central role in apoptosis and inflammation (pathogenic mechanisms in NASH)**
- **Emricasan, an oral pan-caspase inhibitor, has been shown to:**
  - Decrease portal pressure in rodent models of cirrhosis
    - *Eguchi et al. J Mol Med 2018, 96:575-83, Gracia-Sancho et al. Hep Comm 2019 (accepted).*
  - Meaningfully reduce HVPG in a small subset of patients with compensated cirrhosis (HVPG ≥ 12 mmHg) in the setting of an exploratory open-label study in which emricasan was administered at a dose of 25 mg orally BID for 4 weeks
    - *Garcia-Tsao et al. Hepatology 2019, 69:717-28*

# Objectives

## Primary

- To assess whether emricasan decreases HVPG at Wk 24 in patients with NASH cirrhosis and severe portal hypertension (HVPG ≥ 12 mmHg) in the context of a placebo-controlled trial

## Secondary

- To assess safety and tolerability of emricasan
- To assess whether emricasan decreases mechanistic (caspase 3/7, cCK18) and other (AST, ALT) biomarkers

# Methods: Study Design

- Randomized, placebo-controlled, double-blind 24-week study, with 24-week extension / continued randomized treatment (investigators remained blinded)
- 59 sites: 42 U.S. and 17 Europe
- Planned enrollment 240 patients with NASH cirrhosis and HVPG ≥12 mmHg
- Randomized 1:1:1:1 to emricasan 5 mg, 25 mg, or 50 mg, or placebo administered orally twice a day
- HVPG performed at screening and at Wk 24 (primary endpoint)
- Continued randomized treatment to Wk 48 to evaluate safety and other exploratory endpoints

# Methods: Key Inclusion criteria

- **NASH cirrhosis**
  - Cirrhosis based on biopsy or clinical criteria (platelet, AST/ALT, nodular liver, splenomegaly)
  - NASH etiology based on prior or current biopsy, or at least 2 metabolic risk factors for at least 5 years prior to cirrhosis
- **Compensated cirrhosis or “early” decompensated cirrhosis (only one decompensating event)**
- **HVPG ≥ 12 mmHg on screening HVPG**
- **If on non-selective beta blockers (NSBB), stable dose for at least 3 months**

# Methods: Key Exclusion criteria

- **Severe decompensation:**
  - More than one decompensating event
  - More than one episode of VH or HE needing hospitalization
  - Ascites requiring more than one large volume paracentesis or spontaneous bacterial peritonitis or hepatorenal syndrome
- **Severe hepatic impairment (Child Pugh C)**
- **ALT >3X ULN or AST >5X ULN**
- **Estimated creatinine clearance < 30 mL/min**
- **Prior transjugular intrahepatic portosystemic shunt**
- **Known portal vein thrombosis**
- **Alpha-fetoprotein >50 ng/mL**
- **Change in diabetes meds within 3 months or HbA1c >9%**
- **Malignancies unless curatively treated, or significant systemic illness**

# Methods: HVPG and Statistics

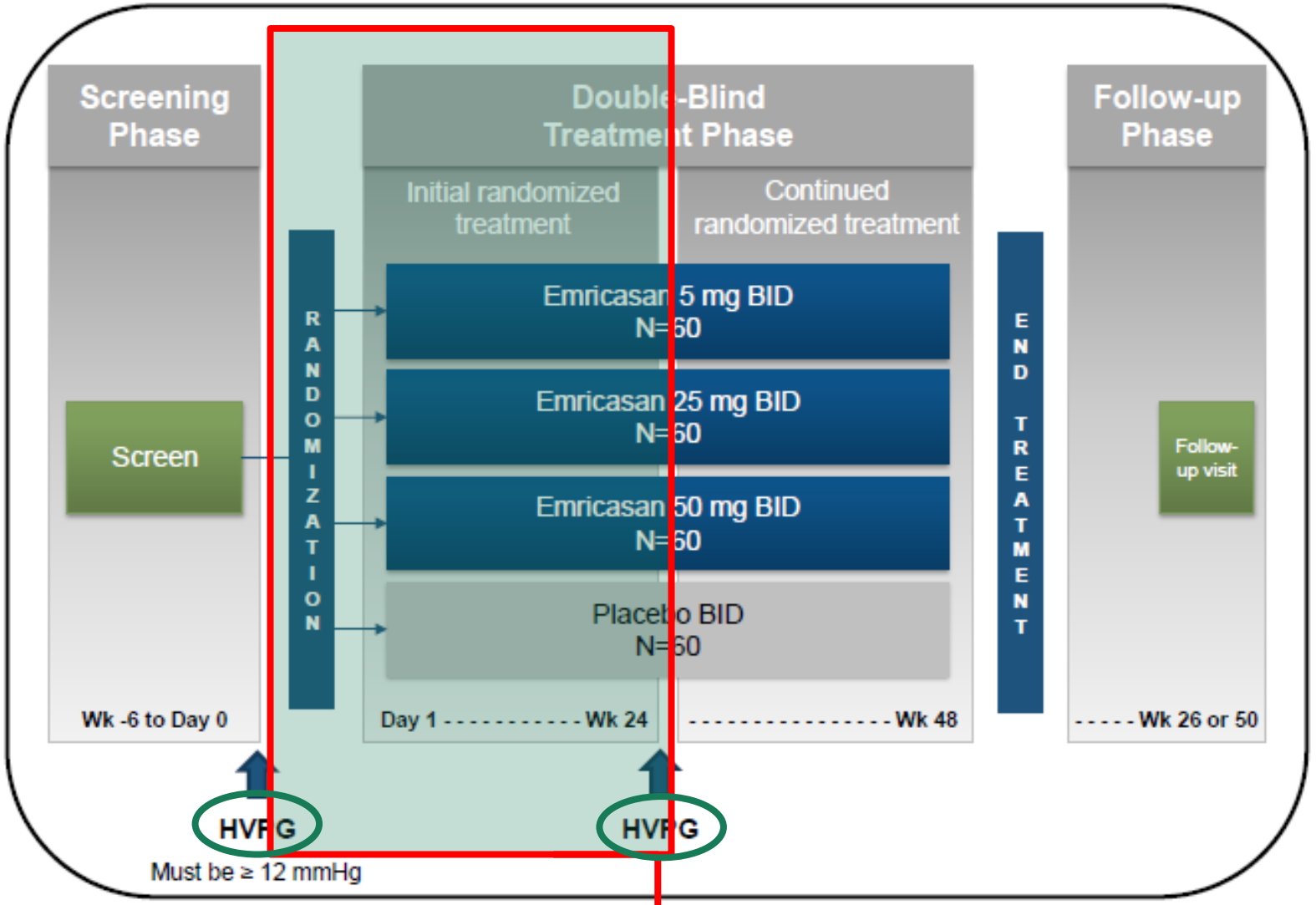
## Hepatic venous pressure gradient (HVPG)

- All screening and Wk 24 HVPGs read by single expert reader (GGT)
- Had to be recorded in either paper or electronic tracings
- WHVP - FHVP in triplicate

## Statistics

- Primary endpoint: mean change in HVPG from baseline to Wk 24
  - Fixed effects ANCOVA adjusting for compensated status, NSBB use, and baseline HVPG
  - Multiple imputation (under the missing-at-random assumption) used to handle missing Wk 24 HVPG data
- Pre-specified subgroup analyses: compensated/decompensated

# Study Schema

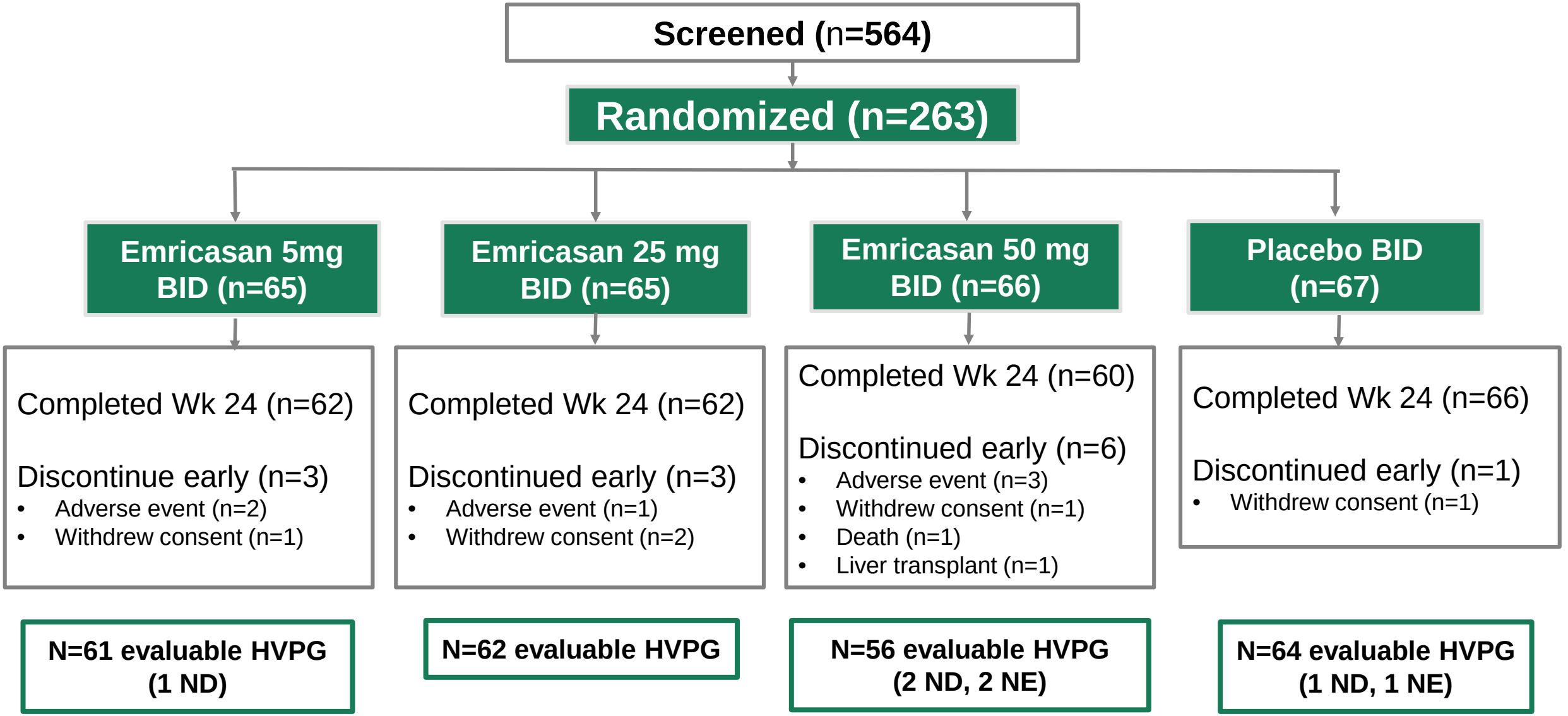



Results reported today

**Subjects were stratified according to :**

- **Compensated (76%) or early decompensated (24%) status**
- **Non-selective beta-blocker use or not**

# Enrollment and Disposition




ND=not done, NE=not evaluable

# Subject Characteristics

| | All Subjects (N=263) | Emricasan 5 mg (N=65) | Emricasan 25 mg (N=65) | Emricasan 50 mg (N=66) | Placebo (N=67) |
|---|---|---|---|---|---|
| Age - mean (SD) | **61 (9)** | 60 (9) | 62 (9) | 60 (9) | 61 (8) |
| Gender (%Female) | **57%** | 57% | 54% | 50% | 67% |
| Race (%Caucasian) | **91%** | 89% | 89% | 91% | 96% |
| BMI - mean (SD) | **35 (7)** | 35 (7) | 34 (6) | 36 (6) | 36 (8) |
| Type 2 diabetes (%) | **79%** | 80% | 80% | 71% | 84% |
| Hypertension (%) | **76%** | 77% | 75% | 77% | 75% |

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| Hypertension (%) | **76%** | 77% | 75% | 77% | 75% |
| Compensated (%) | **76%** | 75% | 75% | 73% | 82% |
| Decompensated (%) | **24%** | 25% | 25% | 27% | 18% |
| Varices (%) | **73%** | 71% | 79% | 71% | 72% |
| Small | **41%** | 32% | 42% | 38% | 51% |
| Medium or Large | **32%** | 38% | 35% | 33% | 19% |
| NSBB use (%) | **41%** | 43% | 40% | 39% | 40% |

# Baseline Labs, Fibroscan®, and HVPG

| Mean (SD) | All Subjects (N=263) | Emricasan 5 mg (N=65) | Emricasan 25 mg (N=65) | Emricasan 50 mg (N=66) | Placebo (N=67) |
|---|---|---|---|---|---|
| Total bilirubin (mg/dL) | **1.1 (0.8)** | 1.2 (0.7) | 1.1 (0.6) | 1.2 (1.0) | 1.0 (0.7) |
| Albumin (mg/dL) | **4.0 (0.4)** | 4.0 (0.5) | 4.0 (0.4) | 4.0 (0.5) | 3.9 (0.4) |
| INR | **1.2 (0.1)** | 1.2 (0.2) | 1.2 (0.1) | 1.2 (0.1) | 1.2 (0.1) |
| Creatinine (mg/dL) | **1.0 (0.1)** | 1.0 (0.1) | 1.0 (0.1) | 1.0 (0.2) | 1.0 (0.1) |
| AST (U/L) | **47 (19)** | 46 (22) | 48 (18) | 46 (20) | 47 (18) |
| ALT (U/L) | **35 (16)** | 34 (17) | 35 (13) | 36 (16) | 34 (17) |
| Platelet (K/mm$^3$) | **98 (39)** | 102 (39) | 107 (48) | 91 (31) | 95 (34) |
| Child Pugh score | **5.5 (0.8)** | 5.5 (1.0) | 5.4 (0.7) | 5.6 (0.9) | 5.4 (0.8) |
| MELD score | **9.0 (2.5)** | 9.2 (2.7) | 9.1 (2.2) | 9.2 (2.5) | 8.4 (2.5) |
| Liver stiffness (kPa) | **38.8 (19.2)** | 39.1 (18.1) | 44.7 (21.1) | 34.2 (17.3) | 36.8 (18.9) |

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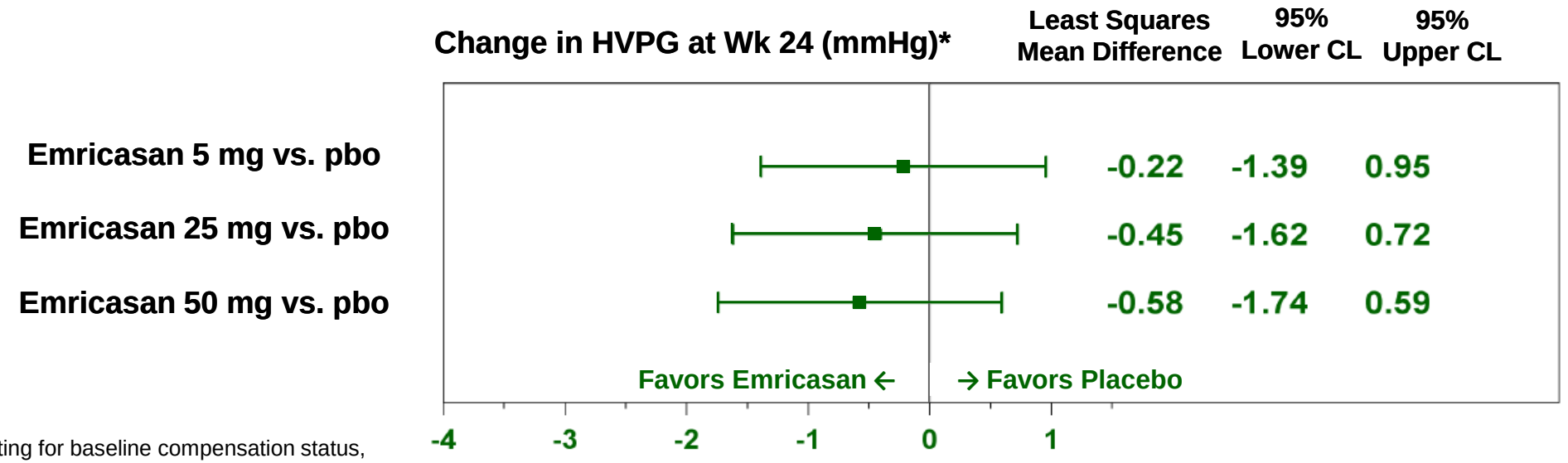
| Liver stiffness (kPa) | **38.8 (19.2)** | 39.1 (18.1) | 44.7 (21.1) | 34.2 (17.3) | 36.8 (18.9) |
| **Caspase 3/7 (RLU)** | **3340 (1422)** | 3195 (1143) | 3243 (1339) | 3355 (1553) | 3558 (1601) |
| **cCK18 (U/L)** | **391 (233)** | 408 (311) | 394 (197) | 395 (214) | 366 (194) |
| **HVPG (mmHg)** | **17.0 (3.6)** | 16.9 (3.6) | 17.3 (3.3) | 16.9 (3.8) | 16.8 (3.7) |

# Primary Analysis:
# Overall, no significant change in HVPG at Wk 24 with Emricasan vs. Placebo

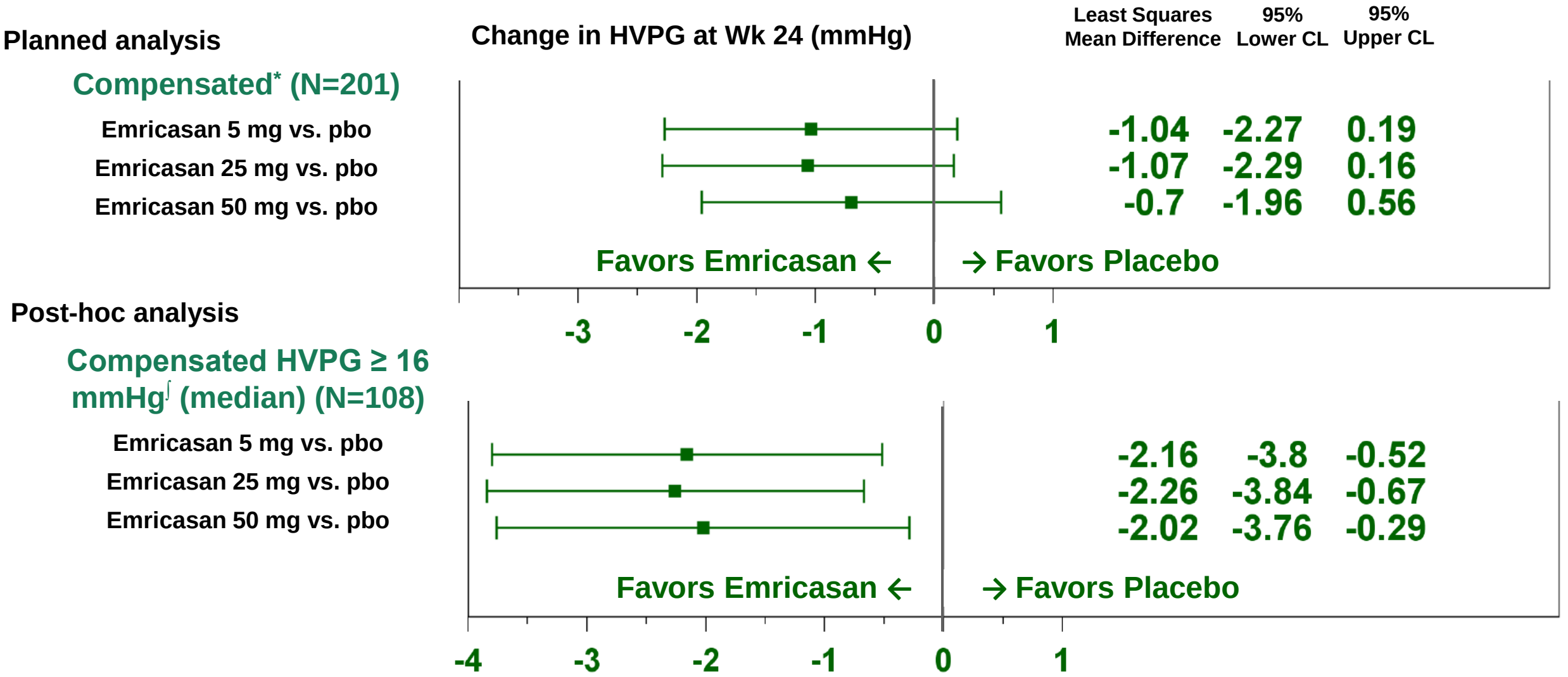
| Mean (SD) | Emricasan 5 mg (N=65) | Emricasan 25 mg (N=65) | Emricasan 50 mg (N=66) | Emricasan All doses (N=196) | Placebo (N=67) |
|---|---|---|---|---|---|
| Baseline HVPG (mmHg) | 16.9 (3.6) | 17.3 (3.3) | 16.9 (3.8) | 17.0 (3.5) | 16.8 (3.7) |
| Wk 24 HVPG (mmHg) | 16.5 (4.4) | 16.6 (4.2) | 15.8 (3.7) | 16.3 (4.1) | 16.6 (4.3) |
| Mean Change (mmHg) | -0.48 (3.4) | -0.81 (3.7) | -0.70 (3.4) | -0.66 (3.5) | -0.18 (3.0) |
| Median Change (mmHg) | 0.0 | -1.0 | -1.0 | -0.5 | +0.25 |




*ANCOVA model adjusting for baseline compensation status, NSBB use, and baseline HVPG, using multiple imputation for missing Wk 24 data

CL=confidence limit

# Subgroup analyses: In compensated cirrhosis, no change in HVPG; in compensated with baseline HVPG >16 mmHg, a clinically meaningful decrease

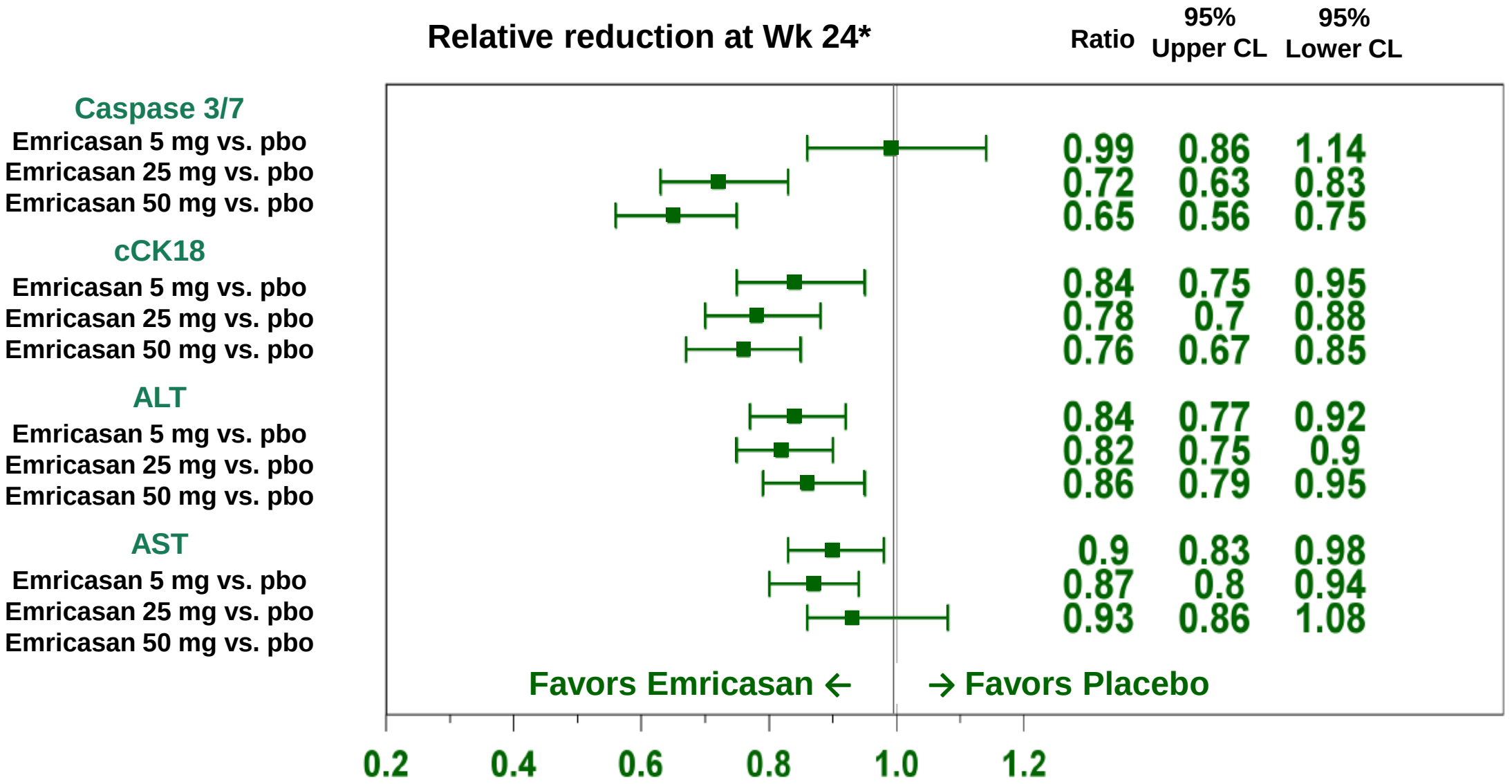



* ANCOVA model adjusting for baseline NSBB use and HVPG, using multiple imputation for missing wk 24 data

∫ ANCOVA model adjusting for baseline HVPG (observed cases)

**CL=confidence limit**

# Biomarkers: Caspase, cCK18, ALT, and AST were decreased with emricasan




*ANCOVA model adjusting for baseline compensation status, NSBB use, and baseline HVPG (observed case)

CL=confidence limit

# Safety Summary

| | Emricasan 5 mg (N=65) | Emricasan 25 mg (N=65) | Emricasan 50 mg (N=66) | Placebo (N=67) |
|---|---|---|---|---|
| Subjects with TEAEs | 51 (79%) | 57 (88%) | 52 (79%) | **55 (82%)** |
| Subjects with moderate TEAEs | 35 (54%) | 34 (52%) | 38 (58%) | **31 (46%)** |
| Subjects with severe TEAEs | 9 (14%) | 10 (15%) | 11 (17%) | **6 (9%)** |
| Subjects with serious TEAEs | 10 (15%) | 12 (19%) | 13 (20%) | **8 (12%)** |
| Subjects with med-related TEAEs | 10 (15%) | 17 (26%) | 23 (35%) | **16 (24%)** |
| Subjects with TEAEs leading to study discontinuation* | 2 (3%) | 1 (2%) | 3 (5%) | **0** |

*Single events occurred across various system organ classes: cardiac failure and aortic stenosis (n=1), asthenia and hepatorenal syndrome (n=1), diarrhea (n=1), colon cancer (n=1), hepatocellular carcinoma (n=1), interstitial lung disease (n=1)

**No clinically significant changes in routine labs, vital signs, or ECG (QTc)**

**TEAEs = treatment-emergent adverse events**
Adverse event data includes data up to expected Wk 24 visit for a given subject

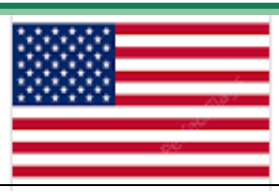
# Frequent (>5%) treatment-emergent AEs (TEAEs) were similar among groups

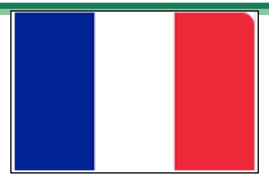
| | Emricasan 5 mg (N=65) | Emricasan 25 mg (N=65) | Emricasan 50 mg (N=66) | Placebo (N=67) |
|---|---|---|---|---|
| Edema peripheral | 8 (12%) | 10 (15%) | 5 (8%) | 3 (4%) |
| Nausea | 6 (9%) | 8 (12%) | 6 (9%) | 8 (12%) |
| Urinary tract infection | 5 (8%) | 10 (15%) | 5 (8%) | 6 (9%) |
| Diarrhea | 6 (9%) | 6 (9%) | 4 (6%) | 10 (15%) |
| Abdominal pain upper | 3 (5%) | 4 (6%) | 7 (11%) | 3 (4%) |
| Fatigue | 3 (5%) | 5 (8%) | 6 (9%) | 5 (8%) |
| Muscle spasms | 5 (8%) | 4 (6%) | 5 (8%) | 1 (2%) |
| Headache | 2 (3%) | 5 (8%) | 4 (6%) | 4 (6%) |
| Ascites | 3 (5%) | 4 (6%) | 3 (4%) | 4 (6%) |
| Abdominal pain | 4 (6%) | 1 (2%) | 4 (6%) | 4 (6%) |

# Summary

- **Oral emricasan for 24 weeks did not meet statistical significance for decreasing mean HVPG in patients with NASH cirrhosis and severe portal hypertension (HVPG ≥ 12 mmHg) However:**
  - A trend for decreases in HVPG with 25 mg BID and 50 mg BID was observed
  - Decreases in caspase 3/7, cCK18, and ALT demonstrated biologic activity
  - Clinically meaningful decreases in HVPG were observed in compensated patients with higher baseline HVPG (≥ 16 mmHg)
- **Treatment-emergent adverse events similar vs. placebo**
- **Await completion of 48-week study for full safety data set and clinical outcome events**
- **These results support additional exploration of emricasan in patients with severe portal hypertension**

# Acknowledgements : Investigators from 42 U.S. sites, 17 European (Spain, France, Germany, Switzerland) sites



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