Hepatitis B Medications

Entecavir (Baraclude)

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Entecavir (ETV)
Summary of Key Studies

- **Phase 3 Trials**
  - BeHOLD (HBeAg+): ETV versus 3TC in HBeAg-Positive
  - BeHOLD (HBeAg-): ETV versus 3TC in HBeAg-Negative
Entecavir versus Lamivudine in HBeAg-Negative
BEHoLD: HBeAg-Positive, Week 48
Entecavir versus Lamivudine: 48 Week Data BEHoLD (HBeAg-Positive): Study Design

- **Background**
  - Phase 3, randomized, double-blind controlled trial
  - 137 centers in Americas, Asia, Australia, Europe, & Middle East

- **Subjects (n = 709)**
  - Age ≥16 years with documented HBeAg-positive
  - Excluded: prior nucleoside/nucleotide active against HBV >12 weeks
  - Excluded: coinfection with HIV, HCV, or HDV

- **Regimens**
  - Entecavir: 0.5 mg once daily (n = 354)
  - Lamivudine: 100 mg once daily (n = 355)

- **Study End-Points**
  - Primary: hepatic histologic improvement
  - Secondary: changes in HBV DNA, HBeAg seroconversion, normalization of ALT

Entecavir versus Lamivudine in HBeAg-Negative BEHoLD (HBeAg-Positive): Study Design

Entecavir versus Lamivudine in HBeAg-Negative BEHoLD (HBeAg-Positive): Results

HBeAg-Positive Study Participants: Week 48 Treatment Response

Conclusions: “Among patients with HBeAg-positive chronic hepatitis B, the rates of histologic, virologic, and biochemical improvement are significantly higher with entecavir than with lamivudine. The safety profile of the two agents is similar, and there is no evidence of viral resistance to entecavir.”
Entecavir versus Lamivudine in HBeAg-Negative BEHoLD: HBeAg-Positive, Week 96
Entecavir versus Lamivudine: 96 Week Data 
BEHoLD (HBeAg-Positive): Conclusions

• **Background**
  - Phase 3, randomized, double-blind controlled trial
  - 146 centers in Europe, Asia, Americas, Australia & Middle East

• **Subjects**
  - N = 715 with chronic HBeAg-positive
  - Excluded: prior lamivudine therapy x >12 weeks or any prior entecavir
  - Week 52 “virologic responders” (HBV DNA to <700,000 copies/mL & HBeAg loss): continue blinded treatment to week 96

• **Regimens**
  - Entecavir 0.5 mg once daily
  - Lamivudine 100 mg once daily

• **Study End-Points**
  - Virologic Response: HBV DNA level <300 copies/mL
  - Serologic Response: HBeAg seroconversion, HBsAg loss

Source: Gish RG, et. al. Gastroenterology. 2007;133:1437-44.
Entecavir versus Lamivudine: 96 Week Data
BEHoLD (HBeAg-Positive): Study Design

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>48</th>
<th>52</th>
<th>96</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Randomized</td>
<td>Analysis for Virologic Response</td>
<td>Continuation for Virologic Responders</td>
<td>Final Analysis</td>
</tr>
</tbody>
</table>

**Entecavir:**
- Week 48: 0.5 mg/day (n = 243)
- Week 52: 0.5 mg/day (n = 243)

**Lamivudine:**
- Week 48: 100 mg/day (n = 164)
- Week 52: 100 mg/day (n = 164)

Source: Gish RG, et. al. Gastroenterology. 2007;133:1437-44.
Entecavir versus Lamivudine: 96 Week Data
BEHoLD (HBeAg-Positive): Results

HBeAg-Positive Study Participants: Week 96 Treatment Response

Source: Gish RG, et. al. Gastroenterology. 2007;133:1437-44.
## Entecavir versus Lamivudine: 96 Week Data
### BEHoLD (HBeAg-Positive): Safety & Adverse Events

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Entecavir (n = 354)</th>
<th>Lamivudine (n = 355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event ≥5%, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Increased ALT levels</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Serious adverse event, %</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Adverse event leading to discontinuation, no.</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Lab abnormalities, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 4 ALT (&gt;10x ULN) and &gt;2x baseline</td>
<td>12* (3)</td>
<td>23** (7)</td>
</tr>
</tbody>
</table>

*11 of 12 of these flares resolved within 1-7 weeks. 11 of 12 were also associated with ≥2 log10 decline in HBV DNA
**11 of 23 associated with increasing HBV DNA level that preceded or coincided with the flare

Source: Gish RG, et. al. Gastroenterology. 2007;133:1437-44.
Conclusions: “Entecavir treatment through 96 weeks results in continued benefit for patients with HBeAg-positive chronic hepatitis B.”
Entecavir versus Lamivudine in HBeAg-Negative
BEHoLD: HBeAg-Negative
Entecavir versus Lamivudine in HBeAg-Negative
BEHoLD (HBeAg-Negative): Study Design

• **Background**
  - Phase 3, randomized double-blind controlled trial
  - 146 centers in Europe, Asia, Americas, Australia & Middle East

• **Subjects**
  - N = 638 with chronic HBeAg-negative
  - Excluded: prior lamivudine therapy >12 weeks or any prior entecavir

• **Regimens**
  - Entecavir 0.5 mg QD (n = 325)
  - Lamivudine 100 mg QD (n = 313)

• **Study End-Points at week 48**
  - Primary: Histologic improvement (≥2 points on Knodell necroinflammatory score, and no worsening on Knodell fibrosis score)
  - Secondary: HBV DNA < 300 copies/ml; decrease in Ishak fibrosis score; normalization of ALT

Entecavir versus Lamivudine in HBeAg-Negative BEHoLD (HBeAg-Negative): Study Design

Randomized

Key Participant Features
- HBeAg-negative (n = 638)
- Compensated liver disease
- HBV DNA 0.7 MEq/mL by bDNA assay
- ALT 1.3-10 x ULN

Week 48

Entecavir: 0.5 mg/day (n = 325)

Lamivudine: 100 mg/day (n = 313)

Entecavir versus Lamivudine in HBeAg-Negative
BETHoLD (HBeAg-Negative): Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristic</th>
<th>Entecavir (n = 325)</th>
<th>Lamivudine (n = 313)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (±SD), years</td>
<td>44 ±11</td>
<td>44 ±11</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>248 (76)</td>
<td>236 (75)</td>
</tr>
<tr>
<td>Race, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>193 (59)</td>
<td>176 (56)</td>
</tr>
<tr>
<td>Asian</td>
<td>122 (38)</td>
<td>129 (41)</td>
</tr>
<tr>
<td>Black</td>
<td>8 (2)</td>
<td>7 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (&lt;1)</td>
<td>1 (&lt;1)</td>
</tr>
<tr>
<td>Knodell inflammatory score, mean (±SD)</td>
<td>7.6 ±1.8</td>
<td>7.6 ±1.7</td>
</tr>
<tr>
<td>Ishak fibrosis score, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥3 (bridging fibrosis)</td>
<td>43</td>
<td>41</td>
</tr>
<tr>
<td>≥4 (cirrhosis)</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Alanine aminotransferase, IU/mL (±SD)</td>
<td>141 ±114.7</td>
<td>143 ±119.4</td>
</tr>
<tr>
<td>Prior treatment w/ interferon or lamivudine, no. (%)</td>
<td>49 (15)</td>
<td>45 (14)</td>
</tr>
</tbody>
</table>

Entecavir versus Lamivudine in HBeAg-Negative BEHoLD (HBeAg-Negative): Results

- **HBV DNA <300 copies/mL**: 90% (Entecavir) vs. 72% (Lamivudine), $P<0.001$
- **ALT Normalization**: 78% (Entecavir) vs. 71% (Lamivudine), $P=0.045$
- **Histologic Improvement**: 70% (Entecavir) vs. 61% (Lamivudine), $P=0.01$

Conclusions: “Among patients with HBeAg-negative chronic hepatitis B who had not previously been treated with a nucleoside analogue, the rates of histologic improvement, virologic response, and normalization of alanine aminotransferase levels were significantly higher at 48 weeks with entecavir than with lamivudine. The safety profile of the two agents was similar, and there was no evidence of viral resistance to entecavir.”