20 January 2011
EMA/CHMP/794988/2010
Human Medicines Development and Evaluation

CHMP variation assessment report

Type II variation EMEA/H/C/000623/II/0033

Invented name/name:	Baraclude
International non-proprietary name/common name:	entecavir
Indication summary (as last approved):	Treatment of chronic hepatitis B virus infection
Marketing authorisation holder (MAH):	Bristol-Myers Squibb Pharma EEIG

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted.

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8316
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. Scientific discussion

1.1. Introduction

Worldwide, approximately 350-450 million persons are chronically infected with hepatitis B virus (HBV) (WHO 2008). Among individuals who have developed chronic HBV infection (CHB), morbidity and mortality are linked to progression to cirrhosis and hepatocellular carcinoma (HCC). Up to 40% of patients with CHB develop cirrhosis over their lifetime, at a reported rate of 2% to 6% per year.[1] Among CHB patients with cirrhosis, per year, 3% to 5% progress to decompensated cirrhosis and 2% to 5% develop HCC.[1,2] Patients with decompensated cirrhosis have significant liver-related morbidity and mortality, due to development of progressive liver failure and HCC. [3]

The rates of worsening hepatic decompensation and HCC in patients with CHB and decompensated cirrhosis have not been defined. Mortality data are available and reported rates are high.
In 1 study, the reported 1-year survival for patients with decompensated cirrhosis was 61% compared with 94% for patients with compensated cirrhosis.[4]

There are limited data on the efficacy and safety of HBV therapy in patients with CHB and decompensated liver disease. The interferons are contraindicated in this population due to the risk of worsening liver failure and death reported in patients receiving this therapy. [3]
Lamivudine and subsequently adefovir were registered several years ago for the treatment of patients with decompensated liver disease. However, these therapeutic options are far from being optimal options in such vulnerable population.

Nowadays, the treatment of CHB almost exclusively relies on tenofovir and entecavir which are widely acknowledged as being the gold standards, due to their potent antiviral activity and their high genetic barrier to resistance, which is critical in such a long lasting disease. Tenofovir has been very recently granted an extension of indication for the treatment of patients with decompensated liver disease (Var II 97, July 2010), (refer to EPAR of the product for details).

With the current type II application, the MAH is seeking an extension of the indication for BARACLUDE to include the treatment of adult patients with decompensated chronic hepatitis B. This indication is based on 48 week data of study AI463048, "Comparison of the Efficacy and Safety of Entecavir Versus Adefovir in Subjects Chronically Infected with Hepatitis B Virus and Evidence of Hepatic Decompensation". These data were previously assessed in Follow-Up Measure 005 (FUM 005).

References:

1 Chu C-M and Liaw Y-F. Hepatitis B virus-related cirrhosis: Natural history and treatment. Seminars in Liver Disease 2006;26(2):142-152.

2 Fattovich G, Stroffolini T, Zagni I, et al. Hepatocellular carcinoma in cirrhosis: Incidence and risk factors. Gastroenterology 2004;127:S35-S50.

3 Fontana RJ. Management of patients with decompensated HBV cirrhosis. Seminars in Liver Disease 2003;23(1):89-100.

4 D'Amico G, Morabito A, Pagliaro L, et al. Survival and prognostic indicators in compensated and decompensated cirrhosis. Dig Dis Sci 1986;31(5):468-475.

The variation submitted is the following:

Variation(s) requested		Type
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

Extension of indication to include treatment of patients with decompensated liver disease.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision (P/152/2010).

- On the agreement of a paediatric investigation plan (PIP)

The PIP is not yet completed

1.2. Clinical aspects

1.2.1 FUM 005

TITLE OF STUDY: Comparison of the Efficacy and Safety of Entecavir Versus Adefovir in Subjects Chronically Infected with Hepatitis B Virus and Evidence of Hepatic Decompensation

INVESTIGATORS/STUDY CENTERS: Fifty-two centers randomized subjects in this global study

STUDY PERIOD: Study Initiation Date: 08-Aug-2003. Study Data Cutoff Date: 04-June-2009.The study is ongoing

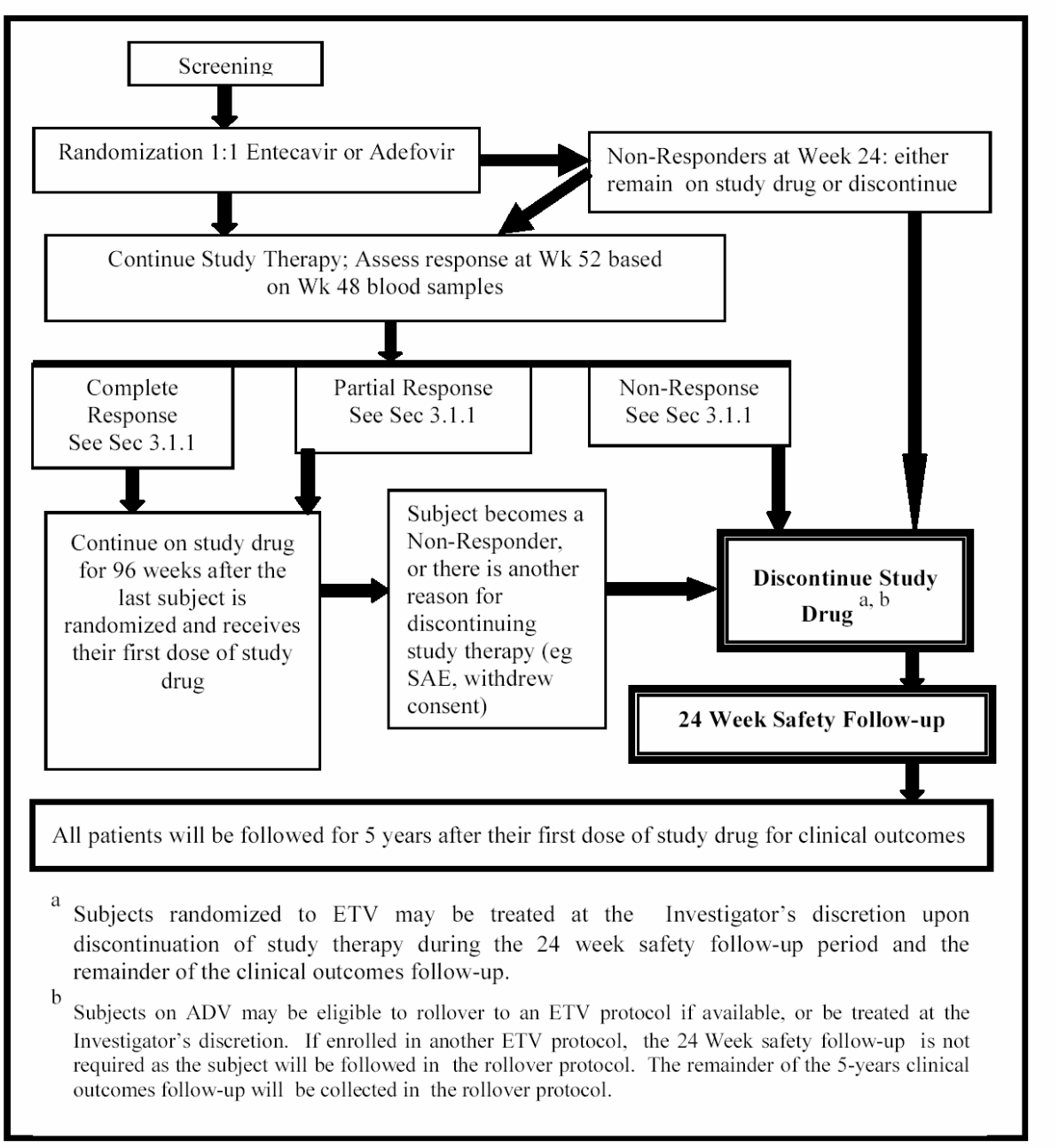
STUDY DESIGN: This is a randomized, open-label study that compares the safety and efficacy of ETV 1.0 mg QD with ADV 10 mg QD administered for up to 96 weeks from the date of last patient first treatment (LPFT) in subjects with chronic HBV infection who have evidence of hepatic decompensation.

The primary efficacy endpoint for the study was the mean reduction in serum HBV DNA determined by PCR assay (log10 copies/mL) at Week 24 adjusted for baseline HBV DNA by PCR and lamivudine resistance (LVDr) status. Non-responders at Week 24 (defined as subjects who evidence a < 1 log10 reduction in HBV DNA from baseline at this time point) could be discontinued from study drug and managed at the discretion of the investigator. Subjects who continued study therapy beyond Week 24 were evaluated for treatment response at Week 52, based on results of laboratory assessments performed at the Week 48 visit; subsequent study management was based on the assessment made at the Week 52 visit. Subjects who were assessed as responding to study therapy could continue on therapy for up to 96 weeks from the date of LPFT.

NUMBER OF SUBJECTS (Planned and Analyzed): The targeted sample size for this study was a minimum of 168 subjects. A total of 431 subjects were enrolled: 195 randomized (ETV 101; ADV 94) and 191 subjects treated (ETV 100; ADV 91). Two subjects were randomized to ADV, but were treated

with ETV for the entire dosing period. These subjects are included in the ADV treatment group for the efficacy analyses and in the ETV group for the safety analyses.

Thus, the planned duration for treatment within the study is for 96 weeks after the randomisation of the last subject. The study is ongoing. A schematic of the study structure is provided below:



DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

The study population is comprised of hepatitis B e antigen (HBeAg)-positive and -negative subjects with chronic HBV infection and hepatic decompensation, defined by a Child-Pugh score ≥ 7. Subjects who were post-liver transplant were eligible to participate. However, liver transplant recipients who were experiencing graft rejection or who were < 90 days post-transplant at the time of enrollment were excluded. Subjects were either HBV treatment-naive or previously treated with interferon alpha,

lamivudine, immunomodulators, or other drugs with anti-HBV activity. However, prior treatment with ETV, ADV, or tenofovir was exclusionary.

CRITERIA FOR EVALUATION:

Primary Efficacy Endpoint: Mean reduction in serum HBV DNA determined by PCR assay (log10 copies/mL) at Week 24 adjusted for baseline HBV DNA and LVDr status.

Key Secondary Endpoints:
• Change from baseline in HBV DNA at Week 48
• Proportion of subjects in each group with HBV DNA < 300 copies/mL by PCR at Weeks 24 and 48
• Normalization of serum ALT in subjects with abnormal ALT at baseline at Weeks 24 and 48
• Improvement in Child-Pugh score from baseline through Week 48, as measured by:
- Improvement or no worsening in Child-Pugh score
- Child-Pugh Class compared with baseline Class (improvement in Child-Pugh Class)
• Improvement in MELD scores from baseline through Week 48, as measured by mean change from baseline in MELD score in each group.

Safety Endpoints:

Key Safety Endpoints:
• Survival (ie, death, as assessed by cumulative rates and the rate at Week 24)
• Renal impairment, as defined by confirmed creatinine increase ≥ 0.5 mg/dL from baseline
• Discontinuation due to AE.

Other Safety Endpoints: Additional safety endpoints assessed and presented include AEs, Grade 3/4 AEs, SAEs, malignant neoplasms (HCC and non-HCC), as assessed by event rates, and events of special interest (eg, ALT flares [defined as ALT > 2 x baseline and > 10 x upper limit of normal {ULN}]).

STATISTICAL CONSIDERATIONS: Subjects were randomized (1:1) to receive either ETV or ADV. All efficacy analyses, unless otherwise noted, are based on treated subjects (analyzed as randomized). Safety analyses shown are cumulative, based on all available data on all treated subjects (analyzed as treated).

The primary efficacy analysis was based on a linear regression model for HBV DNA by PCR at Week 24 (and comparisons at other key time points; eg, Week 48), adjusting for baseline HBV DNA by PCR and LVDr status. Subjects with available Week 24 (analysis week) measurement of HBV DNA were included in this analysis.

A second analysis based on the principle of intention-to-treat (ITT) was added to compare the proportion of subjects with HBV DNA < 300 copies/mL at week 24 (and at other key time points). HBV DNA change from baseline and proportion of subjects who achieved an HBV DNA < 300 copies/mL was assessed across the 2 groups for all treated subjects and for the following subgroups: LVDr versus LVD-susceptible (based on the presence or absence of LVDr mutations by genotyping at baseline), and HBeAg-positive versus HBeAg-negative.

Binary variables (eg, ALT normalization, HBV DNA < 300 copies/mL) are summarized by counts and proportions. Continuous variables (eg, HBV DNA) are summarized using the mean, median, standard error, and minimum and maximum values. The potential roles of prognostic factors such as baseline

LVDr and HBeAg status were examined through subgroup analyses. For the binary efficacy endpoints, missing data are handled using both non-completer = failure (NC=F) and NC = missing (NC=M) methods. Non-completers are defined as subjects who did not have any of the following measurements in a visit window: HBV DNA by PCR assay, HBeAg, hepatitis B e antibody, or ALT. In the non-completer = failure (NC = F) analysis, NCs are included in the denominator and counted as failures (ie, non-responders) for that endpoint. In the NC = M analysis, NCs are excluded from the analysis. Completers are treated as failures for the analysis of any measurement for which their data are missing. For the ALT normalization endpoint (≤ 1.0 x ULN), subjects with a normal ALT at baseline were excluded from the analysis.

Improvement in Child-Pugh status was assessed by 2 measures: improvement or no worsening in Child-Pugh score from baseline (defined as a decrease or no change from baseline in score) and improvement in Child-Pugh class (defined as change from class C to A or B to A, for subjects who were class C or B at baseline, respectively).

MELD score change from baseline was assessed across the 2 groups for all treated subjects. Safety analyses tabulate the frequency of cumulative on-treatment events for AEs, Grade 3/4 AEs, SAEs, and discontinuations due to AEs. Death and malignancy data are cumulative, and include events identified on treatment or during post-dosing follow-up. ALT flares were identified as events of ALT > 10 x ULN and > 2 x baseline (National Institute of Health consensus definition). Time to death was also assessed, but no treatment comparisons were performed.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: Disposition data through Week 48 are shown in Table 1. Of the 133 subjects who were treated for at least 48 weeks, as of database lock, 81 had been treated for at least 2 years, 43 were in their second year of therapy, and the remaining 9 subjects had been discontinued from treatment, the majority due to either death, AE, or lack of efficacy.

Table 1: Subject Disposition Through 48 Weeks

	Number of Subjects (%)		
	Treatment Regimen		
	ETV 1.0 mg N = 101	**ADV 10 mg N = 94**	**Total N = 195**
Enrolled			431 (100)
Never Randomized			236 (55)
Randomized	101	94	195
Never Treated	1 (< 1)	3 (3)	4 (2)
Treated (As Randomized)	100 (99)	91 (97)	191 (98)
Discontinued in First 48 Weeks of Treatment	29 (29)	29 (31)	58 (30)
Death	16 (16)	17 (18)	33 (17)
Adverse event	4 (4)	3 (3)	7 (4)
Other	9 (9)	9 (10)	18 (9)
Completed First 48 Weeks of Treatment	71 (70)	62 (66)	133 (68)
As Treated	102	89	191

Two subjects were randomized to ADV, but were treated with ETV for the entire dosing period. Therefore, the ETV treated (as randomized) count is 2 less than the ETV as-treated count, and the ADV treated (as randomized)

count is 2 more than the ADV as-treated count. Unless otherwise noted, the as-randomized population is used in the analysis of efficacy.
Other reasons included subject withdrew consent, lack of efficacy, lost to follow-up, subject no longer meets study criteria, and poor/non-compliance.

[c] The as-treated population is used in the analysis of safety.

Table 2 presents a summary of baseline demographics and HBV characteristics in treated subjects. ETV-treated and ADV-treated subjects had comparable baseline demographics. HBV disease characteristics were generally comparable across the 2 groups.

Table 2: Baseline Demographics and HBV Characteristics - Treated Subjects (As Randomized)

	Treatment Regimen		
	ETV 1.0 mg N = 100	**ADV 10 mg N = 91**	**Total N = 191**
Age (Years)			
Mean (SE)	51 (1.2)	53 (1.1)	52 (0.8)
Gender: N (%)			
Male	78 (78)	64 (70)	142 (74)
Race: N (%)			
Asian	55 (55)	49 (54)	104 (54)
White	35 (35)	28 (31)	63 (33)
Black/African American	5 (5)	5 (5)	10 (5)
Other [a]	5 (5)	9 (10)	14 (7)
HBe Antigen status: N (%)			
HBeAg-positive	54 (54)	50 (55)	104 (54)
HBV DNA by PCR (log_{10} copies/mL)			
Mean (SE)	7.53 (0.183)	8.16 (0.228)	7.83 (0.146)
ALT (SGPT) (U/L)			
Mean (SE)	99.2 (11.12)	100.0 (8.56)	99.6 (7.09)
LVDr Mutation [b]			
Present: N (%)	36 (36)	30 (33)	66 (35)
Child-Pugh Score			
Mean (SE)	8.81 (0.198)	8.35 (0.190)	8.59 (0.139)
Child-Pugh Class: N (%)			
A	7 (7)	10 (11)	17 (9)
B	63 (63)	61 (67)	124 (65)
C	30 (30)	20 (22)	50 (26)
MELD Score			
Mean (SE)	17.07 (0.500)	15.30 (0.484)	16.23 (0.354)

[a] Other includes Asian Indian, South African color, mixed ancestry, and mixed race.

[b] LVDr mutations: I552 (or 204I), V552 (or 204V), and M528 (or 180M).

Efficacy Results:

Efficacy endpoints through Week 48 are summarised in Table 3.

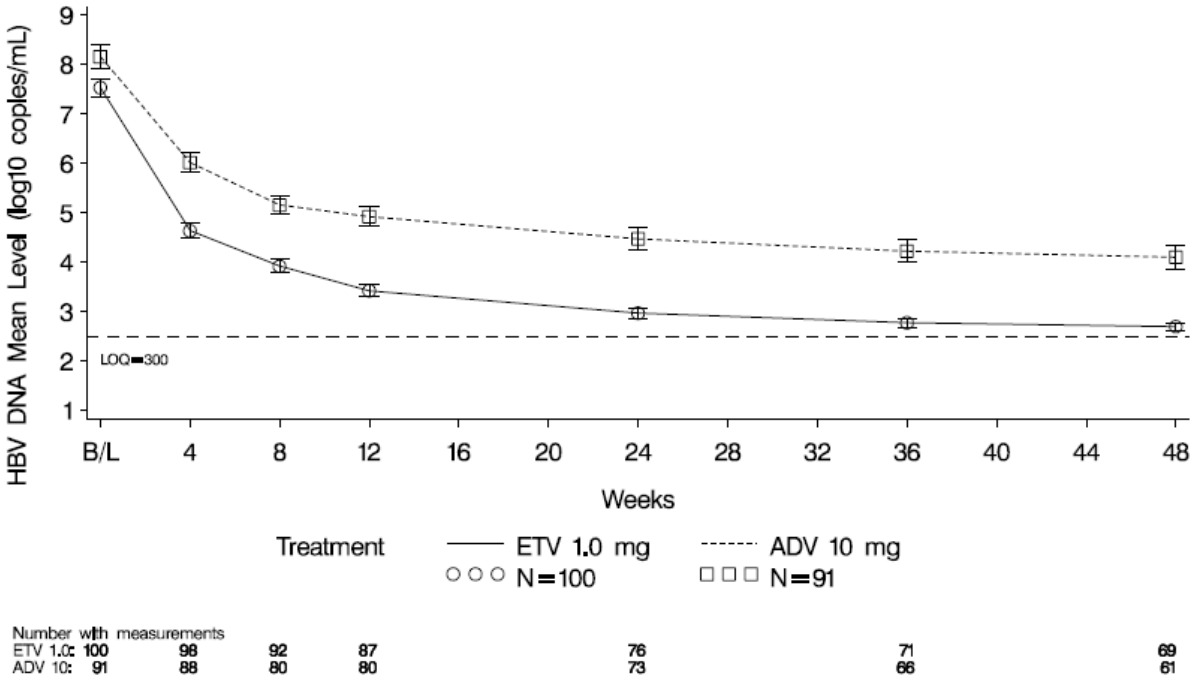
Table 3: Efficacy Endpoints Through Week 48 - Treated Subjects (As Randomized) - Study AI463048

	Week 24		Week 48	
Parameter	**ETV 1.0 mg (N = 100)**	**ADV 10 mg (N = 91)**	**ETV 1.0 mg (N = 100)**	**ADV 10 mg (N = 91)**
HBV DNA [a]				
Proportion Undetectable (< 300 copies/mL)	49% [e]	16%	57% [h]	20%
Mean Change from Baseline (log $_{10}$ copies/mL) [b]	-4.48 [f]	-3.40	-4.66	-3.90
ALT Normalization (≤1.0 x ULN) [c]	46/78 (59%) [g]	28/71 (39%)	49/78 (63%) [i]	33/71 (46%)
HBeAg loss	0/54 (0%)	7/51 (14%)	6/54 (11%)	9/51 (18%)
HBeAg seroconversion	0/54 (0%)	6/51 (12%)	3/54 (6%)	5/51 (10%)
HBsAg Loss	1/100 (1%)	0/91 (0%)	5/100 (5%)	0/91 (0%)
Child-Turcotte-Pugh Score				
Improvement or No Worsening	66/100 (66%)	65/91 (71%)	61/100 (61%)	61/91 (67%)
Class Improvement [d]	25/93 (27%)	22/81 (27%)	35/93 (38%)	29/81 (36%)
MELD Score Mean Change from Baseline [b]	-2.0	-0.9	-2.6	-1.7
Normalization of Hepatic Function: [c]				
Albumin (≥ 1 x ULN)	20/82 (24%)	14/69 (20%)	32/82 (39%)	20/69 (29%)
Total Bilirubin (≤ 1 x ULN)	12/75 (16%)	10/65 (15%)	15/75 (20%)	18/65 (28%)
Prothrombin Time (≤ 1 x ULN)	9/95 (9%)	6/82 (7%)	8/95 (8%)	7/82 (9%)

[a] Roche COBAS Amplicor PCR assay (LLOQ = 300 copies/mL).
[b] Analysis method is Non-Completer = Missing. N = 100 (ETV) and 91 (ADV) subjects.
[c] Denominator is the number of subjects with abnormal values at baseline.
[d] Improvement defined as Child-Turcotte-Pugh class change from B to A or C to A.
[e] Treatment difference 33% (95% CI: 20.2, 45.2; p value < 0.0001).
[f] Treatment difference -1.74 (95% CI: -2.30, -1.18; p < 0.0001).
[g] Treatment difference 19.2% (95% CI: 3.7, 34.6; p = 0.0193).
[h] Treatment difference 38% (95% CI: 24.8, 50.3; p < 0.0001).
[i] Treatment difference 16.4% (95% CI: 0.9, 32.0; p = 0.0425).

Primary Efficacy Endpoint: The primary efficacy analysis, which compared HBV DNA at Week 24, adjusted for baseline HBV DNA and LVDr status, showed a greater reduction in HBV DNA for the ETV group compared with the ADV group (treatment difference -1.74 (95% confidence interval [CI] [- 2.30, -1.18], p-value < 0.0001).

Figure 1: **HBV DNA Mean by PCR Through Week 48 - Treated Subjects, As Randomized**



Key Secondary Efficacy Endpoints:

Virologic: ETV-treated subjects evidenced a greater mean decline from baseline in HBV DNA by PCR than ADV-treated subjects at all time points measured, at Weeks 24 and 48: -4.48 versus -3.40 and -4.66 versus -3.90 log10 copies/mL respectively, see figure 1.

In the ITT analysis, the ETV group evidenced a greater proportion of subjects with HBV DNA < 300 copies/mL by PCR compared with the ADV group at Week 24 (ETV 49%, ADV 16%; treatment difference 33%; 95% CI [20.2, 45.2]; p-value < 0.0001) and at Week 48 (ETV 57%, ADV 20%; treatment difference 38%; 95% CI [24.8, 50.3]; p-value < 0.0001) (NC = F).

For the analyses related to change from baseline in HBV DNA and proportion < 300 copies/mL, the difference in the HBV DNA responses at Weeks 24 and 48 favoring ETV persisted when analyzed by subgroup (ie, LVDr, LVD-susceptible, HBeAg-negative, and HBeAg-positive), although the magnitude of the treatment differences varied across subgroups.

Biochemical: The rates of ALT normalization were greater in the ETV group compared with the ADV group at Week 24 (ETV 59%; ADV 39%) and Week 48 (ETV 63%; ADV 46%).

Improvement in Child-Pugh Status:

Comparable results were observed across the ETV and ADV groups at Weeks 24 and 48 for the rates of improvement in Child-Pugh status, as defined by either an improvement or no worsening in score or an improvement in Child-Pugh Class (see table 4.3 above). The mean change from baseline in the Child-Pugh score was also comparable between the 2 groups at Week 24 (ETV -1.2; ADV -0.7) and at Week 48 (ETV -1.7; ADV -1.3).

In addition, the proportion of treated subjects who achieved a ≥ 2-point reduction in Child-Pugh score through Week 48 was comparable between the 2 groups (ETV 35%; ADV 27%).

Improvement in MELD Score and individual liver function tests: Both groups showed an improvement in MELD score at Weeks 24 and 48, as assessed by the mean change from baseline in MELD score, which ranged from approximately 2 - 3 points. Approximately half the subjects in both treatment groups had either an improvement or no worsening in their MELD scores at Weeks 24 (ETV 62%; ADV 56%) and 48 (ETV 53%; ADV 52%).

Through Week 48, both groups showed an improvement in liver function, as assessed by change from baseline in measures of total bilirubin, PT and platelets. Results for each of these parameters were comparable between the groups (TB [mg/dL]: ETV -0.61; ADV -0.10, PT [sec]: ETV -0.99; ADV -0.52, and platelets [x 1000 mm3]: ETV 10.19; ADV 3.05). Albumin levels remained essentially unchanged from baseline in both groups (ETV 0.49; ADV 0.34) Rates of normalization in measures of liver function at Week 48 were comparable between groups, for each parameter assessed: (TB: ETV 20%; ADV 28%, PT: ETV 8%; ADV 9%, platelets: ETV 7%; ADV 1%, and albumin: ETV 39%; ADV 29%.

Drug resistance

Development of resistance to study drug on-treatment was measured by genotypic analysis, assaying for the appearance of mutations previously identified as conferring loss of antiviral activity to ETV and ADV. Subjects who failed to evidence a 1 log10 or greater decline in HBV DNA by PCR analysis at Week 24 or who experienced virological breakthrough following an initial response to treatment were assessed for drug resistance. A total of 37 subjects (ETV 5; ADV 32) met criteria for resistance testing. In the ETV group, all 5 subjects who met criteria were LVDr at baseline; on testing, 3 of the 5 subjects evidenced ETVr. For all 3 subjects, ETVr was first detected at $\geq$Week 144 of study. In one subject, at Week 144 M204I+T184I was detected; in another, at w147, M204V+S202G was found; in a third, at w176, M204V + S202G was noted.

Six of 27 subjects in whom testing was performed evidenced ADVr: 4 were LVD-susceptible and 2 were LVDr at baseline

Table A:

Genotypic Resistance of Study Drug by Baseline LVDr Status- On Treatment - Treated Subjects - As-Treated

Category	Treatment Regimen				
	ETV 1.0 mg (N = 102)			ADV 10 mg (N = 89)	
	LVD	LVDr Status		LVD	
LVDr Status	Susceptible	LVDr	Missing	Susceptible	LVDr
Missing					
Treated subjects	65	36	1	57	30
2					
Meet Any Testing Criteria*	0	5	0	18	14
1					
Genotypic Resistance Detected	0	3	0	4	2
0					
Through Week 48	0	0	0	1	0
0					
From Week 48 Through Week 96	0	0	0	1	1
0					
From Week 96 Through Week 144	0	2	0	0	1
0					
After Week 144	0	1	0	2	0
0					
Missing**	0	0	0	1	4
1					
Tested, not meeting testing criteria	0	0	0	1	2
0					

ETVr - LVD-resistance (M204V/I/S +/- L180M) plus additional changes at T184, S202, or M250.
ADVr - A181T/V or N236T.
*: Subjects with virological breakthrough on treatment; or achieve less than 1 log10 HBV DNA reduction by the Week 24 visit.
**: Specimen not available, HBV DNA could not be amplified or other technical reason.

Safety Results:

The current safety results reflect a mean on-treatment exposure of approximately 2 years in both treatment groups (ETV: 109 weeks; ADV: 97 weeks), and a median treatment exposure of about 1.5 years (ETV: 75 weeks; ADV: 76 weeks).

Table B: Extent of Study Drug Exposure On Treatment - Treated Subjects

	Treatment Regimen	
	ETV 1.0 mg N = 102	ADV 10 mg N = 89
Average Daily Dose (mg)		
MEAN (SE)	0.89 (0.017)	9 (0.2)
MEDIAN	0.98	10
MIN, MAX	0.32, 1.14	5, 11
Cumulative Dose (mg)		
MEAN (SE)	678.3 (58.9)	6292.7 (584.3)
MEDIAN	444.0	4520.0
MIN, MAX	1.0, 1996.5	30.0, 18970.0
Time on Therapy (Weeks)		
MEAN (SE)	108.8 (9.0)	96.6 (8.4)
MEDIAN	74.9	75.7
MIN, MAX	0.1, 285.9	0.4, 272.0

Table 4 summarizes cumulative safety data in treated subjects. For SAEs and Grade 3/4 AEs, the majority of events reported were expected in this study population, with the most frequently reported SAEs and Grade 3/4 AEs being hepatic failure, a specific manifestation of hepatic failure (eg, blood bilirubin increased, prothrombin time prolonged, hepatic encephalopathy), or a complication associated with a manifestation of decompensated cirrhosis, such as ascites (eg, bacterial peritonitis, sepsis/septic shock). The cumulative rates of serum creatinine increase ≥ 0.5 mg/dL were also comparable between the groups.

Table 4: Cumulative Safety Data - On Treatment, As Treated

	Number (%) of Subjects	
	ETV 1.0 mg	ADV 10 mg
	N = 102	N = 89
Any AE	91 (89)	86 (97)
Grade 3/4 AEs	55 (54)	42 (47)
SAEs	70 (69)	59 (66)
Deaths [a]	23 (23)	29 (33)
Hepatocellular Carcinoma	12 (12)	18 (20)
Discontinuations Due to AEs	7 (7)	5 (6)
Confirmed Creatinine Increase ≥ 0.5 mg/dL	17 (17)	21 (24)

a Five additional enrolled subjects died prior to initiation of treatment.

Through Week 48, the rate of treatment-related Grade 2 through 4 AEs was the same in both groups (12%).

The spectrum of reported Grade 2-4 related events through Week 48 in this study is generally comparable to the spectrum reported in the ETV phase 3 program, as outlined in the ETV label. Grade 2 - 4 related AEs not appearing in the ETV label that were observed through Week 48 in Study AI463048 include blood bicarbonate decreased (ETV 2% and ADV 0%) and renal failure (ETV < 1% and ADV 2%).

As expected, cumulative death rates in treated subjects were high in both treatment groups (ETV 23 [23%]; ADV 29 [33%]).

As of database lock, a total of 57 deaths were reported. Five of the 57 deaths occurred prior to randomization. The remaining 52 deaths occurred in treated subjects (ETV 23, ADV 29), giving cumulative death rates in the ETV and ADV treatment groups of 23% and 33%, respectively. Death rates during the first 24 weeks of study in both groups were 12%. The primary causes of death in treated subjects were as expected in this study population: ETV (10 liver failure, 6 infection/sepsis, 3 cardiopulmonary, 2 gastrointestinal [GI] bleed/shock, 1 multi-organ failure, and 1 unknown); ADV (15 liver failure, 7 HCC, 3 infection/sepsis, 3 GI bleed/shock, and 1 cardiac).

The most frequently reported on-treatment SAEs were clinical manifestations of decompensated cirrhosis, such as hepatic encephalopathy (ETV 10; ADV 9), bacterial peritonitis (ETV 6; ADV 6), ascites (ETV 4; ADV 4), and upper GI hemorrhage (ETV 4; ADV 3); laboratory manifestations of decompensated cirrhosis, such as PT prolonged (ETV 14; ADV 13), blood bilirubin increased (ETV 8; ADV 6) and hyponatremia (ETV 3;ADV 2); hepatic neoplasm malignant (ETV 12; ADV 15); hepatic failure/chronic hepatic failure (ETV 12; ADV 2); and high risk events associated with decompensated cirrhosis, such as infection (i.e., sepsis [ETV 5; ADV 3] and septic shock [ETV 4; ADV 1]). All of these events are expected occurrences in patients with decompensated cirrhosis. Table C presents on-treatment SAEs reported in $\geq$5% of subjects in either group.

Table C: **Serious Adverse Events Reported in ≥ 5% of Subjects in Either Treatment Group - On Treatment**

SYSTEM ORGAN CLASS PREFERRED TERM	Number of Subjects (%) ETV 1.0 mg N = 102	 ADV 10 mg N = 89
ANY ADVERSE EVENT	70 (69)	59 (66)
INVESTIGATIONS	27 (26)	23 (26)
PROTHROMBIN TIME PROLONGED	14 (14)	13 (15)
BLOOD BILIRUBIN INCREASED	8 (8)	6 (7)
INTERNATIONAL NORMALISED RATIO INCREASED	5 (5)	5 (6)
INFECTIONS AND INFESTATIONS	21 (21)	16 (18)
PERITONITIS BACTERIAL	6 (6)	6 (7)
SEPSIS	5 (5)	3 (3)
SEPTIC SHOCK	4 (4)	1 (1)
HEPATOBILIARY DISORDERS	19 (19)	14 (16)
HEPATIC FAILURE	10 (10)	2 (2)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	13 (13)	15 (17)
HEPATIC NEOPLASM MALIGNANT	12 (12)	15 (17)
NERVOUS SYSTEM DISORDERS	13 (13)	13 (15)
HEPATIC ENCEPHALOPATHY	10 (10)	9 (10)
SURGICAL AND MEDICAL PROCEDURES	7 (7)	1 (1)
LIVER TRANSPLANT	7 (7)	0

Liver transplants:
Eleven ETV-treated subjects and 3 ADV-treated subjects underwent liver transplantation on study or during 24-week follow-up. Five (ETV 5, ADV 0) of these 14 subjects, underwent liver transplantation in the first 48 weeks (336 days) of study. In the ETV group, 3 subjects underwent liver transplantation for treatment of HCC, 6 for liver failure, 1 for treatment of both HCC and liver failure, and in 1 case, the reason was not specified. For the ADV group, 2 subjects underwent liver transplantation for treatment of HCC and 1 for treatment of both HCC and liver failure.

Malignant Neoplasms:
As of database lock, 32 events of malignant neoplasm (ETV 14; ADV 18) had been reported on treatment or during 24-week follow-up. Thirty of the 32 events were HCC (ETV 12; ADV 18), giving cumulative rates for HCC in ETV- and ADV-treated subjects of 12% and 20%, respectively. All subjects who developed HCC had at least 2 identified risk factors in addition to the primary risk factors of chronic HBV infection and cirrhosis (data not shown). The remaining 2 of 32 events were non-HCC malignancies (ETV 2; ADV 0). One of the 2 non-HCC malignancies was a recurrent non Hodgkin's lymphoma (a tumor for which chronic HBV appears to be a risk factor), and the remaining event was a basal cell carcinoma.

ALT Flares:
No subjects in either group experienced an on-treatment ALT flare (> 2 x baseline and > 10 x ULN) within the first 48 weeks of therapy. Using the lower ALT threshold, 2 (2%) ETV-treated subjects and 0 (0%) ADV-treated subjects experienced an on-treatment ALT flare. For 1 of the 2 subjects, the ALT flare occurred at Day 58, and was associated with a 3 log10 copies/mL decline from baseline in HBV DNA by PCR assay, and worsening of laboratory measures of hepatic function. The event resolved and treatment continued uninterrupted. In the second subject, the ALT flare occurred at Days 13 and 27, and was similarly associated with worsening AST and liver function; however, the HBV DNA decline from baseline was substantially less (approximately 1 log10 copies/mL.

In the cumulative analysis, 3 subjects (ETV 2, ADV 1) had an on-treatment ALT flare (> 2 x baseline and > 10 x ULN) after Week 48.

Conclusion on study AI463048 (FUM 005):

At the time of FUM 005 submission, two nucleos(t)ides had European labelling for the treatment of HBV in patients with decompensated cirrhosis – that is lamivudine and adefovir. However, treatment paradigms in this field have rapidly been changing. Already, EASL guidelines primarily recommend tenofovir or entecavir (the latter provided no lamivudine resistance) in decompensated patients, though neither agent yet had the label (EASL, J Hepatol 2007). Furthermore, adefovir monotherapy is no longer recommended in patients with lamvidine resistance. Neither is entecavir monotherapy a favoured option in these patients.

The 24- and 48 week data from study AI463048 demonstrate that entecavir has superior virological efficacy compared to adefovir in a decompensated population with mixed baseline characteristics as regards HBeAg positivity and lamivudine resistance. All in all, this finding is not unexpected given previous data. In terms of improvement of hepatic function, however, no definite advantage was demonstrated within the scope of this trial, perhaps due to the limited duration of on-treatment observation. Longer-term data on change of hepatic function will be provided at Week 96. Rates of functional improvement were roughly similar in both treatment arms. After assessing the original study

report as well as the responses to the request for supplementary information, there are no signs that the safety and tolerability of entecavir would be worse than that of the comparator adefovir.

Available data are sufficiently compelling for entecavir to be granted the indication for the treatment of patients with HBV infection and decompensated liver disease. However, entecavir should not be used as monotherapy to treat patients with decompensated liver disease and lamivudine resistant virus.

The following issues were noted:

1). The CHMP pondered that the labelled dose in nucleoside-naive patients with compensated cirrhosis is 0.5 mg/day to be taken without food restrictions. This was the dose studied in the phase III programme in nucleoside naive patients, HBeAg+ or -, with compensated liver disease. A clear dose response was demonstrated and a threshold dose of 0.01 mg was identified. The selected dose of ETV of 0.5 mg for nucleoside-naïve subjects was based on superiority in HBV DNA reduction by PCR at Week 22 compared with the ETV 0.1 mg dose. The analyses of dose-response suggested a flattening of the curve in the 0.1-0.5 mg range. Consequently, the 0.5 mg was chosen for further phase III development. Due to adverse events (mainly nervous system) which were not confirmed in phase III trials particularly seen with 0.5 mg, higher dose in this population has not been investigated. Thus, while a dose response was seen from 0.1 to 0.5 mg, none was so from 0.5mg to 1 mg in study -004.

At the time of initial authorization, not only were the phase III studies in nucleoside naive patients performed with the dose of 0.5 mg, but according to assessment there was no PK/PD rationale to intimate that a higher dose would have been more efficacious. Also, a PK study in patients with moderate and severe hepatic impairment showed no PK effects warranting a dose adjustment.

However, the MAH clarified that the logic behind the argument in support of the 1.0 mg dose for nucleoside-naïve patients with decompensated liver disease is based on:

• the fact that empiric observations supporting the use of entecavir (ETV) in this population are limited to those made using the 1.0 mg dose in Study AI463048; and

• general clinical principles regarding antiviral management.

The MAH stated that while PK/PD modeling is a powerful tool, and an essential component of primary dose selection, it provides insights that are distinct from those provided by directly observed clinical datasets. The MAH recognized that at least two small external datasets have been developed in patients with decompensated liver disease (though with decompensation of varying degrees of severity) using the current labeled dosing regimens for ETV (0.5 mg for naive patients and 1.0 mg for lamivudine (LVD)-refractory). These datasets suggest that the 0.5 mg dose in naive patients with decompensated liver disease has efficacy and represents a viable alternate dosing approach, without apparent risk from an efficacy perspective. However, the MAH prefers to recommend a universal 1.0 mg dose in the decompensated population, based on the fact that the controlled clinical efficacy and safety dataset that supports this indication reflects use of the 1.0 mg dose.

The CHMP remained of the opinion that 0.5 mg/d is likely to be sufficient for nucleoside naïve patients with decompensated liver disease as it is considered to be in those with compensated liver disease. Furthermore, it is observed that, notwithstanding the argument of the MAH, the clinical rationale for recommending a higher dose in patients with decompensated liver disease may not seem immediately

straightforward to the prescriber unaware of its evidence base. The empirical basis for this dose will, however be reflected in the SPC. The CHMP accepts that there are no defined particular differential safety concerns regarding the two doses. Hence, the higher dose (1.0 mg) as universal dose in decompensated patients can be accepted.

2). Furthermore, it is recognised that patients with lamivudine-resistant HBV are at higher risk of developing subsequent entecavir resistance than patients without lamivudine resistance. The cumulative probability of emerging genotypic entecavir resistance after 1, 2, 3, 4 and 5 years treatment in the lamivudine-refractory studies was 6%, 15%, 36%, 47% and 51%, respectively (Baraclude SPC). As regards guidelines, EASL (J Hepatol 2009) recommends the addition of tenofovir in case of lamivudine resistance, and notes that lamivudine resistance reduces entecavir efficacy, but not tenofovir. The AASLD gudielines (Lok and McMahon, Hepatology 2009) note, in case of lamivudine resistance, that "entecavir is not an optimal therapy because of increasing risk of resistance to entecavir over time". CHMP recommends labelling changes in section 4.4. SPC indicating the need for co-treatment with an agent lacking cross-resistance to entecavir and/or lamivudine, in case entecavir is used in a lamivudine refractory patients, taking into account that 3/36 patients with prior lamivudine resistance developed entecavir resistance during the follow-up reported in this FUM, as well as previous findings of the risk of entecavir resistance in patients with prior lamivudine resistance and the vulnerability of decompensated patients in case of viral breakthrough.

3) Safety profile: from the dataset it is shown that ETV treatment is associated with a lower risk for death and discontinuation, and Child-Pugh class C with a higher risk for death and hepatic adverse events. It may also be that patients with increased baseline ALT had an increased risk of hepatic failure. Although the safety profile of entecavir is no worse than that of adefovir, it still seems doubtless that the incidence of severe hepatic adverse events is higher in patients with decompensated liver disease, notwithstanding fact that the causality may be debatable in most cases. Therefore to alert prescribers it seems reasonable to retain a warning in section 4.4, amended with the updated information about the underlying dataset. In addition, a cross reference to sections 4.8 and 5.1 should be amended.

1.2.2 Variation II-33

1.2.2.1 Further issues concerning environmental risk and the risk management plan

During the assessment of the current variation, no update to the environmental risk assessment was required. It was however confirmed that a method used is in accordance with 1 June 2006 "*Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use*" EMEA/CHMP/SWP/4447/00 and a preferred method according to the Draft Q&A on the same guideline from 24-Jun-2010 EMA/CHMP/SWP/44609/2010.

An update of the Risk-Management Plan (RMP) was requested however. Indeed, it is considered that RMP Version 5 included both a summary of the 48-week safety data from Study AI463048, the most relevant available clinical trial data in patients with decompensated liver disease and an extensive discussion concerning reports of lactic acidosis, the only event of special interest identified to date in post-marketing surveillance with respect to patients with decompensated liver disease. However, the

CHMP conclusions on FUM 005 (regarding study A463048) raising the need to avoid entecavir monotherapy in patients with decompensated liver disease and lamivudine resistance should be implemented in the submitted RMP and the MAH was requested to update the relevant parts of the RMP as the safety specification part and routine risk minimisation activity.

1.2.2.2 Product information adopted by the CHMP:

Further to the assessment of MAH proposals to amend the Product Information and in the light of the assessment of the submitted data, the Product Information was revised as follows (wording in bold are the adopted changes to various sections of SmPC/PL):

4.1 Therapeutic indications

Baraclude is indicated for the treatment of chronic hepatitis B virus (HBV) infection **(see section 5.1)** in adults with:

- compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active inflammation and/or fibrosis.
- **decompensated liver disease (see section 4.4)**

For both compensated and decompensated liver disease, this indication is based on clinical trial data in nucleoside naive patients with HBeAg positive and HBeAg negative HBV infection. With respect to patients with lamivudine-refractory hepatitis B, see sections 4.4 and 5.1.

4.2 Posology and method of administration

Therapy should be initiated by a physician experienced in the management of chronic hepatitis B infection.

Baraclude should be taken orally, once-daily.

Compensated liver disease

Nucleoside naïve patients: the recommended dose is 0.5 mg once daily, with or without food.

Lamivudine-refractory patients (i.e. with evidence of viraemia while on lamivudine or the presence of lamivudine resistance [LVDr] mutations) (see sections 4.4 and 5.1): the recommended dose is 1 mg once daily, which must be taken on an empty stomach (more than 2 hours before or more than 2 hours after a meal) (see section 5.2).

Decompensated liver disease

The recommended dose for patients with decompensated liver disease is 1 mg once daily, which must be taken on an empty stomach (more than 2 hours before or more than 2 hours after a meal) (see section 5.2). For patients with lamivudine-refractory hepatitis B, see sections 4.4 and 5.1.

Duration of therapy
The optimal duration of treatment is unknown. Treatment discontinuation may be considered as follows:

- In HBeAg positive patients, treatment should be administered at least until HBe seroconversion (HBeAg loss and HBV DNA loss with anti-HBe detection on two consecutive serum samples at least 3-6 months apart) or until HBs seroconversion or there is loss of efficacy (see section 4.4).
- In HBeAg negative patients, treatment should be administered at least until HBs seroconversion or there is evidence of loss of efficacy. With prolonged treatment for more than 2 years, regular reassessment is recommended to confirm that continuing the selected therapy remains appropriate for the patient.

In patients with decompensated liver disease or cirrhosis, treatment cessation is not recommended.

Elderly: no dosage adjustment based on age is required. The dose should be adjusted according to the patient's renal function (see dosage recommendations in renal impairment and section 5.2).

Gender and race: no dosage adjustment based on gender or race is required.

Renal impairment: the clearance of entecavir decreases with decreasing creatinine clearance (see section 5.2). Dose adjustment is recommended for patients with creatinine clearance < 50 ml/min, including those on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). A reduction of the daily dose using Baraclude oral solution, as detailed in the table, is recommended. As an alternative, in case the oral solution is not available, the dose can be adjusted by increasing the dosage interval, also shown in the table. The proposed dose modifications are based on extrapolation of limited data, and their safety and effectiveness have not been clinically evaluated. Therefore, virological response should be closely monitored.

Creatinine clearance (ml/min)	**Baraclude dosage***	
	Nucleoside naïve patients	**Lamivudine-refractory or decompensated liver disease**
≥ 50	0.5 mg once daily	1 mg once daily
30 - 49	0.25 mg once daily* OR 0.5 mg every 48 hours	0.5 mg once daily
10 - 29	0.15 mg once daily* OR 0.5 mg every 72 hours	0.3 mg once daily* OR 0.5 mg every 48 hours
< 10 Haemodialysis or CAPD**	0.05 mg once daily* OR 0.5 mg every 5-7 days	0.1 mg once daily* OR 0.5 mg every 72 hours

* for doses < 0.5 mg Baraclude oral solution is recommended.
** on haemodialysis days, administer entecavir after haemodialysis.

Hepatic impairment: no dose adjustment is required in patients with hepatic impairment.

Paediatric population: the safety and efficacy of Baraclude in children below 18 years of age have not yet been established. No data are available.

4.4 Special warnings and precautions for use

[…]

Exacerbations of hepatitis: spontaneous exacerbations in chronic hepatitis B are relatively common and are characterised by transient increases in serum ALT. After initiating antiviral therapy, serum ALT may increase in some patients as serum HBV DNA levels decline (see section 4.8). Among entecavir-treated patients on-treatment exacerbations had a median time of onset of 4-5 weeks. In patients with compensated liver disease, these increases in serum ALT are generally not accompanied by an increase in serum bilirubin concentrations or hepatic decompensation. **Patients with advanced liver disease or** cirrhosis may be at a higher risk for hepatic decompensation following hepatitis exacerbation, and therefore should be monitored closely during therapy.

Acute exacerbation of hepatitis has also been reported in patients who have discontinued hepatitis B therapy **(see section 4.2).** Post-treatment exacerbations are usually associated with rising HBV DNA, and the majority appears to be self-limited. However, severe exacerbations, including fatalities, have been reported.

[…]
Patients with decompensated ***liver disease****:* a higher rate of serious hepatic adverse events **(regardless of causality**) has been observed in patients with decompensated **liver disease, in particular in those with Child-Turcotte-Pugh (CTP) class C disease**, compared with rates in patients with compensated liver function. **Also**, patients with decompensated **liver disease** may be at higher risk for lactic acidosis **and for specific renal adverse events such as hepatorenal syndrome. Therefore, clinical and laboratory parameters should be closely monitored in this patient population (see also sections 4.8 and 5.1).**

[…]

Resistance and specific precaution for lamivudine-refractory patients: mutations in the HBV polymerase that encode lamivudine-resistance substitutions may lead to the subsequent emergence of secondary substitutions, including those associated with entecavir associated resistance (ETVr). In a small percentage of lamivudine-refractory patients, ETVr substitutions at residues rtT184, rtS202 or rtM250 were present at baseline. Patients with lamivudine-resistant HBV are at higher risk of developing subsequent entecavir resistance than patients without lamivudine resistance. The cumulative probability of emerging genotypic entecavir resistance after 1, 2, 3, 4 and 5 years treatment in the lamivudine-refractory studies was 6%, 15%, 36%, 47% and 51%, respectively. Virological response should be frequently monitored in the lamivudine-refractory population response after 24 weeks of treatment with entecavir, a modification of treatment should be considered (see sections 4.5 and 5.1).
Pre-existing lamivudine-resistant HBV is associated with an increased risk for subsequent entecavir resistance regardless of the degree of liver disease; in patients with decompensated liver disease,virologic breakthrough may be associated with serious clinical complications of the underlying liverdisease. Therefore, in patients with both decompensated liver disease and lamivudine-resistant HBV, combination use of entecavir plus a second antiviral agent (which does not share cross-resistance with either lamivudine or entecavir) should be considered in preference to entecavir monotherapy.

4.8 Undesirable effects

[…]

c. Description of selected adverse reactions

Laboratory test abnormalities: In clinical studies with nucleoside-naive patients, 5% had ALT elevations > 3 times baseline, and < 1% had ALT elevations > 2 times baseline together with total bilirubin > 2 times **upper limit of normal (ULN)** and > 2 times baseline. Albumin levels < 2.5 g/dl occurred in < 1% of patients, amylase levels > 3 times baseline in 2%, lipase levels > 3 times baseline in 11% and platelets < 50,000/mm^3 in < 1%.

[…]

d. Other special populations

Experience in patients with decompensated liver disease: the safety profile of entecavir in patients with decompensated liver disease was assessed in a randomized open-label comparative study in which patients received treatment with entecavir 1 mg/day (n = 102) or adefovir dipivoxil 10 mg/day (n = 89) (study 048). Relative to the adverse reactions noted in section *b. Tabulated list of adverse reactions*, one additional adverse reaction [decrease in blood bicarbonate (2%)] was observed in entecavir-treated patients through week 48. The on-study cumulative death rate was 23% (23/102), and causes of death were generally liver-related, as expected in this population. The on-study cumulative rate of hepatocellular carcinoma (HCC) was 12% (12/102). Serious adverse events were generally liver-related, with an on-study cumulative frequency of 69%. Patients with high baseline CTP score were at higher risk of developing serious adverse events (see section 4.4).

Laboratory test abnormalities: through week 48 among entecavir-treated patients with decompensated liver disease, none had ALT elevations both > 10 times ULN and > 2 times baseline, and 1% of patients had ALT elevations > 2 times baseline together with total bilirubin > 2 times ULN and > 2 times baseline. Albumin levels < 2.5 g/dl occurred in 30% of patients, lipase levels > 3 times baseline in 10% and platelets < 50,000/mm^3 in 20%.

5.1 Pharmacodynamic properties

[…]

Clinical experience: the demonstration of benefit is based on histological, virological, biochemical, and serological responses after 48 weeks of treatment in active-controlled clinical trials of 1,633 adults with chronic hepatitis B infection, evidence of viral replication **and compensated liver disease. The safety and efficacy of entecavir were also evaluated in an active-controlled clinical trial of 191 HBV-infected patients with decompensated liver disease and in a clinical trial of 68 patients co-infected with HBV and HIV.**

In studies **in patients with compensated liver disease**, histological improvement was defined as a ≥ 2-point decrease in Knodell necro-inflammatory score from baseline with no worsening of the Knodell fibrosis score. Responses for patients with baseline Knodell Fibrosis Scores of 4 (cirrhosis) were comparable to overall responses on all efficacy outcome measures (all patients had compensated liver disease). High baseline Knodell necroinflammatory scores (> 10) were associated with greater histological improvement in nucleoside-naive patients. Baseline ALT levels ≥ 2 times ULN and baseline HBV DNA ≤ 9.0 $\log_{10}$ copies/ml were both associated with higher rates of virologic response (Week 48 HBV DNA < 400 copies/ml) in nucleoside-naive HBeAg-positive patients. Regardless of baseline characteristics, the majority of patients showed histological and virological responses to treatment.

[…]

*Experience in lamivudine-refractory patients **with compensated liver disease**:*
In a randomised, double-blind study in HBeAg positive lamivudine-refractory patients (026), with 85% of patients presenting LVDr mutations at baseline, patients receiving lamivudine at study entry either switched to entecavir 1 mg once daily, with neither a washout nor an overlap period (n = 141), or continued on lamivudine 100 mg once daily (n = 145). Results at 48 weeks are presented in the table.

[…]

Special populations
Patients with decompensated liver disease: **in study 048, 191 patients with HBeAg positive or negative chronic HBV infection and evidence of hepatic decompensation, defined as a CTP score of 7 or higher, received entecavir 1 mg once daily or adefovir dipivoxil 10 mg once daily. Patients were either HBV-treatment-naïve or pretreated (excluding pretreatment with entecavir, adefovir dipivoxil, or tenofovir disoproxil fumarate). At baseline, patients had a mean CTP score of 8.59 and 26% of patients were CTP class C. The mean baseline Model for End Stage Liver Disease (MELD) score was 16.23. Mean serum HBV DNA by PCR was 7.83 $\log_{10}$ copies/ml and mean serum ALT was 100 U/l; 54% of patients were HBeAg positive, and 35% of patients had LVDr substitutions at baseline. Entecavir was superior to adefovir dipivoxil on the primary efficacy endpoint of mean change from baseline in serum HBV DNA by PCR at week 24. Results for selected study endpoints at weeks 24 and 48 are shown in the table.**

	Week 24		Week 48	
	ETV 1 mg once daily	Adefovir Dipivoxil 10 mg once daily	ETV 1 mg once daily	Adefovir Dipivoxil 10 mg once daily
n	100	91	100	91
HBV DNA[a]				
Proportion undetectable (<300 copies/ml)[b]	49%*	16%	57%*	20%
Mean change from baseline (log_{10} copies/ml)[c]	-4.48*	-3.40	-4.66	-3.90
Stable or improved CTP score[b,d]	66%	71%	61%	67%
MELD score Mean change from baseline[c,e]	-2.0	-0.9	-2.6	-1.7
HBsAg loss[b]	1%	0	5%	0
Normalization of:[f]				
ALT (≤1 X ULN)[b]	46/78 (59%)*	28/71 (39%)	49/78 (63%)*	33/71 (46%)
Albumin (≥1 X LLN)[b]	20/82 (24%)	14/69 (20%)	32/82 (39%)	20/69 (29%)
Bilirubin (≤1 X ULN)[b]	12/75 (16%)	10/65 (15%)	15/75 (20%)	18/65 (28%)
Prothrombin time (≤1 X ULN)[b]	9/95 (9%)	6/82 (7%)	8/95 (8%)	7/82 (9%)

[a] Roche COBAS Amplicor PCR assay (LLOQ = 300 copies/ml).

[b] NC=F (noncompleter=failure), meaning treatment discontinuations before the analysis week, including reasons such as death, lack of efficacy, adverse event, noncompliance/loss-to-follow-up, are counted as failures (e.g., HBV DNA ≥ 300 copies/ml)

[c] NC=M (noncompleters=missing)

[d] Defined as decrease or no change from baseline in CTP score.

[e] Baseline mean MELD score was 17.1 for ETV and 15.3 for adefovir dipivoxil.

[f] Denominator is patients with abnormal values at baseline.

* p<0.05

ULN=upper limit of normal, LLN=lower limit of normal.

The time to onset of HCC or death (whichever occurred first) was comparable in the two treatmentgroups; on-study cumulative death rates were 23% (23/102) and 33% (29/89) for patients treated with entecavir and adefovir dipivoxil, respectively, and on-study cumulative rates of HCC were 12% (12/102) and 20% (18/89) for entecavir and adefovir dipivoxil, respectively.
For patients with LVDr substitutions at baseline, the percentage of patients with HBV DNA <300 copies/ml was 44% for entecavir and 20% for adefovir at week 24 and 50% for entecavir and 17% for adefovir at week 48.

[…]

Paediatric population: **the European Medicines Agency has deferred the obligation to submit the results of studies with Baraclude in one or more subsets of the paediatric population with chronic hepatitis B (see section 4.2 for information on paediatric use).**

Clinical resistance: patients in clinical trials initially treated with entecavir 0.5 mg (nucleoside-naive) or 1.0 mg (lamivudine-refractory) and with an on-therapy PCR HBV DNA measurement at or after Week 24 were monitored for resistance.
Through Week 240 in nucleoside-naive studies, genotypic evidence of ETVr substitutions at rtT184, rtS202, or rtM250 was identified in 3 patients treated with entecavir, 2 of whom experienced virologic breakthrough (see table). These substitutions were observed only in the presence of LVDr substitutions (rtM204V and rtL180M).

PL

2. BEFORE YOU TAKE BARACLUDE

[…]

Taking Baraclude with food and drink
In most cases you may take Baraclude with or without food. However, if you have had a previous treatment with a medicine containing the active substance lamivudine you should consider the following. If you were switched over to Baraclude because the treatment with lamivudine was not successful, you should take Baraclude on an empty stomach once daily. **If your liver disease is very advanced, your doctor will also instruct you to take Baraclude on an empty stomach.** Empty stomach means at least 2 hours after a meal or at least 2 hours before your next meal.

[…]

3. HOW TO TAKE BARACLUDE

Your dose will depend on:
- whether you have been treated for HBV infection before, and what medicine you received.
- whether you have kidney problems. Your doctor may prescribe a lower dose for you or instruct you to take it less often than once a day.
- **the condition of your liver.**

Your doctor will advise you on the dose that is right for you. Always take the dose recommended by your doctor to ensure that your medicine is fully effective and to reduce the development of resistance to treatment. Take Baraclude as long as your doctor has told you. Your doctor will tell you if and when you should stop the treatment.

2. Conclusion

Twenty-four and 48 week data from study AI463048 demonstrate that entecavir has superior virological efficacy compared to adefovir in a decompensated population with mixed baseline characteristics as regards HBeAg status and lamivudine resistance. All in all, this finding is not unexpected given previous data, and, indeed, entecavir is already a first line recommendation for treatment of patients with CHB and decompensated cirrhosis (EASL guidelines J Hepatol 2009). In terms of improvement of hepatic function, however, no definite advantage was demonstrated within the scope of this trial, perhaps due to the limited duration of on-treatment observation. Longer-term data on change of hepatic function will be provided at Week 96 of the study. There are no clear indications that the safety and tolerability of entecavir would be worse than that of the comparator. The risk benefit balance of entecavir for the present indication is considered positive.

On 20 January 2011 the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics/ Package Leaflet.