Long-term Entecavir Therapy Results in Reversal of Fibrosis/Cirrhosis and Continued Histologic Improvement in Patients with HBV(+) and (-) Chronic Hepatitis B: Results from Studies ETV-022, -027 and -901

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Introduction

- Elevated baseline HBV DNA has been demonstrated to be a significant factor in the development of cirrhosis and hepatocellular carcinoma.
- HBV DNA suppression with antiviral therapy can significantly improve liver histology in HBV(+) patients.
- Entecavir (ETV) (1 mg daily demonstrated superior histologic, virologic and biochemical activity compared to lamivudine (LVD) (150 mg daily in nucleoside-naive HBV(+) and HBV(-)+ patients with chronic hepatitis B (studies ETV-022 and ETV-027/2).
- We present long-term histologic results for a subset of patients treated with ETV for a median of 280 weeks.

Methods

Study population

- The Long-term Histology Cohort (n=57) is a subset of the ETV-901 study population.
  - It consists of nucleoside-naive HBV(+) and HBV(-) patients treated with ETV in studies ETV-022 or ETV-027 who:
    - had a liver biopsy in study ETV-021 and
    - received a minimum of 5 years of cumulative ETV therapy from Phase 3 baseline to the time of their last observed biopsy.
- Patients received ETV 0.5 mg once daily in studies ETV-022 and -027.
- All patients received ETV 1 mg once in study ETV-091.
- Initially, due to ongoing blinding of Phase 2-3 studies, patients enrolling into study ETV-901 may have received a brief period of combination ETV 1 mg and LVD 1 mg daily.

Efficacy Evaluable Cohort

- The Efficacy Evaluable Cohort (n=57) comprises patients who had an adequate Phase 3 baseline biopsy
  - and a baseline Knodell necroinflammatory score of ≥2
  - an adequate long-term biopsy sample in Study ETV-091.

Analysis endpoints: liver histology

- Co-primary endpoints:
  - Histologic improvement (≥2-points decrease in Knodell fibrosis score and no worsening of Knodell necroinflammation score compared to baseline).
  - Improvement in Ishak fibrosis score (≥2-point decrease) compared to baseline.

Other histologic endpoints:

- Change from baseline in Knodell necroinflammatory score.
- Change from baseline in Ishak fibrosis score.

- Proportion of patients with baseline advanced fibrosis/cirrhosis (Ishak score ≥4) who demonstrated Ishak score improvement.
- Proportion of subjects with baseline histologic activity index (HAI) score of ≥6 who achieved a Knodell HAI score ≥3.

Analysis endpoints: virologic, biochemical, serologic and safety

- All efficacy analyses were conducted on samples that matched the time of long-term biopsy (±12 weeks) and compared with Phase 3 baseline.
- Proportions of patients with HBV DNA <300 copies/mL by PCR, Alanine aminotransferase (ALT) ≤ULN, HBsAg loss, HBsAg seroconversion and HBsAg loss were assessed among patients with available samples (Non-completer/missing).
- Safety was evaluated from entry in Study ETV-091 to date of database lock (28 April 2008).

Results

Table 1: Demographics and Baseline Characteristics of Patients in Phase 3 Studies Compared with Efficacy Evaluable Cohort

<table>
<thead>
<tr>
<th></th>
<th>ETV-022 (n=325)</th>
<th>ETV-027 (n=226)</th>
<th>ETV-901 (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>49 (29–69)</td>
<td>50 (28–68)</td>
<td>50 (38–67)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>69 (81)</td>
<td>73 (83)</td>
<td>70 (100)</td>
</tr>
<tr>
<td>Race</td>
<td>Asian (%)</td>
<td>Asian (%)</td>
<td>Asian (%)</td>
</tr>
<tr>
<td>Chinese (%)</td>
<td>55 (67)</td>
<td>54 (67)</td>
<td>56 (100)</td>
</tr>
<tr>
<td>Korean (%)</td>
<td>40 (48)</td>
<td>41 (45)</td>
<td>4 (7)</td>
</tr>
</tbody>
</table>
| Proportion of patients with HBV DNA <300 copies/mL by PCR, Alanine aminotransferase (ALT) ≤ULN, HBsAg loss, HBsAg seroconversion and HBsAg loss were assessed among patients with available samples (Non-completer/Missing).
- Safety was evaluated from entry in Study ETV-091 to date of database lock (28 April 2008).

- Median time on treatment at the time of long-term biopsy was 280 weeks.

Table 2: Comparison of Results Between Efficacy Evaluable Cohort and ETV-022 and ETV-027 at Week 48

<table>
<thead>
<tr>
<th></th>
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<th>ETV-901 (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of subjects with baseline advanced fibrosis/cirrhosis (Ishak score ≥4) who demonstrated Ishak score improvement</td>
<td>32%</td>
<td>32%</td>
<td>48%</td>
</tr>
<tr>
<td>Proportion of patients with baseline histologic activity index (HAI) score of ≥6 who achieved a Knodell HAI score ≥3</td>
<td>70%</td>
<td>70%</td>
<td>78%</td>
</tr>
</tbody>
</table>

- Following 48 Weeks of treatment the majority (73%) of patients achieved histologic improvement.
- The proportion of patients who achieved histologic improvement increased to 90% following long-term treatment.
- Improvement in Ishak fibrosis score was observed in 32% of patients following 48 Weeks of treatment.
- This increased to 88% following long-term treatment.

Table 4: Change in Ishak Fibrosis Scores from Baseline

<table>
<thead>
<tr>
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<th>ETV-901 (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement in Ishak fibrosis score, n (%)</td>
<td>15 (37)</td>
<td>121 (41)</td>
<td>3 (20)</td>
</tr>
</tbody>
</table>

Reversal of advanced fibrosis/cirrhosis

- Ten patients had baseline advanced fibrosis/cirrhosis (Ishak fibrosis score ≥4, 5 or 6).
- All demonstrated an improvement in Ishak fibrosis score (-3-point improvement).
- Four patients had a liver biopsy with cirrhosis at baseline; all demonstrated an improvement of Ishak fibrosis score.
- The median change in Ishak fibrosis score was a 3-point decrease (range: -1 to -4).

Summary of Results

- Ninety-six percent of patients in the Long-term Histology Cohort who received continuos treatment with ETV achieved histologic improvement.
- All patients with advanced fibrosis/cirrhosis at baseline (Ishak fibrosis score ≥4) demonstrated an improvement in fibrosis.
- At the time of long-term biopsy:
  - all patients had HBV DNA <300 copies/mL,
  - eighty-one percent of patients had ALT ≤ULN.
- Week 48 results for the Efficacy Evaluable Cohort were comparable to the respective Phase 3 patient studies (ETV-022 and ETV-027).
- Safety profile was consistent with previously reported experience.

Conclusion

The results from this cohort demonstrate that long-term ETV treatment result in durable suppression of viral replication and regression of fibrosis/cirrhosis.

Disclosures
