Efficacy and Safety of Entecavir Versus Adefovir in Chronic Hepatitis B Patients With Hepatic Decompensation: A Randomized, Open-Label Study

Yun-Fan Liaw,[1] Maria Raptopoulou-Gigi,[2] Hugo Cheinquer,[3] Shiv Kumar Sarin,[4] Tawesak Tanwandee,[5] Nancy Leung,[6] Cheng-Yuan Peng,[7] Robert P. Myers,[8] Robert S. Brown Jr,[9] Lennox Jeffers,[10] Naoky Tsai,[11] Jolanta Bialkowska,[12] Shijie Tang,[13] Suzanne Beebe,[13] and Elizabeth Cooney[13]

A randomized, open-label comparative study of entecavir versus adefovir therapy was performed in subjects with chronic hepatitis B who had hepatic decompensation (Child-Turcotte-Pugh score ≥7). Adult subjects were randomized and treated (n = 191) with entecavir 1.0 mg or adefovir 10 mg daily for up to 96 weeks from the date of last subject randomization. Subjects were positive or negative for hepatitis B e antigen and experienced or naive for treatment with nucleos(t)ide analogues. The primary efficacy endpoint was the mean reduction in serum hepatitis B virus (HBV) DNA, as determined by polymerase chain reaction, at week 24, adjusted for baseline HBV DNA and lamivudine resistance status by linear regression analysis. Entecavir demonstrated superiority to adefovir for this endpoint (treatment difference 1.74 $\log_{10}$ copies/mL [95% confidence interval −2.30, −1.18]; $P < 0.0001$). The entecavir group showed a greater change from baseline in HBV DNA at all time points through week 48 and a higher proportion of subjects who achieved HBV DNA < 300 copies/mL at weeks 24 (entecavir 49%; adefovir 16%; $P < 0.0001$) and 48 (entecavir 57%; adefovir 20%; $P < 0.0001$). Approximately two-thirds of subjects in both groups showed improvement/stabilization in Child-Turcotte-Pugh status. Model for End-Stage Liver Disease score change at week 48 was −2.6 for entecavir and −1.7 for adefovir. Adverse event rates were comparable between groups. Cumulative hepatocellular carcinoma rates were 12% for entecavir and 20% for adefovir. Cumulative death rates were 23% for entecavir and 33% for adefovir. Week 24 mortality rates were 12% for both groups. *Conclusion:* Entecavir demonstrated superior virologic efficacy to adefovir in a population of patients with chronic hepatitis B who had hepatic decompensation. Biochemical and clinical benefits were also demonstrated. Entecavir was well tolerated, and early mortality rates were consistent with rates observed in similar populations treated with lamivudine. (HEPATOLOGY 2011;54:91-100)

Hepatic decompensation is a serious clinical complication associated with high mortality. The reported 5-year survival rate for patients with chronic hepatitis B (CHB) with decompensated cirrhosis is considerably lower than rates reported in patients with compensated cirrhosis (14%-35% versus 80%-86%, respectively).[1]

Studies have shown that interferon-α is contraindicated in this patient population.[2,3] The majority of data on nucleos(t)ide analogue therapy in decompensated

Abbreviations: ADV, adefovir; AE, adverse event; ALT, alanine aminotransferase; CHB, chronic hepatitis B; CTP, Child-Turcotte-Pugh; ETV, entecavir; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; LVD, lamivudine; LVDr, lamivudine-resistant; MELD, Model for End-Stage Liver Disease; PCR, polymerase chain reaction; SAE, serious adverse event.

From the [1]Liver Research Unit, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taipei, Taiwan; [2]Second Department of Internal Medicine, Aristotle University of Thessaloniki, Thessaloniki, Greece; [3]Universidade Federal Do Rio Grande Do Sul, Porto Alegre, Brazil; [4]Department of Gastroenterology, G. B. Pant Hospital, New Delhi, India; [5]Department of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand; [6]Alice Ho Miu Ling Nethersole Hospital, Hong Kong, China; [7]China Medical University Hospital, Taichung, Taiwan; [8]Liver Unit, University of Calgary, Calgary, Alberta, Canada; [9]Center for Liver Disease and Transplantation, Columbia University Medical Center, New York, NY; [10]Miami Veterans Affairs Medical Center, Miami, FL; [11]John A. Burns School of Medicine, University of Hawaii, Honolulu, HI; [12]Department of Infectious Diseases, Medical University, Lodz, Poland; and [13]Research and Development, Bristol-Myers Squibb Co., Wallingford, CT.

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Address reprint requests to: Yun-Fan Liaw, M.D., Liver Research Unit, Chang Gung University and Memorial Hospital, 199, Tung Hwa North Road, Taipei 105, Taiwan. E-mail: liveryfl@gmail.com; fax: 886-3-3282824.

patients are from noncomparative or uncontrolled lamivudine (LVD) and adefovir (ADV) studies, which demonstrated high virologic and biochemical response rates, and many patients demonstrated improvement in Child-Turcotte-Pugh (CTP) and/or Model for End-Stage Liver Disease (MELD) scores.[4-7] On the basis of these, international HBV treatment guidelines recommend initiating nucleos(t)ide analogues as early as possible in this patient population.[1,2,8] However, LVD is limited by high resistance rates, as demonstrated in other populations,[9,10] and ADV is limited by suboptimal potency and the potential for renal toxicity.[11-13] The risk of renal impairment with ADV is especially significant in decompensated patients, because they are already at higher risk of renal dysfunction from the disease itself and/or concomitant medications for treating complications of decompensation.[14,15] Therefore, potent HBV agents with a rapid onset of action, high genetic barrier to resistance, and improved safety profile are warranted for this population.[1]

Entecavir (ETV) is a potent HBV antiviral with superior virologic and biochemical benefits after 48 weeks of therapy as compared to LVD or ADV in nucleoside-naive patients with CHB, including those patients with advanced fibrosis or cirrhosis.[16-19] Long-term virologic suppression continued through 6 years of ETV treatment in nucleoside-naive patients, with minimal emergence of resistance,[20,21] and was associated with improvement in liver necroinflammation and reversal of fibrosis/cirrhosis.[21] In LVD-refractory patients, ETV was superior to continued LVD treatment across histologic, virologic, and biochemical endpoints through 48 weeks.[22]

We conducted a prospective, randomized, open-label trial to assess the safety and efficacy of ETV as compared to ADV in patients with CHB who had hepatic decompensation. Multiple safety and efficacy measures were employed, including assessment of hepatocellular carcinoma (HCC) and death rates. We report on the first 48 weeks of efficacy and cumulative safety.

Patients and Methods

Study Design. This is a multicenter, comparative open-label study. Subjects were randomly assigned 1:1 to receive ETV 1.0 mg/day or ADV 10 mg/day. The 1.0 mg ETV dose was selected because of the inclusion of both LVD-experienced and nucleos(t)ide-naive subjects. Study regimens were continued for up to 96 weeks from the date the last randomized subject received their first dose of study drug. At the end of the treatment phase, subjects were managed at the discretion of the treating investigator, by either being continued on the same treatment or receiving an alternative HBV regimen. Randomization was not blocked or stratified; treatment comparisons for some efficacy endpoints were performed on patients stratified by baseline serostatus or lamivudine-resistant (LVDr) status.

Subjects. Study participants were subjects with CHB who had hepatic decompensation (CTP score $\geq$7, no upper limit), aged $\geq$16 years, without coinfection with hepatitis C virus, hepatitis D virus, human immunodeficiency virus, or other known liver disease. Subjects were recruited from 52 sites worldwide from 2003 onward. Subjects were required to have detectable hepatitis B surface antigen (HBsAg) for $\geq$6 months, were either hepatitis B e antigen (HBeAg)-positive or HBeAg-negative, and were HBV nucleos(-t)ide-naive or LVD experienced; subjects previously treated with ETV, ADV, or tenofovir were excluded. Subjects who were receiving LVD at the time of screening were required to stop LVD at the time of randomization. Other entry criteria included HBV DNA $\geq 10^5$ copies/mL, alanine aminotransferase (ALT) level $\leq$15$\times$ upper limit of normal, serum creatinine $\leq$2.5 mg/dL, α-fetoprotein $<$400 ng/mL, and no liver mass consistent with HCC on imaging performed within 4 weeks prior to randomization.

The study was conducted in accordance with good clinical practice and all applicable regulations, including the Declaration of Helsinki and local regulatory

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Potential conflict of interest: This study was sponsored by Bristol-Myers Squibb Pharmaceutical Research Institute. Professor Liaw received grant/research support from Bristol-Myers Squibb, Novartis, Roche, and Gilead Sciences and serves as a consultant to Bristol-Myers Squibb, Novartis, and Roche. Professor Cheinquer received research grants from Bristol-Myers Squibb and Roche and serves on advisory boards of Bristol-Myers Squibb and Roche. Dr. Tsai serves on the speakers bureaus of Bristol-Myers Squibb, Gilead Sciences, and Roche/Genentech; serves as a consultant to Bristol-Myers Squibb and Gilead Sciences; has received honoraria from Bristol-Myers Squibb, Gilead Sciences, and Roche/Genentech; and has received research grants from Bristol-Myers Squibb, Gilead Sciences, Roche/Genetech, and Novartis. Dr. Peng serves on the advisory boards of Bristol-Myers Squibb, Novartis, and Roche. S. Tang, S. Beebe, and E. Cooney are employees of Bristol-Myers Squibb. The following individuals have nothing to disclose: Professor Raptopoulou-Gigi, Dr. Sarin, Dr. Tanwandee, Professor Leung, Dr. Myers, Dr. Brown, and Dr. Jeffers.

requirements, and was approved by the ethics committee. Written informed consent was obtained from each subject before enrollment.

Study Assessments and Follow-Up. Baseline and on-study laboratory assessments included routine hematologic analysis, hepatobiliary enzymes, hepatic synthetic function, HBV DNA, and serologic analysis. HBV genotype and baseline LVDr substitutions (INNO-LiPA assay) were also assayed. A blood sample was collected for future assessment of baseline ADV or ETV resistance in the event that a subject qualified for on-study resistance testing, which was performed in subjects who failed to achieve a ≥ 1 $\log_{10}$ decline from baseline in HBV DNA at week 24 or those who had experienced virologic breakthrough on-treatment (a confirmed rise from nadir in HBV DNA of ≥ 1 $\log_{10}$ copies/mL) at any time prior to database lock. Resistance mutations related to ETV[23] or ADV[24] were measured by genotypic analysis (TRUGENE HBV Direct Gene Sequencing). The INNO-LiPA assay was the only assay available at study initiation and therefore was used to assess baseline resistance. The TRUGENE assay was subsequently used for on-treatment resistance analyses.

CTP score was calculated using standard clinical and laboratory measures.[25] MELD score was calculated as described in the literature.[26] HCC surveillance with serum α-fetoprotein and liver imaging was performed every 24 weeks.

Serum bicarbonate levels were monitored every 4 weeks through week 96. Prospective monitoring of serum lactate was not mandated by protocol. However, investigators were provided with guidelines for managing treatment-emergent toxicities using modified World Health Organization toxicity grading criteria and hyperlactemia management guidelines, based on previously published algorithms.[27] Subjects were managed at the discretion of the treating physician.

Serum creatinine, urea, and phosphorus were measured every 4 weeks. On-treatment dose reductions for ETV and ADV were made according to published algorithms, employing calculated creatinine clearance.[23,24]

Efficacy Endpoints. The primary efficacy endpoint was mean reduction in serum HBV DNA ($\log_{10}$ copies/mL) at week 24 (COBAS Amplicor polymerase chain reaction [PCR] assay version 2.0; lower limit of quantification = 300 copies/mL (57 IU/mL); Roche, Pleasanton, CA). Key secondary endpoints included mean change from baseline in serum HBV DNA at week 48 and the following endpoints at weeks 24 and 48: proportion of subjects with HBV DNA $<$ 300 copies/mL; serum ALT normalization in subjects with abnormal baseline ALT; improvement in total bilirubin, prothrombin time, albumin, and platelets; improvement in MELD scores as measured by mean change from baseline; and improvement in CTP status.

Safety Endpoints. Safety analyses included cumulative rates of on-treatment adverse events (AEs), serious adverse events (SAEs), discontinuations due to AEs, death, HCC, renal impairment (a confirmed increase in serum creatinine ≥ 0.5 mg/dL from baseline) and hepatic flare (ALT $>2\times$ baseline and $>10\times$ upper limit of normal). Rates of deaths and malignancies included events identified on-treatment or during post-dosing follow-up.

Statistical Analyses. All efficacy analyses were based on treated subjects and randomized treatment assignment (as randomized). Safety analyses were based on treated subjects and treatment received (as treated). The primary endpoint was based on a linear regression model with covariates of baseline HBV DNA and LVDr status. In addition, virologic analyses by baseline HBeAg or LVD status were performed. For the proportion of subjects achieving ALT normalization or HBV DNA $<$ 300 copies/mL, missing data were handled using both "noncompleter = failure" and "noncompleter = missing" methods. Comparisons of MELD scores at weeks 24 and 48 were based on a covariate-adjusted model; factors included in the model were treatment, baseline age, sex, MELD score, and HBeAg and LVDr status. Improvement in CTP status was assessed by improvement or no worsening in CTP score (reduction ≥ 1 point or no change from baseline), ≥ 2-point reduction from baseline in CTP score, and improvement in CTP class (change from class C to B or B to A). Kaplan-Meier curves were used to describe the time to HCC and HCC-free survival. HCC-free survival rate was compared across the two groups based on a Cox-proportional hazard model adjusted for age, sex, and race.

Results

Subject Disposition. Of the 431 subjects enrolled in the study, 195 were randomized (ETV, n = 101; ADV, n = 94) and 191 were treated with ETV (n = 100) or ADV (n = 91). Two subjects were randomized to ADV but were treated with ETV; these were considered "as randomized" for efficacy analyses (ETV, n = 100; ADV, n = 91) and "as treated" for safety analyses (ETV, n = 102; ADV, n = 89).

The disposition of subjects through 48 weeks is shown in Fig. 1. The baseline demographics and

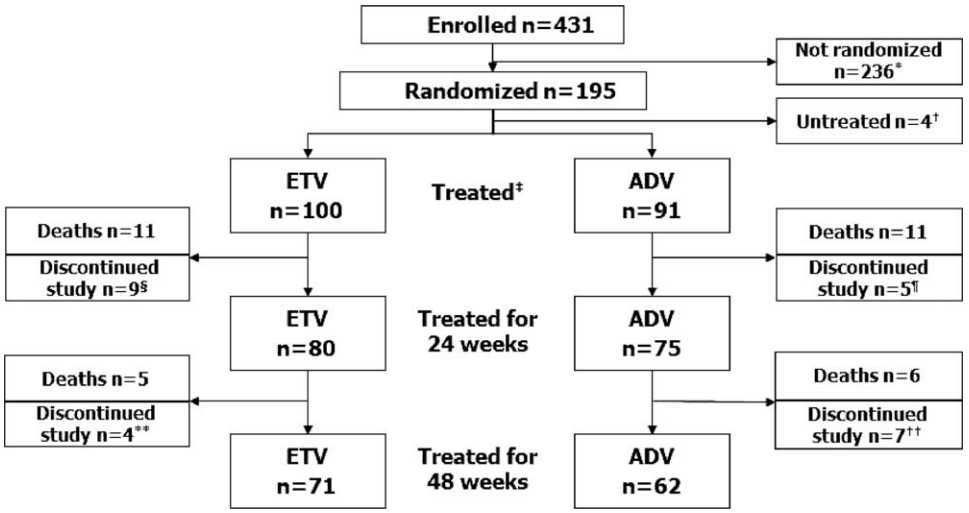

Fig. 1. Flow chart of subject disposition. *No longer met study criteria (the most common reason for no longer meeting study criteria was a change in disease status (either an improved CTP score [<7] or worsening hepatic status due to acute change), n = 213; consent withdrawn, n = 6; death, n = 3; AE, n = 1; lost to follow-up, n = 1; administrative reason, n = 1; other, n = 11. †No longer met study criteria, n = 2; subject withdrew consent, n = 1; subject elected alternative therapy, n = 1. ‡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 or no compliance.

disease characteristics of the two treatment groups were well balanced. Of the study subjects, 74% were male, 35% evidenced LVDr, and 54% were HBeAg-positive. The mean baseline MELD score was higher in the ETV than in the ADV group (Table 1). Five ETV and four ADV subjects initiated study therapy at a reduced dose (ETV) or frequency (ADV) due to renal insufficiency, as defined by creatinine clearance, at baseline.

Virological Response. For the primary efficacy endpoint at week 24, ETV demonstrated superiority to ADV (treatment difference −1.74 $\log_{10}$ copies/mL [95% confidence interval −2.30, −1.18]; $P < 0.0001$). ETV-treated subjects also demonstrated a greater change from baseline in HBV DNA at all on-treatment time points assessed through week 48 (Fig. 2). A sensitivity analysis, which was based on a linear regression model and accounted for other potentially confounding variables related to the subject (age, sex), virus (HBeAg status, genotype), or disease status (CTP score), supported the findings of the primary efficacy analysis, with a greater treatment effect seen in the ETV group. The proportion of subjects achieving HBV DNA < 300 copies/mL was also greater with ETV than ADV at weeks 24 (ETV, 49%; ADV, 16%; $P < 0.0001$) and 48 (ETV 57%; ADV 20%; $P < 0.0001$) (Table 2). Although the results differed across the four subgroups for each analysis performed (Table 3), the overall findings were similar, showing a greater proportion of ETV-

Table 1. Baseline Demographics and Disease Characteristics of Study Population

Parameter	ETV 1.0 mg (n = 100)	ADV 10 mg (n = 91)	Total (n = 191)
Age, years (SE)	51 (1.2)	53 (1.1)	52 (0.8)
Male, n (%)	78 (78)	64 (70)	142 (74)
Race, n (%)			
Asian	55 (55)	49 (54)	104 (54)
White	35 (35)	28 (31)	63 (33)
Black/African	5 (5)	5 (5)	10 (5)
Other	5 (5)	9 (10)	14 (7)
HBV DNA by PCR, $\log_{10}$ copies/mL (SE)	7.53 (0.18)	8.16 (0.23)	7.83 (0.15)
ALT, U/L (SE)	99.2 (11.1)	100 (8.6)	99.6 (7.09)
Total bilirubin, mg/dL (SE)	2.8 (0.21)	2.5 (0.21)	2.7 (0.15)
Albumin, g/dL (SE)	3.0 (0.06)	3.1 (0.07)	3.0 (0.04)
Platelets, $\times 10^9$ (SE)	87.3 (4.77)	93.3 (4.95)	90.2 (3.43)
Prothrombin time, seconds (SE)	16.3 (0.23)	15.3 (0.20)	15.8 (0.16)
Creatinine, mg/dL (SE)	0.9 (0.03)	0.9 (0.03)	0.9 (0.02)
MELD score (SE)	17.1 (0.50)	15.3 (0.48)	16.23 (0.35)
CTP score (SE)	8.81 (0.20)	8.35 (0.19)	8.59 (0.14)
CTP class, n (%)			
A	7 (7)*	10 (11)*	17 (9)
B	63 (63)	61 (67)	124 (65)
C	30 (30)	20 (22)	50 (26)
Prior LVD treatment, n (%)	39 (39)	34 (37)	73 (38)
Prior LVD duration, weeks			
Mean (SD)	126 (98.2)	122 (81.8)	124 (90.4)
Median (range)	115 (0.1-459)	121 (0.4-321)	121 (0.1-459)
LVD-resistant, n (%)	36 (36)	30 (33)	66 (35)
HBeAg-positive, n (%)	54 (54)	50 (55)	104 (54)

All data are mean unless otherwise stated. SE, standard error.
*CTP score at time of eligibility determination was ≥7.

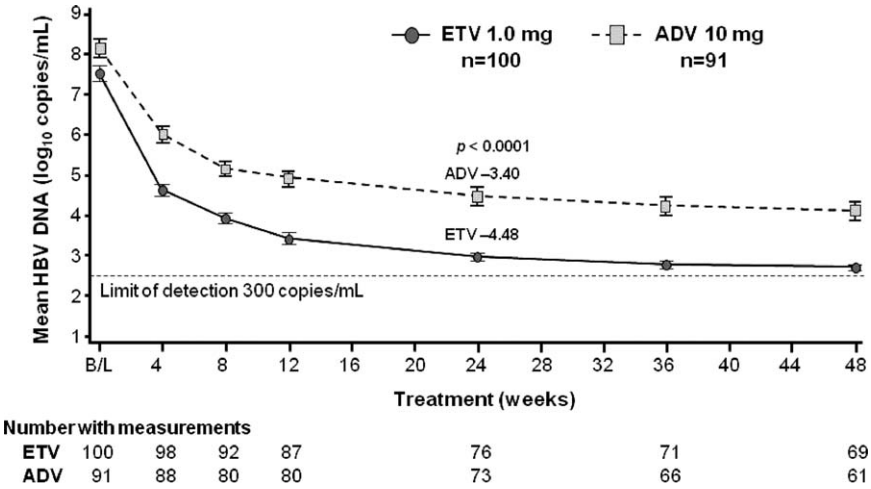

Fig. 2. Mean HBV DNA change from baseline by PCR through week 48 (as randomized). The differences in HBV DNA responses favoring ETV persisted when analyzed by subgroup (LVDr or HBeAg status), although the magnitude of the differences varied across subgroup. B/L, baseline.

treated versus ADV-treated subjects achieving HBV DNA < 300 copies/mL at weeks 24 and 48.

Resistance. At the time of the week 48 analysis, 37 subjects (ETV = 5; ADV = 32) met criteria for resistance testing; no patients showed resistance in either group. Beyond week 48, 37 subjects (ETV = 5; ADV = 32) met criteria for resistance testing. Three of the five ETV subjects had ETV resistance detected at week 144 and beyond; all three were LVDr at baseline. Five of the 32 ADV subjects were not tested due to logistical or technical issues. Of the remaining 27 subjects, six showed ADV resistance (two each between weeks 48 and 96, weeks 96 and 144, and at week 144 and beyond). Four subjects were LVD susceptible and two were LVDr at baseline.

Biochemical Response. The proportion of subjects with serum ALT normalization was significantly greater in the ETV group compared with the ADV group at weeks 24 and 48 (Table 2).

Serologic Response. HBeAg loss and seroconversion rates were higher with ADV at week 24, but became comparable by week 48. Five ETV-treated subjects (one HBeAg-positive and four HBeAg-negative at baseline) versus no ADV-treated subjects evidenced HBsAg loss by week 48 (Table 2).

Changes in MELD and CTP Scores. Both treatment groups demonstrated an improvement in MELD and CTP scores at week 48. The mean change from baseline in MELD score at week 48 was −2.6 for the ETV group and −1.7 for the ADV group (Table 4). A covariate-adjusted model showed that this difference was partly explained by the difference in baseline MELD score, which was higher in ETV versus ADV subjects. Approximately two-thirds of subjects in each group showed either an improvement or stabilization in CTP score, and approximately one-third of each group showed a reduction by ≥2 points in CTP score and/or an improvement in CTP class (Table 4).

Among those with baseline hepatic encephalopathy, clinical improvement was observed in 17/22 (77.3%) ETV-treated and 10/23 (43.5%) ADV-treated patients. Similarly, in patients with baseline ascites, reversal was seen in 26/63 (41.3%) ETV-treated and 23/61 (37.7%) ADV-treated patients. The study was not powered to compare CTP scores and its components.

Changes in Hepatic Synthetic Function. Through week 48, both groups showed an improvement in hepatic function, as assessed by change from baseline in total bilirubin, prothrombin time, albumin, and platelets; the degrees of improvement were comparable across the two groups (total bilirubin [mg/dL]: ETV

Table 2. Virological, Biochemical, and Serological Response Rates Through Week 48

	Week 24		Week 48	
	ETV	ADV	ETV	ADV
HBV DNA <300 copies/mL, n (%) NC=F	49/100 (49)	15/91 (16)	57/100 (57)	18/91 (20)
	$P < 0.0001$		$P < 0.0001$	
ALT normalization, n (%)* NC=F	46/78 (59)	28/71 (39)	49/78 (63)	33/71 (46)
	$P = 0.0193$		$P = 0.0425$	
ALT normalization, n (%)* NC=M	46/63 (73)	28/62 (45)	49/58 (84)	33/53 (62)
	$P = 0.0010$		$P = 0.0066$	
HBeAg loss (%)† NC=F	0/54 (0)	7/51 (14)	6/54 (11)	9/51 (18)
HBeAg seroconversion, n (%)† NC=F	0/54 (0)	6/51 (12)	3/54 (6)	5/51 (10)
HBsAg loss, n (%) NC=F	1/100 (1)	0/91 (0)	5/100 (5)	0/91 (0)

All data are n (%) unless otherwise stated.
*Analysis limited to patients with abnormal ALT at baseline.
†Analysis limited to HBeAg-positive patients at baseline.
NC=F (noncompleter = failure); NC=M (noncompleter = missing).

Table 3. Mean Change in HBV DNA from Baseline by PCR and HBV DNA <300 Copies/mL (Noncompleter = Failure) at Week 48 According to Subgroup

	Mean Change in HBV DNA (SE)		HBV DNA <300 Copies/mL (%)	
Subgroup	ETV	ADV	ETV	ADV
LVD-resistant	N = 27	N = 23	18/36 (50)	5/30 (17)
	-4.73 (0.350)	-3.91 (0.473)	$P = 0.0047$	
LVD-susceptible	N = 42	N = 37	39/63 (62)	13/59 (22)
	-4.62 (0.251)	-4.01 (0.493)	$P < 0.0001$	
HBeAg-negative	N = 35	N = 30	32/46 (70)	9/40 (23)
	-4.27 (0.241)	-3.58 (0.467)	$P < 0.0001$	
HBeAg-positive	N = 34	N = 31	25/54 (46)	9/51 (18)
	-5.07 (0.319)	-4.21 (0.528)	$P = 0.0016$	

−0.9, ADV −0.6; prothrombin time [seconds]: ETV −0.9, ADV −0.6; platelets [10^9 copies/L]: ETV +2, ADV +1; albumin [g/dL]: ETV +0.6, ADV +0.5) (Fig. 3).

Safety Results. Cumulative safety results are shown in Table 5. The mean time on therapy at database lock was 108.8 weeks and 96.6 weeks for ETV- and ADV-treated subjects, respectively. The frequency of AEs, SAEs, and grade 3 or 4 AEs was comparable between treatment groups. For SAEs and grade 3 or 4 AEs, the majority of events were expected in this study population; the most frequently reported events were hepatic failure or a manifestation or secondary complication of decompensated cirrhosis. The rates of serum creatinine increase ≥0.5 mg/dL were also comparable across the two groups (ETV = 17%; ADV = 24%). Ten (11%) ETV-treated subjects and one (1%) ADV-treated subject had dose reduction for a change in renal function at one or more time points while on treatment. Nine of these 11 patients had viral load data after their dose reduction; none had confirmed viral rebound through week 48. Seven (7%) ETV-treated subjects and five (6%) ADV-treated subjects discontinued study therapy due to AEs (Table 5).

On-treatment ALT flare was not observed within the first 48 weeks of study, but developed in three subjects (ETV = 2; ADV = 1) after week 48 (Table 5). ALT flares in both ETV subjects were well tolerated. One ETV subject had developed ETV resistance and was switched to tenofovir. The ADV subject experienced virologic rebound and worsening hepatic decompensation; this subject met criteria for resistance testing but was not tested due to lack of a sample at the time of event. The subject was discontinued from study therapy and study, and at the last available time point, this subject was alive and had not undergone liver transplantation.

The cumulative rates of HCC were 12% (12/102) for ETV and 20% (18/89) for ADV. Eight of the 12 (67%) ETV subjects and 4/18 (22%) ADV subjects had HBV DNA < 300 copies/mL at the time of reported HCC diagnosis. If subjects with HCC detected within 6 months were excluded (ETV = 4; ADV = 3), the rates of HCC were 8% for ETV and 17% for ADV. The mean time to HCC did not differ across the two treatment groups (Fig. 4A).

At the time of this analysis, 57 deaths were reported; 52 of these occurred in treated subjects (ETV = 23%; ADV = 33%); the remaining five deaths occurred prior to randomization. Six deaths occurred in the first 30 days of treatment (ETV = 2; ADV = 4). The week 24 mortality rates were 12% for both ETV and ADV. The majority of deaths were due to a hepatic-related event. A total of 22 subjects had a baseline MELD score ≥ 22 (ETV = 15; ADV = 7); 7/15 ETV-treated subjects and 5/7 ADV-treated subjects died. Eight of these 12 deaths occurred within the first 6 months of initiating study therapy. HCC-free survival did not significantly differ between the two groups (Fig. 4B).

Grade 2 lactic acidosis was reported in one ETV-treated subject on day 1293; it required no treatment and resolved on continued ETV treatment. The reported lactate level was 2.5 mmol/L (normal range, 0.43-2.04 mmol/L) and the serum bicarbonate level was 16 mEq/L (normal range, 21-33 mEq/L). No arterial pH data were provided. The baseline MELD score was 21. The subject had no underlying medical

Table 4. MELD and CTP Score Change Through Week 48

	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)

*Noncompleter = failure.
†CTP class C or B to class A only.
SE, standard error.

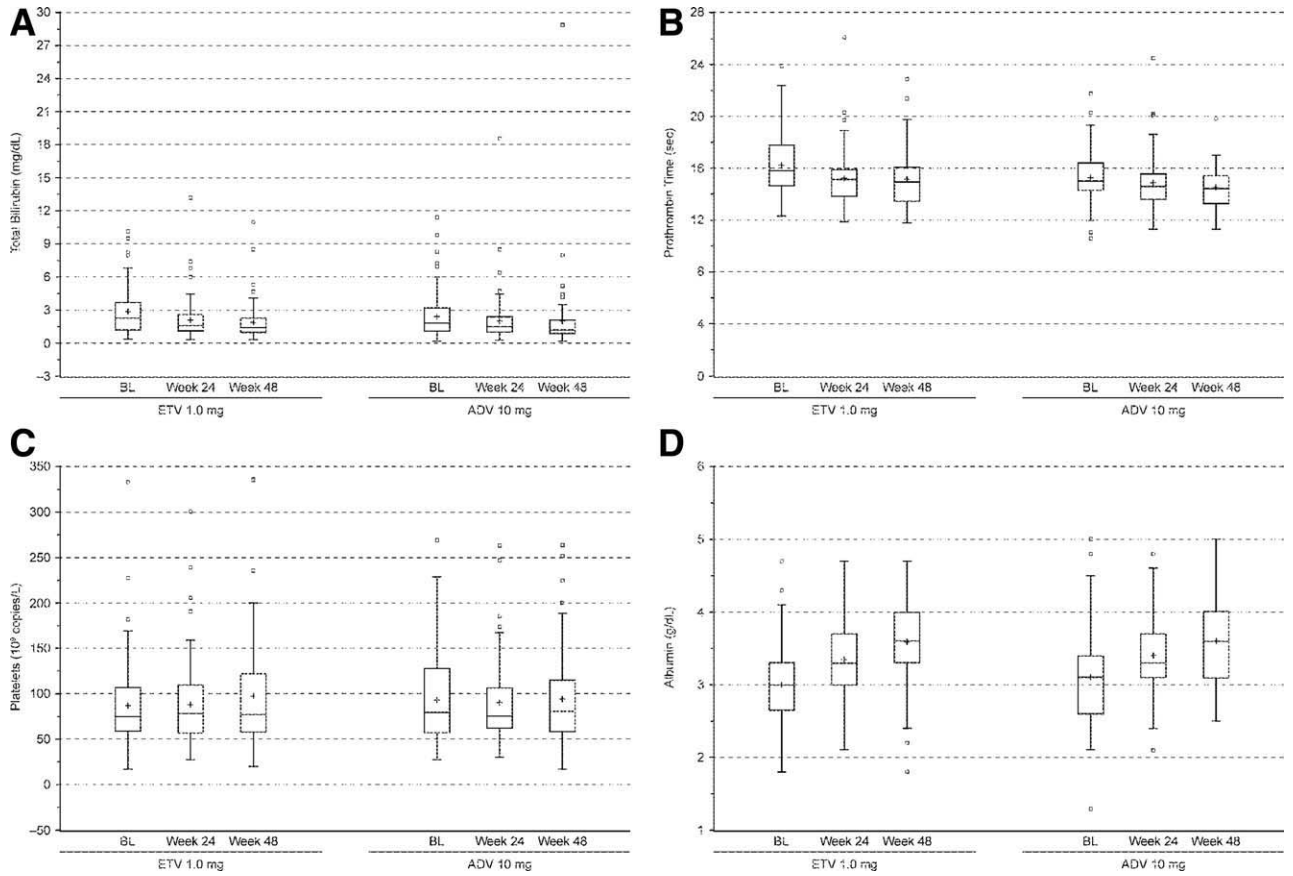

Fig. 3. Change in measures of hepatic synthetic function from baseline through week 48: (A) total bilirubin, (B) prothrombin time, (C) platelets, and (D) albumin.

conditions or AEs of hepatic decompensation that would predispose to lactic acidosis. Three of 100 (3%) ETV subjects and 4/86 (5%) ADV subjects experienced grade 3 to 4 hypocarbia. Four of these subjects died due to infection (ETV = 1; ADV = 1), liver failure (ADV = 1), or sudden death (ETV = 1). Four AEs of grade 1 to 2 decrease in serum bicarbonate were reported (ETV = 2; ADV = 2); no subject had temporally related AEs with an associated risk of metabolic acidosis. The two events in the ETV subjects resolved during continued ETV therapy. The two ADV subjects were discontinued from the study due to poor efficacy; in both cases, the events of hypocarbia were reported as unresolved and ongoing at the time of study discontinuation.

Discussion

The present study differs from other recently reported clinical trials conducted in this population[28-30] in that the study enrolled patients with more severe liver disease (baseline CTP and MELD scores of 8.59 and 16.23, respectively). Baseline severity of liver disease is an important factor that could influence subsequent on-study safety findings, in particular, early mortality and AE rates.

Table 5. Cumulative Safety Data

	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 AE, n (%)	55 (54)	42 (47)
Serious AE, n (%)	70 (69)	59 (66)
Death, n (%)	23 (23)	29 (33)
Discontinuation due to AE, n (%)*	7 (7)	5 (6)
Serum creatinine ≥0.5 mg/dL increase from baseline	17 (17)	21 (24)
ALT flare,† n (%)‡	2 (2)	1 (1)
HCC, n (%)	12 (12)	18 (20)
Liver transplantation§	11 (11)	3 (3)

Death and HCC include events that occurred on and off treatment; all other data represent on-treatment events only. SE, standard error.

*Reasons for discontinuation considered to be possibly or probably related to study therapy were, for ETV, pancreatitis (n = 1), increased ALT (n = 1), muscle spasms (n = 1), and hepatic malignant neoplasm (n = 1), and, for ADV, increased creatine phosphokinase (n = 1) and increased creatinine (n = 1).

†ALT flare is defined as ALT >2× baseline and >10× upper limit of normal.

‡One additional event occurred off treatment in the ADV group.

§Only evidence of HCC was requested from the investigators. Other pathology data of transplant hepatectomy was provided in some cases only.

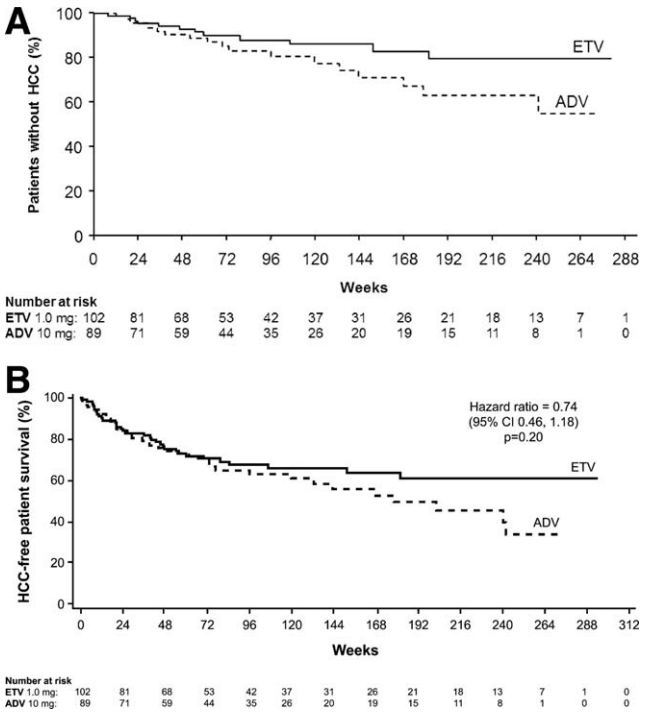

Fig. 4. (A) Cumulative time to HCC in treated patients. (B) HCC-free survival rate in treated patients.

The results from this week 48 analysis demonstrated that ETV and ADV are effective, safe, and well tolerated in this population. ETV 1.0 mg demonstrated superiority over ADV 10 mg for the primary and key secondary virologic endpoints. Moreover, subgroup analyses carried out to address the mixed nature of the study population demonstrated consistent findings across all groups assessed; therefore, our findings were not driven by a particular subpopulation. These results are consistent with prior observations in ETV-treated patients who had less severe HBeAg-positive and HBeAg-negative disease.[16,17,22] These results are also comparable to the results of previous studies with LVD and ADV, which reported effective HBV DNA suppression in this population.[4-7,31] ETV also demonstrated greater biochemical efficacy than ADV at weeks 24 and 48. Comparable HBeAg loss and seroconversion rates were observed between both treatment groups. HBsAg seroclearance occurred in five ETV-treated and no ADV-treated subjects.

ETV and ADV demonstrated improvement of liver status, as assessed by change in CTP and MELD scores and measures of hepatic function. At least one-third of patients demonstrated an improvement in CTP status. The mean MELD score change from baseline at week 48 was seemingly higher for ETV (−2.6 versus −1.7 for ADV), but a covariate-adjusted model showed that the difference between the treatment groups could be explained by the difference in baseline MELD score. Although the virologic superiority of ETV over ADV did not translate into a comparable hepatic improvement, this observation might be related to the baseline severity of disease in this study population and the time required to reverse severe fibrosis once it is established.

In this study, three ETV subjects and six ADV subjects developed resistance to the study drug. Consistent with prior data,[20] all ETV subjects were LVDr at baseline, and the onset of resistance was delayed. In contrast to prior data,[12,13,32] ADV resistance emerged in subjects regardless of preexisting LVDr and had a more variable onset following start of therapy.

Week 24 mortality rates in the present study (12% for each treatment group) were similar to those previously reported (16% mortality with LVD therapy) for this population.[31] Four ADV-treated and two ETV-treated patients (2%) died within 30 days. A recent case-series study reported higher 30-day mortality rate with ETV than LVD treatment (4/36 [11%] versus 2/117 [2%]) in subjects presenting with severe acute exacerbation of CHB (not all presented with hepatic decompensation at baseline).[33] Notably, the number of subjects treated with ETV was very small (n = 36). The data cannot be compared with our study.

Three recent studies have reported on the use of antiviral therapy in patients with CHB who have hepatic decompensation.[28-30] Because of differences in patient characteristics and study design, it is difficult to compare the results of these studies with those of the present study. Virological response rates to ETV (1 mg) in the present study were comparable to those demonstrated with ETV (0.5 mg) in the LVD-naive subgroup of patients included in the phase 2 study involving tenofovir and ETV.[29] Shim and colleagues reported slightly higher virological response rates with ETV (0.5 mg); however, their study included only nucleos(t)ide-naive patients.[28] All three studies also reported an improvement in hepatic function, although these studies enrolled patients with less severe liver disease at baseline (MELD score of 11.5,[28] 10.5,[29] and 14.3,[30] versus 16.2 in the present study). The inclusion of patients with less severe liver disease at baseline may also account for the lower HCC and/or mortality rates reported in the Shim study.[28] Gane and colleagues[30] reported comparable HCC rates to the cumulative data seen with the present study.

Overall safety findings were comparable for ETV- and ADV-treated subjects in this study. The rates and spectrum of AEs and SAEs were similar between the two groups, with the majority of events either due to

hepatic decompensation or a complication from decompensated cirrhosis. These are consistent with previous observations; antiviral therapy in this patient population is generally well-tolerated and that SAEs frequently comprise events related to the underlying CHB disease state.[4,6,29]

SAEs that may be expected in the decompensated population include hepatic flares, lactic acidosis, and renal failure. In this study, none of these events occurred at unusually high frequency relative to the expected experience or rates in decompensated patients. The rates of renal impairment were similar between the two groups (ETV, 17%; ADV, 24%) and consistent with previous data from ADV-treated patients who had decompensated liver disease.[6] The extent to which therapy may contribute to changes in serum creatinine is difficult to assess in decompensated patients, because renal insufficiency may result from disease progression itself and/or treatments used to manage a disease complication.[14,15]

Lactic acidosis is a known risk of severe liver disease and is considered a potential class risk of all nucleos (t)ide analogues.[23,24] ETV does not inhibit mitochondrial DNA *in vitro*,[34] and lactic acidosis was not identified as a risk of ETV therapy in phase 2/3 clinical trials.[16,17] However, postmarketing reports indicated that lactic acidosis developed in 5 of 16 ETV-treated patients with severely impaired liver function (MELD scores $\geq$22); baseline MELD score was suggested as a predictor of subsequent occurrence of lactic acidosis.[35] In the present study, events of lactic acidosis were not prospectively monitored; however, investigators were provided with guidelines for assessing subjects for the occurrence of asymptomatic/symptomatic hyperlactatemia and lactic acidosis based on serum bicarbonate thresholds. Only one asymptomatic event of lactic acidosis was reported in the ETV group; this event occurred after week 48 in a subject with a baseline MELD score of 21. The event was not associated with adverse outcomes and resolved without interruption of drug.

There are some limitations to this study. Randomization was not stratified; however, several subgroup analyses were performed to address this issue. Second, LVD-naive patients received 1 mg of ETV, a higher dose than in patients with compensated liver disease. However, it is important to note that the 1 mg dose used in this study is the recommended dose for nucleoside-naive patients with decompensated cirrhosis.[23] Virological response rates to 1 mg ETV were similar between LVD-susceptible and LVDr patients in the present study (Table 3), and were comparable to those demonstrated in LVD-naive patients treated with 0.5 mg ETV who were included in the phase 2 tenofovir trial.[29] Finally, the duration of observation in this report was relatively short; however, the study is ongoing.

In summary, the current study demonstrates that ETV is superior to ADV in suppressing HBV DNA and achieving ALT normalization through week 48. Both treatments provided clinical improvement, as measured by reduction of CTP and MELD scores. The global registration studies of ETV therapy in patients with compensated liver disease showed that improvement of fibrosis was achieved in 32% of patients after 48 weeks and 88% of a smaller cohort after a median of 6 years' treatment.[21] In patients with CHB who have established severe fibrosis, as reflected by their decompensated liver disease, it is likely that long-term treatment will be required to achieve maximal benefit. This study shows that ETV is safe and efficacious in the subset of patients with LVDr, but consideration is warranted for the known resistance profile of LVD. Ongoing studies of ETV in combination with nucleotides will help inform future treatment options in the LVDr population. With its favorable safety profile, potency, and high barrier to resistance as previously demonstrated in nucleos(t)ide-naive patients with CHB who have compensated liver disease, ETV appears to be a favorable choice for LVD-naive patients who have decompensated liver disease. Long-term follow-up in this patient population is required, and follow-up is ongoing.

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