Background: Before the use of direct-acting antivirals agents (DAAs), recurrent HCV post liver transplantation (LT) was common, often leading to progressive fibrosis and liver failure. Newer DAAs agents have high sustained virologic response (SVR) rates in post LT HCV patients, but many transplanted prior to use have residual fibrosis. Caspases mediate apoptosis and inflammation, contributing to chronic liver disease (CLD) progression. Emricasan (EMR), an oral pan-caspase inhibitor, reduces hepatic inflammation/fibrosis and decreases mechanism-specific (caspase7) and inflammatory (ALT) biomarkers in CLD patients (Fig. 1). The exploratory phase I study assessed EMR’s effect on Ishak fibrosis stage at month 24 in HCV subjects post LT achieving SVR.

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 HCV and/or HBV infection
- Autoimmune diseases
- Chronic liver disease of any other etiology
- Evidence of aloipathic 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/1.73m²
- Renal transplant or severe renal impairment with eGFR <30mL/min/1.73m²
- Active HIV and/or HBV infection
- 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/1.73m²
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Table 1: Baseline Characteristics

| N=64 | LT subjects (Ishak fibrosis stage F2) 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).

Table 2: Month 24 Ishak Fibrosis Stage Results

<table>
<thead>
<tr>
<th>Observed Cases</th>
<th>Improved</th>
<th>Stable</th>
<th>Worsened</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emricasan (N=32)</td>
<td>16 (56.2%)</td>
<td>12 (37.5%)</td>
<td>2 (6.3%)</td>
</tr>
<tr>
<td>F2 (N=4)</td>
<td>8 (80.0%)</td>
<td>0 (0.0%)</td>
<td>1 (10.0%)</td>
</tr>
<tr>
<td>F2-F3 (N=9)</td>
<td>10 (11.1%)</td>
<td>2 (22.2%)</td>
<td>4 (44.4%)</td>
</tr>
<tr>
<td>F4 (N=6)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Placebo (N=19)</td>
<td>12 (63.2%)</td>
<td>2 (10.5%)</td>
<td>5 (26.3%)</td>
</tr>
<tr>
<td>F2 (N=4)</td>
<td>4 (40.0%)</td>
<td>1 (20.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>F2-F3 (N=11)</td>
<td>5 (45.5%)</td>
<td>1 (9.1%)</td>
<td>5 (45.5%)</td>
</tr>
<tr>
<td>F4 (N=3)</td>
<td>3 (100.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Table 3: Safety Overview

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>N</th>
<th>Total no.</th>
<th>Drug-related AEs</th>
<th>Drug-related SAEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emricasan (N=32)</td>
<td>32</td>
<td>29</td>
<td>12/29 (41.4%)</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Placebo (N=20)</td>
<td>20</td>
<td>18</td>
<td>10/18 (55.6%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

References

1Charniot M et al Gastroenterology. 2015;149(3):649-59
5Steffen et al. Alimr Pharm Ther 2010; 31:969-78
7ClinicalTrials.gov identifier: NCT02138253