Poster Number 422

# Efficacy and Safety of Entecavir Versus Adefovir in Chronic Hepatitis B Patients with Evidence of Hepatic Decompensation

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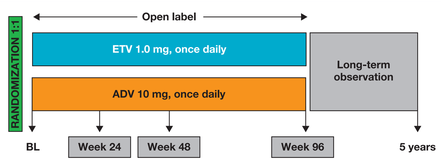
## Introduction

- Decompensated cirrhosis is one of the major sequelae of longstanding hepatitis B virus (HBV) infection. At 5 years, survival of patients with decompensated cirrhosis was 14%, compared to 84% for patients with compensated cirrhosis[1]
- Suppression of viral replication with antiviral therapy has been shown to result in clinical improvement and increased survival[2,3]
- Interferons are contraindicated in this patient population[4,5]
- Data on the safety and efficacy of nucleos(t)ide therapy in patients with chronic hepatitis B (CHB) and decompensated liver disease are limited
- Entecavir (ETV) has demonstrated superior virologic, histologic and biochemical efficacy compared to lamivudine (LVD) in nucleoside-naïve patients with CHB and compensated liver disease at Week 48[6,7]
- Long-term ETV therapy resulted in durable suppression of viral replication and regression of fibrosis/cirrhosis in CHB patients with compensated liver disease[8]
- We present Week 48 results from a randomized, open-label, comparative study of ETV versus adefovir (ADV) in CHB patients with decompensated liver disease

## Methods

**Figure 1: Study design**




- Randomized (1:1), open-label, Phase IIIb study in CHB patients with evidence of hepatic decompensation
- ETV (1.0 mg/day) versus ADV (10 mg/day) treatment until the last randomized patient reaches Week 96
- Key inclusion criteria for study population
  - Male/female aged ≥16 years
  - Child-Turcotte-Pugh (CTP) score ≥7 at screening (no upper limit)
  - HBeAg(+) or HBeAg(-)
  - Nucleos(t)ide naïve or LVD experienced
  - HBV DNA ≥$10^5$ copies/mL
  - Alanine aminotransferase (ALT) ≤15 x upper limit of normal
  - Alfa-fetoprotein <400 ng/mL
  - Absence of confirmed hepatocellular carcinoma (HCC) on imaging
  - Serum creatinine ≤2.5 mg/dL
- Efficacy analyses were performed through Week 48 on treated patients analyzed as randomized, with the exception of time-to-death and time-to-HCC analyses which were performed using as-treated methodology
- Safety analyses were cumulative, performed on treated patients, analyzed as treated
- HBV DNA was assayed by Roche Amplicor® PCR assay (limit of detection <300 copies/mL)
- Mean change in HBV DNA is based on a linear regression model adjusting for baseline HBV DNA and LVD resistance (LVDr) status

### Primary efficacy endpoint

- Mean change from baseline in HBV DNA at Week 24

### Secondary efficacy (Week 24 and 48) endpoints

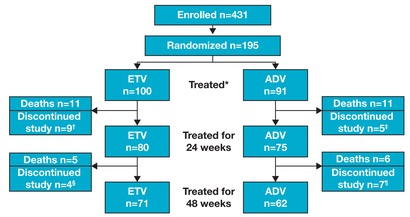
- Proportion of patients with HBV DNA <300 copies/mL
- Proportion of patients with ALT normalization
- Improvement in Model for End-Stage Liver Disease (MELD)/CTP score
- Time-to-death, time-to-HCC (cumulative analysis, treated patients, analyzed as treated)

### Safety (cumulative analysis)

- Adverse events (AE, serious AE, discontinuations due to AE, HCC, ALT flares, death)
- Renal impairment, as defined by confirmed creatinine increase ≥0.5 mg/dL

## Results

**Figure 2: Patient disposition**



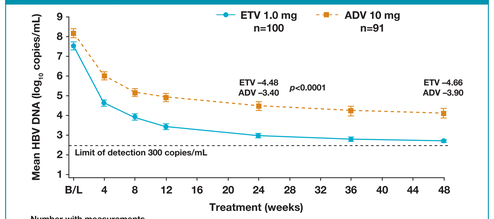

* Two patients were randomized to ADV but were treated with ETV. Efficacy analyses are based on treated patients analyzed as randomized (ETV n=100; ADV n=91). Safety analyses are based on treated patients analyzed as treated (ETV n=102; ADV n=89); † AE, n=2; ‡ AE, n=1; § AE, n=2; ¶ AE, n=2 Other reasons for discontinuations included subject withdrew consent, lack of efficacy, lost to follow-up, patient no longer meets study criteria, and poor/non-compliance

- Of 195 randomized patients, 191 were treated
  - Two patients randomized to ADV were treated with ETV
  - 155 patients completed 24 weeks of treatment (ETV n=80, ADV n=75)
  - 133 patients completed 48 weeks of treatment (ETV n=71, ADV n=62)
  - The database for this analysis includes information on 81 patients who have completed 96 weeks of treatment

**Table 1: Baseline demographics and disease characteristics – treated patients (as randomized)**

| | ETV 1.0 mg (n=100) | ADV 10 mg (n=91) |
|---|---|---|
| Age, mean years (SE) | 51 (1.2) | 53 (1.1) |
| Male, n (%) | 78 (78) | 64 (70) |
| Race, n (%) | | |
| Asian | 55 (55) | 49 (54) |
| White | 35 (35) | 28 (31) |
| Black/African American | 5 (5) | 5 (5) |
| Other | 5 (5) | 9 (10) |
| HBV DNA by PCR, mean $\log_{10}$ copies/mL (SE) | 7.53 (0.18) | 8.16 (0.23) |
| ALT, mean U/L (SE) | 99.2 (11.1) | 100 (8.6) |
| Mean MELD score (SE) | 17.1 (0.50) | 15.3 (0.48) |
| Mean CTP score (SE) | 8.81 (0.20) | 8.35 (0.19) |
| CTP class A, n (%) | 7 (7) | 10 (11) |
| CTP class B, n (%) | 63 (63) | 61 (67) |
| CTP class C, n (%) | 30 (30) | 20 (22) |
| LVD resistant, n (%) | 36 (36) | 30 (33) |
| HBeAg(+), n (%) | 54 (54) | 50 (55) |

**Figure 3: Mean HBV DNA through Week 48 – treated patients (as randomized)**




The difference in HBV DNA responses favoring ETV persisted when analyzed by subgroup (LVDr or HBeAg status), although the magnitude of the differences varied across subgroups

**Table 2: Efficacy analyses**

| | Week 24 | | Week 48 | |
|---|---|---|---|---|
| | ETV | ADV | ETV | ADV |
| HBV DNA <300 copies/mL, n (%) Non-completer = Failure* | 49/100 (49) | 15/91 (16) | 57/100 (57) | 18/91 (20) |
| | $p$<0.0001 | | $p$<0.0001 | |
| HBV DNA <300 copies/mL, n (%) Non-completer = Missing | 49/81 (60) | 15/77 (19) | 57/72 (79) | 18/63 (29) |
| ALT normalization, n (%)† Non-completer = Failure | 46/78 (59) | 28/71 (39) | 49/78 (63) | 33/71 (46) |
| | $p$=0.0193 | | $p$=0.0425 | |
| ALT normalization, n (%)† Non-completer = Missing | 46/63 (73) | 28/62 (45) | 49/58 (84) | 33/53 (62) |
| HBeAg loss, (%)‡ | 0/54 (0) | 7/51 (14) | 6/54 (11) | 9/51 (18) |
| HBeAb seroconversion, n (%)‡ | 0/54 (0) | 6/51 (12) | 3/54 (6) | 5/51 (10) |
| HBsAg loss, n (%) | 1/100 (1) | 0/91 (0) | 5/100 (5) | 0/91 (0) |

* The difference in HBV DNA responses favoring ETV persisted when analyzed by subgroup (LVDr or HBeAg status), although the magnitude of the differences varied across subgroups
† Analysis limited to patients with abnormal ALT at baseline
‡ Analysis limited to HBeAg(+) patients at baseline, Non-completer = Failure

**Table 3: Improvement in MELD/CTP scores**

| | Week 24 | | Week 48 | |
|---|---|---|---|---|
| | ETV | ADV | ETV | ADV |
| Mean MELD score change from baseline (SE) | –2.0 (0.45) | –0.9 (0.46) | –2.6 (0.62) | –1.7 (0.50) |
| CTP score improvement or no worsening, n (%)* | 66/100 (66) | 65/91 (71) | 61/100 (61) | 61/91 (67) |
| CTP score ≥2-point reduction, n (%)* | 32/100 (32) | 22/91 (24) | 35/100 (35) | 25/91 (27) |
| CTP class improvement, n (%)† | 25/93 (27) | 22/81 (27) | 35/93 (38) | 29/81 (36) |

* Non-completer = Failure
† CTP class C/B to class A only

**Figure 4: Overall survival – treated patients**

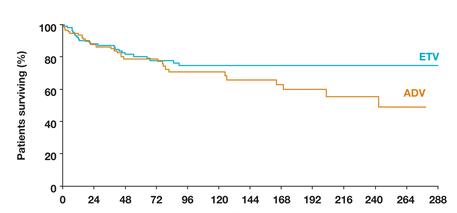
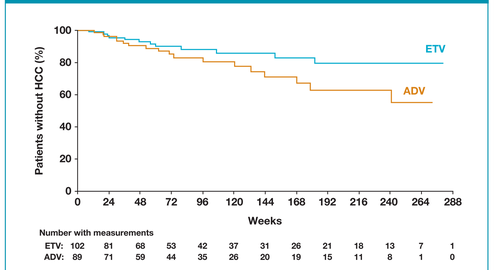



**Figure 5: Time-to-HCC – treated patients**




- In Figures 4 and 5, interpretation of data beyond Week 48 is limited at the time of this analysis. Subsequent data from this ongoing study will provide more robust estimates

**Table 4: Safety – cumulative analysis**

| | ETV (n=102) | ADV (n=89) |
|---|---|---|
| Mean time on therapy, weeks (SE) | 108.8 (9.0) | 96.6 (8.4) |
| Any AE, n (%) | 91 (89) | 86 (97) |
| Grade 3–4 AEs, n (%) | 55 (54) | 42 (47) |
| Serious AEs, n (%) | 70 (69) | 59 (66) |
| Death, n (%) | 23 (23) | 29 (33) |
| Serum creatinine ≥0.5 mg/dL increase from baseline, n (%) | 17 (17) | 21 (24) |
| ALT flare, n (%)* | 2 (2) | 1 (1) |
| HCC, n (%)† | 12 (12) | 18 (20) |
| Discontinuations due to AEs, n (%) | 7 (7) | 5 (6) |

Death and HCC include events which occurred on and off treatment, all other parameters measure on-treatment events only
* One additional event occurred off treatment in the ADV group
† Other remaining malignancies (both in ETV group) were: recurrent non-Hodgkin lymphoma (n=1), basal cell carcinoma (n=1)

### Safety in patients with high MELD scores

- A case series using ETV in decompensated cirrhotic patients has documented a risk for lactic acidosis in patients with high MELD scores (≥22)[9]
- In the study protocol, a total of 22 patients had a baseline MELD score ≥22 (15 ETV and 7 ADV)
- The study design did not include prospective measurements of serum lactate levels
- Clinical safety observation within these patients with high MELD score ≥22 were as follows
  - Deaths: 7/15 ETV; 5/7 ADV
  - One AE of "lactic acidosis" in an ETV-treated patient required no treatment and resolved on continued ETV treatment, it occurred on study day 1293 with bicarbonate 16 mmol/L and creatinine 1.4 mg/dL (no lactate level reported). Lactate levels reported on Days 1340 and 1417 were 2.5 and 2.8 mmol/L, respectively
- Among all treated patients (ETV 102; ADV 89), the following AEs related to lactate or low bicarbonate were identified: 1 event of lactic acidosis described above and 5 events of low bicarbonate (3 ETV and 2 ADV)

## Summary of Results

- ETV 1.0 mg was superior to ADV 10 mg for the primary efficacy endpoint of HBV DNA change from baseline at Week 24
- A greater proportion of ETV- versus ADV-treated patients achieved HBV DNA <300 copies/mL at Weeks 24 and 48
- ETV provided clinical benefit in this setting, as shown by change in CTP and MELD scores, and normalization of measures of hepatic function through Week 48
- Short-term death rates observed in both groups are consistent with on-treatment results previously reported for this population (16%)[2,3]
- Cumulative death and HCC event rates were 23% and 12% in ETV group and 33% and 20% in the ADV group, respectively. Clinical outcome events, such as death and HCC, may require more patients followed for a longer period of time to demonstrate any potential differences between the two treatment groups

## Conclusions

- Both therapies were well tolerated, and the safety experience in each group was comparable and consistent with what would be expected in a CHB population with decompensated liver disease
- Entecavir demonstrated superior antiviral activity to adefovir in this patient population
- Entecavir provided clinical benefit in patients with CHB infection and decompensated cirrhosis

### References

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### Disclosures

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