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

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Introduction

- Entecavir (ETV) provides both potent viral suppression and a high genetic barrier to resistance.[1,2]
- Genetic barrier is defined as the number of mutations required to produce a decrease in susceptibility to the antiviral drug.[3]
- Genotypic resistance to ETV requires both:[1]
  - LVD resistance (M204I/V ± L180M), and
  - ETV-specific change (T184, S202 or M250)
- In nucleoside-naïve patients, ETV resistance (ETVr) was rare through 5 years.[1]
- The barrier to resistance in lamivudine (LVD)-refractory patients is reduced.[1,2]
- The aim of this resistance analysis is to establish genotypic resistance rates through 6 years of ETV therapy in nucleoside-naïve and lamivudine-refractory patient populations.

Methods

Resistance Analysis

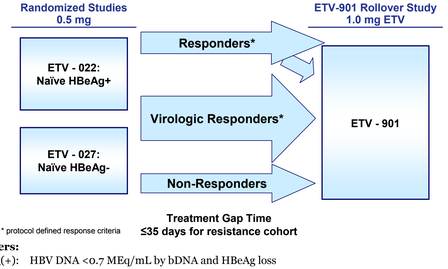
ETV Genotypic Resistance: Population Screening

- 2 cohorts: Naïve and LVD-refractory
- All patients with continuous ETV >12 wk
  - Continuous treatment defined as ≤35 day treatment gap (see **Figures 1 and 3**)
- Genotype performed by population sequencing:[1,2]
  - 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
    - Breakthrough = confirmed ≥1 log increase in HBV DNA from nadir
- Cumulative probability rate calculation[4]
  - P = 1- (1-nx/Nx) (1-nx/Nx)…(1-nx/Nx)
    P = Cumulative Probability
    n = number of patients with events in Year x
    N = number of patients at risk in Year x
    x = Years 1,2,3,4,5,6
    The cumulative probability rate accounts for dropout over time

Results

Nucleoside-Naive

Figure 1. ETV 6-Year Program: Naïve Patient Flow



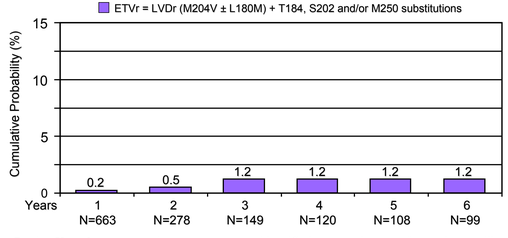
Responders:
HBeAg(+): HBV DNA <0.7 MEq/mL by bDNA and HBeAg loss
HBeAg(-): HBV DNA <0.7 MEq/mL by bDNA and ALT <1.25x ULN

Virologic Responders:
HBeAg(+): HBV DNA <0.7 MEq/mL by bDNA and HBeAg(+)
HBeAg(-): HBV DNA <0.7 MEq/mL by bDNA and ALT≥1.25x ULN HBeAg(-)

Non-Responders: HBV DNA ≥0.7 MEq/mL by bDNA

- Upon leaving phase 3 trials, ETV-022 and ETV-027 , any patient who required further HBV treatment was offered the option to rollover onto 1.0 mg ETV in Study 901.
- The rollover option was provided to all non-responders and virologic responders; responders who relapsed could also qualify although this occurred less often.

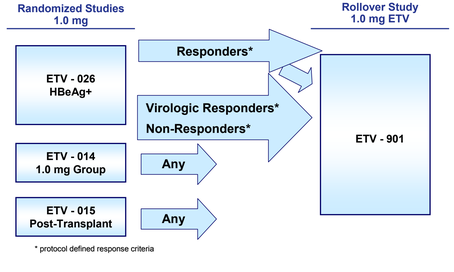
Figure 2. Nucleoside-Naïve Cohort (HBeAg+ & HBeAg-): Cumulative Probability of ETV Resistance Through 6 Years



- During Year 6, no new resistance cases were identified among the 99 naïve patients still on continuous ETV treatment.
- The cumulative probability of genotypic resistance remains stable at 1.2% between years 3 and 6.
- Over 6 years experience, only 3 of 663 patients were identified with ETVr
- 94% of patients at Year 6 (N=99) had HBV DNA <300 c/mL
- Over the cumulative 6 year experience, 89% of those discontinuing treatment early had HBV DNA < 300 c/mL; those with detectable DNA were genotyped and results are included above

Lamivudine-Refractory

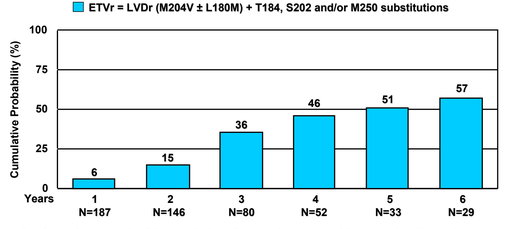
Figure 3. Lamivudine Refractory – Patient Flow



See Figure 1 for definitions of Responders, Virologic Responders, and Non-Responders

- Rollover treatment into Study 901 at the same 1.0 mg dose was available to patients for whom long-term treatment was appropriate, including non-responders.

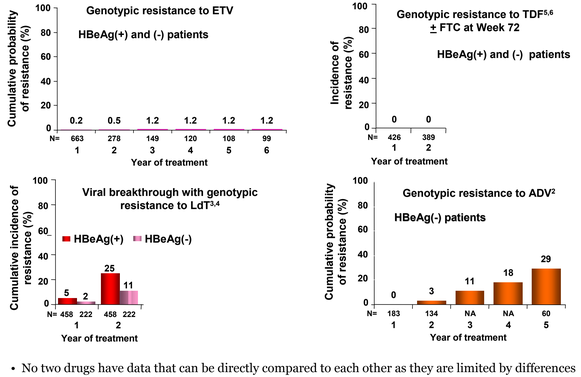
Figure 4. Lamivudine-Refractory Cohort (HBeAg+): Cumulative Probability of ETV Resistance Through 6 Years



- Results through 6 years in this population show an incremental increase in ETV resistance over time, consistent with previous observations.
- The 6 year cumulative probability of genotypic resistance is 57%.
- 74/187 (40%) patients achieved HBV DNA < 300 c/mL while on treatment with ETV; of those 74 patients, only 5 (7%) subsequently developed genotypic ETV resistance.

Discussion

Figure 5. Resistance Rates Across Studies in Nucleoside-Naïve Patients[5-10]



- No two drugs have data that can be directly compared to each other as they are limited by differences in study populations and analysis methodologies.
- The above figure shows that ETV has a favorable resistance profile in naïve patients over a period of multiple years.

Limitations

- For naïve patients, the rollover results in treatment with a higher ETV dose in Study 901.
- The rollover process may have facilitated patient drop-out.
- Study design favored early discontinuation of those who were successfully treated based on patient management endpoints.

Summary of Results

Nucleoside-Naïve:

- Resistance is rare through 6 years
  - 1.2% cumulative probability of genotypic resistance.

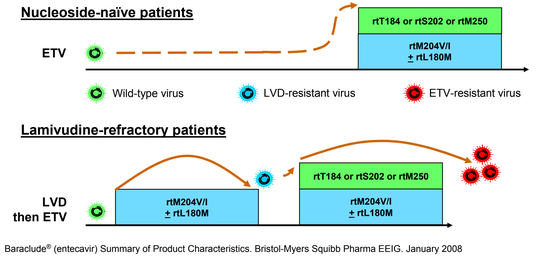
LVD-Refractory:

- The 6 year cumulative probability of genotypic resistance is 57%.
  - 74/187 (40%) patients achieved HBV DNA < 300 c/mL while on treatment with ETV; of those 74 patients, only 5 (7%) subsequently developed genotypic ETV resistance.

Conclusion

- ETV has high potency and high genetic barrier to resistance in nucleoside-naïve patients (**Figure 6**).
- In lamivudine-refractory patients, ETV potency and genetic barrier are reduced and an incremental increase in resistance is demonstrated over time (**Figure 6**).
  - Favorable prognostic subgroups can be identified by early response to treatment.

Figure 6. Genetic Barrier to Entecavir Resistance



Baraclude® (entecavir) Summary of Product Characteristics. Bristol-Myers Squibb Pharma EEIG. January 2008

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Disclosures

- All authors are Bristol-Myers Squibb employees.

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