Entecavir Maintains a High Genetic Barrier to HBV Resistance Through 6 Years in Naïve Patients

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Disclosures

• I am a full-time employee of Bristol-Myers Squibb;
• Data presented are from trials in the entecavir development program
Primary Factors in Antiviral Resistance

Fitness – replication capacity of viral variants

Genetic Barrier – number of substitutions required for resistance

Clinical Efficacy –
Reflects intrinsic drug potency and dose administered

• Inherent potency
• Pharmacologic levels achieved

Impact on viral fitness

Genetic barrier
ETV Genotypic Resistance: Population Screening

- **2 cohorts:** Naïve and LVD-refractory
  - All patients with continuous ETV >12 wks

- **Genotype performed:**
  - All baseline specimens
  - If HBV DNA ≥ 300 c/mL (50 IU/mL) at
    - Annual timepoint (Wks 48, 96, 144, 192, 240, 288)
    - End of Dosing
  - If virologic breakthrough while on treatment (confirmed ≥1 log increase in HBV DNA from nadir)

*consistent with monitoring recommendations in Pawlotsky et al, Gastroenterology 2008*
ETV Genotypic Resistance: Rate Calculation

- Genotypic resistance to ETV requires both:
  - LVD resistance (M204I/V ± L180M), and
  - ETV-specific change (T184, S202 or M250)

- Cumulative probability*

  \[ P = 1 - \frac{1-n_1}{N_1} \cdot \frac{1-n_2}{N_2} \cdots \frac{1-n_x}{N_x} \]

* consistent with monitoring recommendations in Pawlotsky et al, Gastroenterology 2008
ETV 6-Year Program: Naïve Patient Flow

Years 1-2
Randomized Studies
0.5 mg

ETV - 022: Naïve HBeAg+

ETV - 027: Naïve HBeAg-

Responders¹

Virologic Responders¹

Non-Responders

• Treatment Gap Time
≤35 days for resistance cohort

Years 2-6
ETV-901 Rollover Study
1.0 mg ETV
Nucleoside-Naïve Cohort (HBeAg+ & HBeAg-): Cumulative Probability of ETV Resistance Through 6 Years

- HBV DNA <300 c/mL in 94% of patients in Year-6 (N = 99)
- HBV DNA <300 c/mL at last on-treatment visit in 89% of those discontinuing
Resistance Rates Across Studies in Nucleoside-Naïve Patients

Lamivudine-Refractory Patients
Lamivudine Refractory - Patient Flow

**Randomized Studies**

1.0 mg

ETV-026
HBeAg+

ETV-014
1.0 mg group

ETV-015
Post-Transplant

**Rollover Study**

1.0 mg ETV

Responders

Virologic Responders

Non-Responders

Any

Any

1. protocol defined response criteria
Lamivudine-Refractory Cohort (HBeAg+): Cumulative Probability of ETV Resistance Through 6 Years

ETVr = LVDr (M204V ± L180M) + T184, S202 and/or M250 substitutions

- 74/187 (40%) achieved HBV DNA < 300 copies/mL
- 5/74 (7%) with HBV DNA < 300 c/mL had subsequent genotypic ETV resistance
Genetic Barrier to Entecavir Resistance

**Nucleoside-naïve patients**

ETV

- Wild-type virus
- LVD-resistant virus
- ETV-resistant virus

**Lamivudine-refractory patients**

LVD then ETV

- rtM204V/I ± rtL180M
- rtT184 or rtS202 or rtM250

Entecavir Resistance Through 6 Years

Nucleoside-Naïve:
- ETV has high potency and high genetic barrier
- Resistance is rare through 6 years
  - 1.2% genotypic resistance

LVD-refractory:
- ETV potency and genetic barrier are reduced
- Incremental increase in resistance over time
- Favorable prognostic subgroups can be identified by early response to treatment and lower baseline HBV DNA (< $10^7$ copies/mL)
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- >850 patients and
- >340 investigators from
- 30 countries

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