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

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¹Yale University, ²Inselspital, University of Bern, ³Hospital Clinic-IDIBAPS-Ciberehd, ⁴Inland Empire Liver Foundation, ⁵Pinnacle Clinical Research, ⁶Duke University, ⁷Texas Liver Institute, University of Texas Health San Antonio, ⁸Methodist University Hospital, ⁹Indiana University, ¹⁰Bon Secours Liver Institute, ¹¹Gastro One, ¹²Mercy Medical Center, ¹³Hospital Ramon y Cajal, University of Alcala, ¹⁴Conatus Pharmaceuticals, ¹⁵Virginia Commonwealth University

The study was sponsored by Conatus Pharmaceuticals Inc.
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
  - 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
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
Subjects were stratified according to:
- Compensated (76%) or early decompensated (24%) status
- Non-selective beta-blocker use or not

Results reported today
Enrollment and Disposition

**Screened (n=564)**

**Randomized (n=263)**

- Emricasan 5mg BID (n=65)
  - Completed Wk 24 (n=62)
  - Discontinue early (n=3)
    - Adverse event (n=2)
    - Withdrew consent (n=1)
  - N=61 evaluable HVPG (1 ND)
- Emricasan 25 mg BID (n=65)
  - Completed Wk 24 (n=62)
  - Discontinued early (n=3)
    - Adverse event (n=1)
    - Withdrew consent (n=2)
  - N=62 evaluable HVPG
- Emricasan 50 mg BID (n=66)
  - Completed Wk 24 (n=60)
  - Discontinued early (n=6)
    - Adverse event (n=3)
    - Withdrew consent (n=1)
    - Death (n=1)
    - Liver transplant (n=1)
  - N=56 evaluable HVPG
- Placebo BID (n=67)
  - Completed Wk 24 (n=66)
  - Discontinued early (n=1)
    - Withdrew consent (n=1)
  - N=64 evaluable HVPG (1 ND, 1 NE)

ND=not done, NE=not evaluable
# Subject Characteristics

<table>
<thead>
<tr>
<th></th>
<th>All Subjects (N=263)</th>
<th>Emricasan 5 mg (N=65)</th>
<th>Emricasan 25 mg (N=65)</th>
<th>Emricasan 50 mg (N=66)</th>
<th>Placebo (N=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - mean (SD)</td>
<td>61 (9)</td>
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<td>62 (9)</td>
<td>60 (9)</td>
<td>61 (8)</td>
</tr>
<tr>
<td>Gender (%Female)</td>
<td>57%</td>
<td>57%</td>
<td>54%</td>
<td>50%</td>
<td>67%</td>
</tr>
<tr>
<td>Race (%Caucasian)</td>
<td>91%</td>
<td>89%</td>
<td>89%</td>
<td>91%</td>
<td>96%</td>
</tr>
<tr>
<td>BMI - mean (SD)</td>
<td>35 (7)</td>
<td>35 (7)</td>
<td>34 (6)</td>
<td>36 (6)</td>
<td>36 (8)</td>
</tr>
<tr>
<td>Type 2 diabetes (%)</td>
<td>79%</td>
<td>80%</td>
<td>80%</td>
<td>71%</td>
<td>84%</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>76%</td>
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</tr>
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<td><strong>Compensated (%)</strong></td>
<td>76%</td>
<td>75%</td>
<td>75%</td>
<td>73%</td>
<td>82%</td>
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<tr>
<td>** Decompensated (%)**</td>
<td>24%</td>
<td>25%</td>
<td>25%</td>
<td>27%</td>
<td>18%</td>
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<tr>
<td><strong>Varices (%)</strong></td>
<td>73%</td>
<td>71%</td>
<td>79%</td>
<td>71%</td>
<td>72%</td>
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<tr>
<td>Small</td>
<td>41%</td>
<td>32%</td>
<td>42%</td>
<td>38%</td>
<td>51%</td>
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<tr>
<td>Medium or Large</td>
<td>32%</td>
<td>38%</td>
<td>35%</td>
<td>33%</td>
<td>19%</td>
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<tr>
<td><strong>NSBB use (%)</strong></td>
<td>41%</td>
<td>43%</td>
<td>40%</td>
<td>39%</td>
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</table>
## Baseline Labs, Fibroscan® and HVPG

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>All Subjects (N=263)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>1.1 (0.8)</td>
<td>1.2 (0.7)</td>
<td>1.1 (0.6)</td>
<td>1.2 (1.0)</td>
<td>1.0 (0.7)</td>
</tr>
<tr>
<td>Albumin (mg/dL)</td>
<td>4.0 (0.4)</td>
<td>4.0 (0.5)</td>
<td>4.0 (0.4)</td>
<td>4.0 (0.5)</td>
<td>3.9 (0.4)</td>
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<tr>
<td>INR</td>
<td>1.2 (0.1)</td>
<td>1.2 (0.2)</td>
<td>1.2 (0.1)</td>
<td>1.2 (0.1)</td>
<td>1.2 (0.1)</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.0 (0.1)</td>
<td>1.0 (0.1)</td>
<td>1.0 (0.1)</td>
<td>1.0 (0.2)</td>
<td>1.0 (0.1)</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>47 (19)</td>
<td>46 (22)</td>
<td>48 (18)</td>
<td>46 (20)</td>
<td>47 (18)</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>35 (16)</td>
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<td>35 (13)</td>
<td>36 (16)</td>
<td>34 (17)</td>
</tr>
<tr>
<td>Platelet (K/mm³)</td>
<td>98 (39)</td>
<td>102 (39)</td>
<td>107 (48)</td>
<td>91 (31)</td>
<td>95 (34)</td>
</tr>
<tr>
<td>Child Pugh score</td>
<td>5.5 (0.8)</td>
<td>5.5 (1.0)</td>
<td>5.4 (0.7)</td>
<td>5.6 (0.9)</td>
<td>5.4 (0.8)</td>
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<tr>
<td>MELD score</td>
<td>9.0 (2.5)</td>
<td>9.2 (2.7)</td>
<td>9.1 (2.2)</td>
<td>9.2 (2.5)</td>
<td>8.4 (2.5)</td>
</tr>
<tr>
<td>Liver stiffness (kPa)</td>
<td>38.8 (19.2)</td>
<td>39.1 (18.1)</td>
<td>44.7 (21.1)</td>
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<td>36.8 (18.9)</td>
</tr>
<tr>
<td>Caspase 3/7 (RLU)</td>
<td>3340 (1422)</td>
<td>3195 (1143)</td>
<td>3243 (1339)</td>
<td>3355 (1553)</td>
<td>3558 (1601)</td>
</tr>
<tr>
<td>cCK18 (U/L)</td>
<td>391 (233)</td>
<td>408 (311)</td>
<td>394 (197)</td>
<td>395 (214)</td>
<td>366 (194)</td>
</tr>
<tr>
<td>HVPG (mmHg)</td>
<td>17.0 (3.6)</td>
<td>16.9 (3.6)</td>
<td>17.3 (3.3)</td>
<td>16.9 (3.8)</td>
<td>16.8 (3.7)</td>
</tr>
</tbody>
</table>
### Primary Analysis:
Overall, no significant change in HVPG at Wk 24 with Emricasan vs. Placebo

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

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

**Change in HVPG at Wk 24 (mmHg)**

- **Emricasan 5 mg vs. pbo**
  - Least Squares Mean Difference: -0.22
  - 95% Lower CL: -1.39
  - 95% Upper CL: 0.95

- **Emricasan 25 mg vs. pbo**
  - Least Squares Mean Difference: -0.45
  - 95% Lower CL: -1.62
  - 95% Upper CL: 0.72

- **Emricasan 50 mg vs. pbo**
  - Least Squares Mean Difference: -0.58
  - 95% Lower CL: -1.74
  - 95% Upper CL: 0.59

Favors Emricasan ←  →  Favors Placebo

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

### Planned analysis

**Compensated* (N=201)**

- Emricasan 5 mg vs. pbo
- Emricasan 25 mg vs. pbo
- Emricasan 50 mg vs. pbo

<table>
<thead>
<tr>
<th>Change in HVPG at Wk 24 (mmHg)</th>
<th>Least Squares Mean Difference</th>
<th>95% Lower CL</th>
<th>95% Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emricasan 5 mg vs. pbo</td>
<td>-1.04</td>
<td>-2.27</td>
<td>0.19</td>
</tr>
<tr>
<td>Emricasan 25 mg vs. pbo</td>
<td>-1.07</td>
<td>-2.29</td>
<td>0.16</td>
</tr>
<tr>
<td>Emricasan 50 mg vs. pbo</td>
<td>-0.7</td>
<td>-1.96</td>
<td>0.56</td>
</tr>
</tbody>
</table>

### Post-hoc analysis

**Compensated HVPG ≥ 16 mmHg‡ (median) (N=108)**

- Emricasan 5 mg vs. pbo
- Emricasan 25 mg vs. pbo
- Emricasan 50 mg vs. pbo

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<td>Emricasan 5 mg vs. pbo</td>
<td>-2.16</td>
<td>-3.8</td>
<td>-0.52</td>
</tr>
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<td>Emricasan 25 mg vs. pbo</td>
<td>-2.26</td>
<td>-3.84</td>
<td>-0.67</td>
</tr>
<tr>
<td>Emricasan 50 mg vs. pbo</td>
<td>-2.02</td>
<td>-3.76</td>
<td>-0.29</td>
</tr>
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* 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)
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

<table>
<thead>
<tr>
<th>Subjects with TEAEs</th>
<th>Emricasan 5 mg (N=65)</th>
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<tr>
<td>51 (79%)</td>
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<td>35 (54%)</td>
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<td>31 (46%)</td>
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<tr>
<td>9 (14%)</td>
<td>10 (15%)</td>
<td>11 (17%)</td>
<td>6 (9%)</td>
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<tr>
<td>10 (15%)</td>
<td>12 (19%)</td>
<td>13 (20%)</td>
<td>8 (12%)</td>
<td></td>
</tr>
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<td>17 (26%)</td>
<td>23 (35%)</td>
<td>16 (24%)</td>
<td></td>
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<tr>
<td>2 (3%)</td>
<td>1 (2%)</td>
<td>3 (5%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

*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

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<tr>
<td>Edema peripheral</td>
<td>8 (12%)</td>
<td>10 (15%)</td>
<td>5 (8%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (9%)</td>
<td>8 (12%)</td>
<td>6 (9%)</td>
<td>8 (12%)</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>5 (8%)</td>
<td>10 (15%)</td>
<td>5 (8%)</td>
<td>6 (9%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (9%)</td>
<td>6 (9%)</td>
<td>4 (6%)</td>
<td><strong>10 (15%)</strong></td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>3 (5%)</td>
<td>4 (6%)</td>
<td>7 (11%)</td>
<td>3 (4%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (5%)</td>
<td>5 (8%)</td>
<td>6 (9%)</td>
<td>5 (8%)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>5 (8%)</td>
<td>4 (6%)</td>
<td>5 (8%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (3%)</td>
<td>5 (8%)</td>
<td>4 (6%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Ascites</td>
<td>3 (5%)</td>
<td>4 (6%)</td>
<td>3 (4%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>4 (6%)</td>
<td>1 (2%)</td>
<td>4 (6%)</td>
<td>4 (6%)</td>
</tr>
</tbody>
</table>
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
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