Emricasan (IDN-6556) administered orally for 28 days lowers portal pressure in patients with compensated cirrhosis and severe portal hypertension

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Background

Caspases play a central role in apoptosis and inflammation

Caspases produce hemodynamically-active, pro-inflammatory microparticles from apoptotic cells

In cirrhosis, these microparticles appear to contribute to the splanchnic and systemic vasodilatation that maintains and enhances portal hypertension

Rautou PE et al. Gastroenterology 2012;143:166-176

Emricasan (IDN-6556), an oral pan-caspase inhibitor has been shown to reduce portal pressure and improve survival in a murine model of portal hypertension

Objectives

To evaluate, in patients with compensated cirrhosis and portal hypertension, the effect of emricasan on:

• portal pressure (determined by the hepatic venous pressure gradient or HVPG)

• safety and tolerability
Hypothesis

Emricasan lowers portal pressure and is safe in patients with compensated cirrhosis and portal hypertension
Methods

Prospective, proof-of-concept, multi-center (9 U.S. sites), open-label study

Emriscasan administered orally at a dose of 25 mg twice a day for 28 days

Hepatic venous pressure gradient (HVPG) assessed before and after emriscasan

One expert (J.B.) read all HVPG tracings

Investigators had access to all the data
Methods:
Inclusion and Exclusion Criteria

Inclusion criteria
• Cirrhosis (HCV, NASH, limiting alcoholic etiology to <40%)
• Portal hypertension, i.e. HVPG > 5 mmHg

Main exclusion criteria
• Decompensation or HCC at entry
• Use of vasoactive drugs (beta-blockers, nitrates, PDE inhibitors)
• HCV-infected subjects receiving or planning on receiving anti-viral therapy during the course of the study
• Concomitant HIV infection
• Unwillingness to undergo contraception from screening to one month after last dose of emricasan
Study Schema

Screening Phase

Screen

Day -7 to Day 0

Baseline HVPG

Open-Label Treatment Phase

Emricasan 25 mg BID
N=23 treated (22 evaluable)

Day 1 - - - - - - - - - -

Follow-up Phase

Follow-Up

Day 28

Follow-up HVPG

Day 56
Methods:
Study Outcomes

**Primary (Baseline to Day 28)**
- Change in HVPG
- Change in cCK18 serum levels (marker of apoptosis and indicator of caspase activity)

**Secondary (Baseline to Day 28)**
- Change in liver enzymes (ALT, AST), caspase 3/7, MELD, Child-Pugh score
- Development of decompensation

**Safety Variables (Baseline to Day 56)**
- Adverse events
- Vital signs
- Laboratory tests
- EKG (QTc interval)
• Analysis in the entire group

• Post-hoc analyses of baseline HVPG subgroups: <12 or ≥12 mmHg (severe portal hypertension)
  • Post-hoc sensitivity analysis conducted using an HVPG cutoff of 10 mmHg

• Analyses of primary endpoints used parametric tests given no major violations of normality
  • Sensitivity analyses using non-parametric tests yielded similar results
**Results:**

**Baseline Characteristics of the Cohort (N=23)**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Median*</th>
<th>Range (min, max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>59</td>
<td>48-80</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>16 (69.6%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Race (% Caucasian)</td>
<td>21 (91.3%)</td>
<td>N/A</td>
</tr>
<tr>
<td>Etiology of cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- NASH</td>
<td>13 (56.5%)</td>
<td>N/A</td>
</tr>
<tr>
<td>- HCV (± alcohol)</td>
<td>9 (39.1%)</td>
<td>N/A</td>
</tr>
<tr>
<td>- Alcohol alone</td>
<td>1 (4.3%)</td>
<td>N/A</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.4</td>
<td>17.9 – 44.9</td>
</tr>
<tr>
<td>Platelet count (K/mm³)</td>
<td>104</td>
<td>43 - 199</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>25</td>
<td>10 - 99</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>35</td>
<td>16 - 83</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>0.73</td>
<td>0.31 – 3.08</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>4.2</td>
<td>2.7 – 4.9</td>
</tr>
<tr>
<td>INR</td>
<td>1.1</td>
<td>0.9 – 1.6</td>
</tr>
<tr>
<td>Number with Child Class A</td>
<td>20 (87%)</td>
<td>N/A</td>
</tr>
<tr>
<td>MELD score</td>
<td>8</td>
<td>6 - 15</td>
</tr>
<tr>
<td>HVPG (mmHg)</td>
<td>13.5</td>
<td>5.5 – 32.0</td>
</tr>
</tbody>
</table>

*Except where percentages are in parentheses*
Results:
Overall, there were no significant differences in HVPG

Entire Group
(N=22*)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Day 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.3±7.8 mmHg</td>
<td>14.1±6.4 mmHg</td>
</tr>
</tbody>
</table>

Mean change: ↑1.2% (↓1.1±4.6 mmHg), p=0.26

*1 subject withdrew after 1 week due to adverse events of abdominal bloating and conjunctivitis (no follow-up HVPG)
Results:
A clinically meaningful reduction in HVPG was observed in patients with severe portal hypertension (HVPG ≥12 mmHg) at baseline

Baseline HVPG < 12 mmHg (N=10)

Baseline HVPG ≥ 12 mmHg (N=12)

Mean change: ↑ 23.1% (↑ 1.9±3.2 mmHg), p=0.12

Mean change: ↓ 17.2% (↓ 3.7±4.0 mmHg), p<0.003*

8/12 had a ≥10% decrease;
4/12 had a ≥20% decrease;
2/12 HVPG ↓ below 12 mmHg

*p-value not adjusted for multiple testing
Results:
Sensitivity analyses using HVPG cut-off of 10 mmHg (clinically significant portal hypertension) showed similar results

Baseline HVPG < 10 mmHg
(N=7)

Baseline HVPG ≥ 10 mmHg
(N=15)

Mean change: ↑ 25.4% (↑1.9±3.7 mmHg), p=0.23
Mean change: ↓ 10.1% (↓ 2.6±4.3 mmHg), p=0.03*

*p-value not adjusted for multiple testing
Results:
cCK18 levels decreased in entire group but were relatively low at baseline

*p<0.05, not adjusted for multiple testing
NS=not significant
Data are geometric means
# Results:
Changes in clinical, biochemical and biomarker parameters

<table>
<thead>
<tr>
<th></th>
<th>HVPG &lt; 12 mmHg (N=10)</th>
<th></th>
<th>HVPG ≥ 12 mmHg (N=13)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median (Range)</td>
<td>p</td>
<td>Median (Range)</td>
<td>p</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>-2 (-12, 16)</td>
<td>0.85</td>
<td>0 (-14, 17)</td>
<td>0.99</td>
</tr>
<tr>
<td>Heart rate (bpm)</td>
<td>-4 (-22, 10)</td>
<td>0.20</td>
<td>0 (-29, 24)</td>
<td>0.98</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>+0.3 (-0.2, 1.5)</td>
<td>0.05</td>
<td>0 (-1.9, 1.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>Platelet count (K/mm³)</td>
<td>0 (-31, 24)</td>
<td>0.77</td>
<td>-8 (-33, 13)</td>
<td>0.08</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>-2.5 (-23, 68)</td>
<td>0.32</td>
<td>-4 (-29, 8)</td>
<td>0.03</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>0 (-61, 43)</td>
<td>0.44</td>
<td>-5 (-15, 4)</td>
<td>0.008</td>
</tr>
<tr>
<td>Total bilirubin (mg/dL)</td>
<td>-0.1 (-0.6, 0.3)</td>
<td>0.29</td>
<td>0 (-0.4, 0.5)</td>
<td>0.78</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>-0.15 (-0.4, 0.3)</td>
<td>0.16</td>
<td>-0.1 (-0.5, 0.4)</td>
<td>0.40</td>
</tr>
<tr>
<td>INR</td>
<td>0 (-0.1, 0.1)</td>
<td>0.34</td>
<td>0 (-0.2, 0.1)</td>
<td>0.74</td>
</tr>
<tr>
<td>MELD score</td>
<td>0 (-2, 1)</td>
<td>0.38</td>
<td>0 (-2, 2)</td>
<td>0.43</td>
</tr>
<tr>
<td>Caspase 3/7* (RLU)</td>
<td>-746 (-3452, 424)</td>
<td>0.009</td>
<td>-655 (-2337, 1107)</td>
<td>0.06</td>
</tr>
</tbody>
</table>

No correlation was found between changes in these parameters and changes in HVPG

*Excludes 1 outlier

p-values not adjusted for multiple testing
Results:
Emricasan was generally well tolerated

<table>
<thead>
<tr>
<th></th>
<th>Baseline HVPG</th>
<th></th>
<th>All Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;12 mmHg (N=10)</td>
<td>≥12 mmHg (N=13)</td>
<td>(N=23)</td>
</tr>
<tr>
<td>Number of AEs</td>
<td>11</td>
<td>49</td>
<td>60*</td>
</tr>
<tr>
<td>Number of related AEs</td>
<td>7</td>
<td>8</td>
<td>15</td>
</tr>
<tr>
<td>Subjects with AEs</td>
<td>6 (60.0%)</td>
<td>9 (69.2%)</td>
<td>15 (65.2%)</td>
</tr>
<tr>
<td>Subjects with serious AEs</td>
<td>0</td>
<td>1 (7.7%)*</td>
<td>1 (4.3%)</td>
</tr>
<tr>
<td>Subjects with moderate AEs</td>
<td>4 (40.0%)</td>
<td>6 (46.2%)</td>
<td>10 (45.3%)</td>
</tr>
<tr>
<td>Subjects with severe AEs</td>
<td>0</td>
<td>1 (7.7%)**</td>
<td>1 (4.3%)</td>
</tr>
<tr>
<td>Subjects with AEs leading to discontinuation</td>
<td>0</td>
<td>1 (7.7%)</td>
<td>1 (4.3%)</td>
</tr>
</tbody>
</table>

* One subject had 3 serious AEs (SIRS, acute respiratory failure, dyspnea) occurring 10 days after last dose of study drug, assessed unrelated, along with 24 other AEs

** All AEs except 2 (SIRS, anemia in the same subject with 3 SAEs) were mild to moderate in severity

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

No subject developed cirrhosis decompensation (ascites, encephalopathy, hemorrhage)
Limitations

Study is small, not placebo-controlled, relatively short duration

Classification of patients with severe portal hypertension was established post-hoc
Emricasan administered orally for 28 days was associated with a clinically meaningful decrease in portal pressure in patients with compensated cirrhosis and severe portal hypertension

- Although a hemodynamic mechanism cannot be ruled out, concomitant decreases in AST/ALT suggest an intrahepatic effect

Emricasan was generally well-tolerated
Future directions

Trials of longer duration will elucidate potential additional long-term effects due to microvascular remodeling or amelioration of vasodilatation.

Randomized, placebo-controlled Phase 2 studies that will assess different doses of emricasan using an HVPG endpoint at 6 months are planned for 2016.
Acknowledgements

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- McGuire DVAMC (PI: Dr. Fuchs)
- Rutgers New Jersey Medical School (PI: Dr. Pyropoulos)
- University of Mississippi (PI: Dr. Borg)
- University of Pennsylvania (PI: Dr. Reddy)
- University of Utah (PI: Dr. Gallegos)
- Yale University, VA-CT HCS (PI: Dr. Garcia-Tsao)