Poster Number 927

Three Years of Entecavir (ETV) Re-treatment of HBeAg(-) ETV Patients Who Previously Discontinued Treatment: Results from Study ETV-901

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Introduction

- Entecavir (ETV) 0.5 mg daily demonstrated superior virologic, histologic and biochemical activity compared to lamivudine (LVD) 100 mg daily in nucleoside-naïve HBeAg(-) patients (study ETV-027)[1]
- At Week 48, the majority of patients treated in ETV-027 met the protocol-defined criteria of 'Response' and discontinued therapy after Week 52
- During off-treatment follow-up, most of these patients experienced recurrent viremia and increases in alanine aminotransferase (ALT)
- Results from ETV-027 demonstrated that 1 year of treatment with a potent nucleoside analogue is insufficient to achieve sustained suppression of HBV DNA replication
- One-hundred and eleven ETV-treated patients from ETV-027 enrolled in rollover study ETV-901 (1.0 mg ETV daily)
- ETV-901 provides the opportunity to evaluate the effect of long-term ETV re-treatment in patients who previously discontinued therapy

Methods

Study population

- The HBeAg(-) ETV Re-treatment Cohort consists of patients who:
  - were initially treated with ETV in ETV-027
  - subsequently enrolled in ETV-901 with a >60 day treatment gap between ETV-027 and ETV-901

ETV-027 patients enrolling in ETV-901	111
Not treated in ETV-901	2
Treatment gap of ≤60 days between ETV-027 and ETV-901	10
Treatment gap of >60 days (HBeAg(-) ETV Re-treatment Cohort)	**99**

- The HBeAg(-) ETV Re-treatment Cohort is an observational cohort that was defined without regard to:
  - treatment response at end of dosing in ETV-027
  - HBV DNA or ALT measurements at the start of dosing in ETV-901
- Initially, due to ongoing blinding of Phase 2-3 studies, patients enrolling into study ETV-901 received a combination of ETV 1.0 mg and LVD 100 mg daily (the protocol was amended for patients to receive monotherapy with ETV 1.0 mg daily)

Evaluations

- Patients in the HBeAg(-) ETV Re-treatment Cohort were assessed at Weeks 12, 24, 36, 48, 72, 96 and 144 after re-initiation of treatment in ETV-901 (Non-completer = Missing)
- Efficacy assessments evaluated the proportion of patients with available samples for the following parameters:
  - HBV DNA <300 copies/mL by PCR
  - ALT ≤1 x ULN
  - HBsAg loss
- HBV DNA measurements were performed at a central laboratory; ALT measurements were performed at local laboratories
- Direct nucleotide sequencing for resistance testing was conducted on all patients with HBV DNA ≥300 copies/mL at Year 2 or at last observation for patients who discontinued prior to the Year 2 visit
- Resistance testing of samples for the Year 3 analyses is pending
- Safety was assessed by the incidence of clinical adverse events and laboratory abnormalities

Results

Study population

Table 1: Demographics and Disease Characteristics at ETV-901 Baseline

	ETV-901 (n=99)
Age, mean (years)	46
Male (%)	76
Race:	
Asian (%)	28
Non-Asian (%)	72
HBV DNA by PCR, mean (log_{10} copies/mL)	6.6
ALT, mean (U/L)	222
HBV genotype (%)	
A	12
B	15
C	8
D	60
Other/indeterminate/missing	5

- Mean baseline HBV DNA in ETV-901 was 6.64 log_{10} copies/mL vs. 7.6 log_{10} copies/mL at baseline in ETV-027 (all treated patients)
- Mean baseline ALT was 222 U/L in ETV-901 vs. 141 U/L at baseline in ETV-027 (all treated patients)

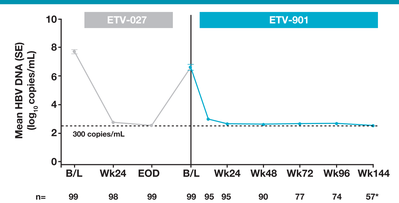
Exposure

- Seventeen patients received ETV monotherapy only for a mean of 154 weeks (median 157 weeks); 11 patients received ETV and LVD combination therapy only for a mean of 36 weeks (median 48 weeks); 71 patients received ETV and LVD combination therapy for a mean of 32 weeks (median 32 weeks) followed by ETV monotherapy for a mean of 134 weeks
- A total of 32 patients discontinued treatment before the Year 3 visit
- The reasons for patient discontinuation included:
  - completed treatment = 19 (59%)
  - patient withdrew = 5 (16%)
  - non-compliance = 2 (6%)
  - other = 6 (19%)
- Among patients who discontinued treatment prior to the Year 3 visit, 24 (75%) had HBV DNA <300 copies/mL on their last PCR measurement

HBV DNA suppression

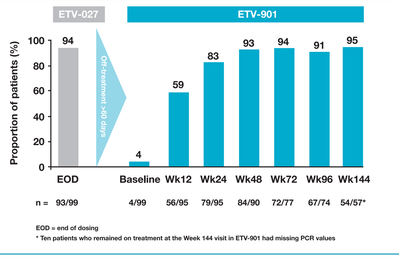
- Ninety-four percent of patients in the HBeAg(-) ETV Re-treatment Cohort had achieved HBV DNA <300 copies/mL by end of dosing in ETV-027
- The majority of patients experienced recurrent viremia during the off-treatment follow-up period

Figure 1: Mean (SE) HBV DNA



B/L = baseline; EOD = end of dosing
* Ten patients who remained on treatment at the Week 144 visit in ETV-901 had missing PCR values

Figure 2: Proportion of Patients with HBV DNA <300 copies/mL



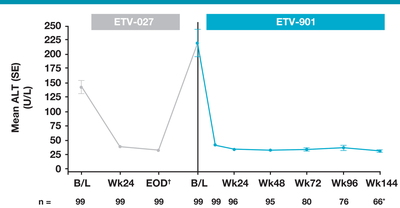
EOD = end of dosing
* Ten patients who remained on treatment at the Week 144 visit in ETV-901 had missing PCR values

- Re-treatment of patients in this cohort resulted in 83% of patients achieving HBV DNA <300 copies/mL by Week 24
- Proportions of patients achieving HBV DNA <300 copies/mL increased to 93% by Week 48 and this was maintained on continued treatment through Year 3

ALT normalization

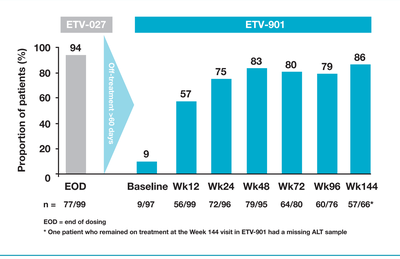
- Seventy-eight percent of patients in the HBeAg(-) ETV Re-treatment Cohort achieved ALT <1 x ULN by end of dosing in ETV-027
- The majority of patients experienced an increase in ALT towards baseline levels (or higher) during the off-treatment follow-up period

Figure 3: Mean (SE) ALT



B/L = baseline; EOD = end of dosing
* One patient who remained on treatment at the Week 144 visit in ETV-901 had a missing ALT sample

Figure 4: Proportion of Patients with ALT ≤1 x ULN



EOD = end of dosing
* One patient who remained on treatment at the Week 144 visit in ETV-901 had a missing ALT sample

- Re-treatment of patients in this cohort resulted in 75% of patients achieving ALT <1 x ULN by Week 24
- Proportions of patients achieving ALT <1 x ULN increased to 83% by Week 48 and this was maintained on continued treatment through Year 3

HBsAg loss

- Among the 99 patients included in this cohort, 1 patient achieved HBsAg loss in ETV-027, no additional patients achieved HBsAg loss with re-treatment in ETV-901

Resistance Analyses

- 7/74 patients analyzed at Year 2 had HBV DNA ≥300 copies/mL
  - Two patients (both with detectable LVD resistance at baseline by nucleotide sequencing) had ETV resistance
    - One of these patients was previously reported[2]
    - The second patient was not detected until Year 2 of ETV-901 and had HBV DNA <300 copies/mL at end of dosing in Phase 3 (Note: This patient did not receive continuous ETV therapy and is not part of the ETV Resistance Cohort)
- 4/23 patients who discontinued from study prior to the Year 2 visit had HBV DNA ≥300 copies/mL
  - All were tested and none had ETVr
- 3/57 patients analyzed at Year 3 and 4/9 patients who discontinued between Years 2 and 3 had HBV DNA ≥300 copies/mL
  - Resistance testing of samples from these seven patients is pending

Safety

Table 2: 3 Year Cumulative Safety: ETV-027 and the HBeAg(-) ETV Re-treatment Cohort

	All ETV-027 n=325 n (%)	HBeAg(-) ETV Re-treatment Cohort n=99 n (%)
Any adverse events*	246 (76)	79 (80)
Serious adverse events	21 (6)	19 (19)
Discontinuation due to adverse events	6 (2)	2 (2)
All deaths	3† (<1)	1 (1)
On-treatment ALT flare ‡	3/324 (<1)	5/99 (5)

* Most common adverse events, occurring in ≥10% of patients: upper respiratory tract infection, arthralgia, nasopharyngitis, headache, ALT increase, upper abdominal pain, back pain, and abdominal pain; † On-treatment and during follow-up, no deaths attributed to study therapy; ‡ On-treatment flare = ALT >2 x baseline and >10 x ULN

Summary of Results

- ETV-027 demonstrated that discontinuation of effective antiviral therapy in HBeAg(-) patients after 1 year of treatment results in rebound of viremia and increases in ALT
- Three years of ETV re-treatment in this cohort resulted in:
  - 95% achieving HBV DNA <300 copies/mL
  - 86% achieving ALT <1 x ULN
- Of the patients who discontinued therapy, the majority (24/32; 75%) had HBV DNA <300 copies/mL
- The safety profile remains consistent with previous reports

Conclusion

- ETV re-treatment of HBeAg(-) CHB patients who discontinued antiviral therapy, resulted in HBV DNA suppression and ALT normalization similar to that achieved prior to treatment discontinuation
- Observations from this cohort demonstrate that long-term treatment with ETV results in durable suppression of HBV DNA replication

Durable suppression with long-term ETV results in regression of fibrosis/cirrhosis **(see Poster 894)**

References

1. Lai CL, Shouval D, Lok AS, et al. N Engl J Med 2006;354:1011-20.
2. Colonno R, Rose R, Baldick CJ, et al. Hepatology 2006;44(6):1656-65.

Study Group

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Disclosures

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