Name of Sponsor/Company: Bristol-Myers Squibb	Individual Study Table Referring to the Dossier	*(For National Authority Use Only)*
Name of Finished Product: Baraclude®		
Name of Active Ingredient: Entecavir		

SYNOPSIS

Week 96 Clinical Study Report for Study AI463111

TITLE OF STUDY: A Comparative Study of Entecavir vs Adefovir plus Lamivudine vs Combination Entecavir plus Adefovir in Lamivudine-Resistant Chronic Hepatitis B Subjects: The DEFINE Study

INVESTIGATORS/STUDY CENTERS: Subjects were randomized at 60 study centers

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 27-Mar-2008 **CLINICAL PHASE:** 3b

Study Completion Date: 03-Jun-2012

This report provides final study results, including those for the primary endpoint at Week 48 and all secondary endpoints at both Weeks 48 and 96.

OBJECTIVES: Primary: To compare the proportion of subjects in the entecavir (ETV) + adefovir (ADV) combination therapy group to the proportion of subjects in the ETV monotherapy treatment group and the ADV+ lamivudine (LVD) treatment group who achieved hepatitis B virus (HBV) deoxyribonucleic acid (DNA) < 50 IU/mL (approximately 300 copies/mL) by polymerase chain reaction (PCR) at Week 48 of treatment using the Roche COBAS® TaqMan HBV Test for use with the High Pure System (HPS) assay.

Secondary: The following secondary end points have been evaluated and described across all 3 treatment groups at Weeks 48 and 96. For selected endpoints, 2 comparisons were pre-specified at Week 48 (ETV+ADV vs LVD+ADV and ETV+ADV vs ETV monotherapy). At Week 96, these comparisons are only provided for the 2 combination groups, as subjects in the original ETV monotherapy arm were permitted to add tenofovoir (TDF) at Week 48, at the investigator's discretion and where approved for the treatment of HBV.

Secondary endpoints included the proportion with HBV DNA < 50 IU/mL (approximately 300 copies/mL) by PCR at Week 96, as well as all of the following endpoints at both Weeks 48 and 96:

- Proportion of subjects who achieved HBV DNA < the lower limit of quantitation (LOQ) for the Roche COBAS TaqMan - HPS assay (LOQ = 29 IU/mL [approximately 169 copies/mL])
- Proportion of subjects who achieved HBV DNA < the lower limit of detection (LOD) for the Roche COBAS Taqman - HPS assay (LOD = 10 IU/mL [approximately 58 copies/mL])
- Proportions of subjects with HBV DNA in relevant categories, eg: < LOQ (29 IU/mL); LOQ (29 IU/mL) to < 50; 50 to < 172; 172 to < 1,720; 1,720 to < 17,200; and ≥ 17,200 IU/mL (approximately < 169; 169 to < 300; 300 to < 10^3; 10^3 to < 10^4; 10^4 to < 10^5; and ≥ 10^5 copies/mL using the Roche COBAS TaqMan - HPS assay
- Mean $\log_{10}$ reduction from baseline in HBV DNA by PCR using the Roche COBAS TaqMan - HPS assay
- Proportion of subjects with alanine aminotransferase (ALT) > 1 x upper limit of normal (ULN) at baseline who achieved ALT normalization (≤ 1 x ULN)
- Proportion of subjects with HBeAg loss

- Proportion of subjects with HBe seroconversion (HBeAg loss and presence of hepatitis B e antibody [HBeAb])
- Proportion of subjects with hepatitis B surface antigen (HBsAg) loss and HBs seroconversion
- Frequency of adverse events (AEs), serious adverse events (SAEs), and discontinuations from study drug due to AEs or laboratory abnormalities
- To describe the rates of resistance in each treatment arm.

METHODOLOGY: This is a 3-arm, comparative, randomized, open-label, multicenter, global study. Subjects were required to have HBeAg-positive chronic hepatitis B (CHB) and documented LVD genotypic resistance (LVDr) at baseline; they were randomized 1:1:1 to receive ETV+ADV combination therapy, ETV monotherapy, or ADV+LVD combination therapy for 100 weeks, with the primary endpoint at Week 48. At the investigator's discretion and where approved for the treatment of HBV, subjects in the original ETV monotherapy arm were permitted to add non-study tenofovoir (TDF) at Week 48. Subjects who discontinued study therapy without starting alternative anti-HBV treatment were to be followed as part of the off-treatment follow-up phase for up to 24 weeks.

Given that 33 of the 140 subjects in the ETV monotherapy group added non-study TDF after Week 48, the following conventions will be used throughout this Week 96 clinical study report (CSR) in referring to that group. When Week 48 or earlier data are being referenced, the term "ETV monotherapy" treatment or group will be used, as was the convention in the Week 48 CSR; when Year 2 or Week 96 data are being referenced, then the term "ETV" treatment or group will be used. Year 2 tables and listings refer to this group as"ETV*" with the asterix footnote indicating that "* = 33 subjects added TDF after Week 48."

NUMBER OF SUBJECTS (Planned and Analyzed): Planned: 420 (140 subjects per treatment arm). Overall, 416 subjects were randomized and 415 subjects were treated.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Male or female HBeAg-positive subjects ≥ 16 years of age (or minimum age of consent in a given country) with chronic hepatitis B (CHB) infection and compensated liver function who were nucleos[t]ide naive (except for LVD) with evidence of LVD resistance (LVDr), HBV DNA > 17,200 IU/mL (approximately 10^5 copies/mL), and ALT of ≤ 10 x ULN.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: The test therapy was ETV+ADV combination therapy. ETV was available as 0.5 mg tablets (batch nos. 7K27643, 8G40042, 9A55890, 9C55583, 9C57820, 9H47146, and 9J56964) and 1 mg tablets (batch nos. 0A58914, 0A62104, 0F62227, 7B26016, 7B26025, 8A41608, 8D35489, 8D35492, 8H37668, 9B47708, 9D54826, and 9J56965). ADV was available as 10 mg tablets (batch nos. 0A61973, 0H53470, 7H26317, 6K19773, 7K22677, 8E41930, 8G42502, 8J35084, 8J42010, 9A55001, 9A55171, 9D52488, 9G48871, and 9G51775).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Reference therapies were ETV monotherapy and ADV+LVD combination therapy. Where allowed by the local health authorities and ethic committees, non-study tenofovir (TDF) could also be added to ETV monotherapy starting at Week 48, with that group subsequently referred to as the "ETV" treatment group. ETV and ADV information is presented above. LVD was available as 100 mg tablets (batch nos. 0B59548, 1D63737, 7H28636, 7K28520, 7L24739, 8F41531, 8K46682, 9A55419, 9G48878, and 9H46508) and as a 5 mg/mL liquid solution (batch no. 9E53873). TDF was available as 300 mg tablets (batch nos. 0B59854, 8F36887, 8G43148, 9C58943, 9H40294, 9K50898, 9K51160, and 10VR001D).

CRITERIA FOR EVALUATION:

Efficacy: The primary endpoint was the proportion of subjects who achieved HBV DNA < 50 IU/mL (approximately 300 copies/mL) by PCR at Week 48 of treatment using the Roche COBAS TaqMan HBV Test for use with the HPS assay.

Secondary endpoints include the proportion with HBV DNA < 50 IU/mL (approximately 300 copies/mL) by PCR at Week 96, as well as all of the following endpoints at both Weeks 48 and 96:Proportion of subjects who achieved HBV DNA < LOQ for the Roche COBAS TaqMan - HPS assay at Week 96 and (LOQ = 29 IU/mL [approximately 169 copies/mL])

- Proportion of subjects who achieved HBV DNA < LOD for the Roche COBAS Taqman - HPS assay at Week 96 (LOD = 10 IU/mL [approximately 58 copies/mL])
- Proportions of subjects with HBV DNA in relevant categories, eg: < LOQ (29 IU/mL); LOQ (29 IU/mL) to < 50; 50 to < 172; 172 to < 1,720; 1,720 to < 17,200; and ≥ 17,200 IU/mL (approximately < 169; 169 to < 300; 300 to < 10^3; 10^3 to < 10^4; 10^4 to < 10^5; and ≥ 10^5 copies/mL) at Week 96 using the Roche COBAS TaqMan - HPS assay
- Mean $\log_{10}$ reduction from baseline in HBV DNA by PCR at Week 96 using the Roche COBAS TaqMan - HPS assay
- Proportion of subjects with ALT > 1 x ULN at baseline who achieved ALT normalization (≤ 1 x ULN) at Week 96
- Proportion of subjects with loss of HBeAg at Week 96
- Proportion of subjects with HBe seroconversion (HBeAg loss and presence of HBeAb) at Week 96
- Proportion of subjects with HBsAg loss and HBs seroconversion at Week 96
- Descriptive rates of resistance in each treatment arm through Weeks 96.

Safety: For both the Week 48 and Week 96 analyses, secondary safety endpoints included the frequency of AEs, SAEs, and discontinuations from study drug due to AEs or laboratory abnormalities.

STATISTICAL CONSIDERATIONS: The analysis for this report includes the primary and all secondary efficacy endpoints based on data available after all subjects have completed 100 weeks of dosing or discontinued study therapy. Efficacy data through Week 100 and all accumulated safety data are included.

Sample Size: A sample size of 420 randomized subjects, 140 per regimen, provides > 85% power to show that the experimental regimen is superior to at least 1 of the reference regimens based on the following assumptions: 1) the proportion of subjects with HBV DNA < 50 IU/mL is 20% (at the Week 48 primary endpoint) for each of the reference regimens, ETV monotherapy and ADV+LVD combination therapy; and 2) the proportion of subjects with HBV DNA < 50 IU/mL is at least 35% (at the Week 48 primary endpoint) for the experimental regimen ETV+ADV. Under these assumptions, and within the Hochberg testing framework, a sample size of 420 randomized subjects provides approximately 80% power for each of the individual comparisons.

Methods: Continuous variables are summarized using the mean, median, standard error, standard deviation, minimum, and maximum values. Binary or discrete variables are summarized by counts and percents. Longitudinal analyses of efficacy and safety parameters use pre-defined visit week windows. Data are summarized at on-treatment visits Weeks 4, 12, 24, 36, 48, 60, 72, 84, and 96. Laboratory parameters are summarized using US standard values and units. Kaplan-Meier estimators are used for time to event analyses.

Comparisons of continuous efficacy variables used t-tests based on linear regression models with covariates for treatment group and corresponding baseline measurements. Comparisons of binary endpoints are based on the differences in proportions. Confidence intervals for the difference in proportions are based on the normal approximation to the binomial distribution, with pooled proportions used in the computation of the standard error of the difference. The only comparisons presented are ETV+ADV vs. ETV monotherapy and ETV+ADV vs. ADV+LVD for endpoints assessed at Week 48, and comparisons are further limited to ETV+ADV vs. ADV+LVD at Week 96 due to the addition of non-study TDF in some ETV subjects.

Subjects who had normal ALT (≤ 1.0 x ULN) at baseline or whose baseline (day 1) serologies had negative HBeAg results were excluded from the analyses for ALT normalization or HBeAg loss and seroconversion, respectively.

SAEs and deaths were reported for enrolled subjects. Primary safety analyses were based on all treated subjects, and are presented by treatment period (all on-treatment; and off-treatment). AEs were summarized by severity and relationship to study medication. Laboratory abnormalities were summarized by modified World Health Organization grades. Additional analyses for specific safety measures (deaths, AEs [Grade 2 - 4, related], AEs leading to discontinuation, and malignant neoplasms and select treatment emergent laboratory abnormalities) are presented for the on-treatment period through Week 100 only; these additional safety analyses are also provided for the 33 subjects randomized to ETV monotherapy who added non-study TDF after Week 48, but for the on treatment period subsequent to the addition of TDF only.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: A total of 629 subjects were enrolled, 416 were randomized, and 415 were treated (Table 1). Overall, 76% of subjects were enrolled from study sites in Korea. The number of subjects who discontinued study therapy was small and comparable across the groups.

Twenty-four subjects (6%) entered off-treatment follow up, and 14 completed off-treatment follow up (5 [4%], 7 [5%], and 2 [1%] in the ETV+ADV, ADV+LVD, and ETV groups, respectively). Thirty-three subject in the ETV monotherapy group added TDF at or after Week 48, as permitted by Amendment 06 to the protocol.

As shown in Table 2, baseline demographics and disease characteristics were comparable across all 3 groups. The mean age of the study population was 44 years, and the majority of subjects were male and Asian.

Table 1: Subject Disposition (Randomization to End of Treatment) - Randomized Subjects

Subject Disposition	Number of Subjects (%) Treatment Group ETV+ADV N=138	ETV* N=140	ADV+LVD N=138	TOTAL N=416
RANDOMIZED	138(100.0)	140(100.0)	138(100.0)	416(100.0)
NEVER TREATED	0	0	1 (0.7)	1 (0.2)
SUBJECT WITHDREW CONSENT	0	0	1 (0.7)	1 (0.2)
TREATED	138(100.0)	140(100.0)	137 (99.3)	415 (99.8)
DISCONTINUED PRIOR TO WEEK 48 VISIT	4 (2.9)	2 (1.4)	2 (1.4)	8 (1.9)
ADVERSE EVENT	1 (0.7)	1 (0.7)	1 (0.7)	3 (0.7)
DEATH	1 (0.7)	0	0	1 (0.2)
LOST TO FOLLOW-UP	1 (0.7)	0	0	1 (0.2)
OTHER	0	0	1 (0.7)	1 (0.2)
SUBJECT WITHDREW CONSENT	1 (0.7)	1 (0.7)	0	2 (0.5)
DISCONTINUED AT OR AFTER WEEK 48 THROUGH WEEK 96	3 (2.2)	9 (6.4)	6 (4.3)	18 (4.3)
ADVERSE EVENT	0	2 (1.4)	1 (0.7)	3 (0.7)
LACK OF EFFICACY	1 (0.7)	6 (4.3)	0	7 (1.7)
LOST TO FOLLOW-UP	1 (0.7)	0	3 (2.2)	4 (1.0)
OTHER	0	0	1 (0.7)	1 (0.2)
SUBJECT WITHDREW CONSENT	1 (0.7)	1 (0.7)	1 (0.7)	3 (0.7)
COMPLETED TREATMENT	131 (94.9)	129 (92.1)	129 (93.5)	389 (93.5)

*=33 subjects added TDF after Week 48.
LIBRARY: S:\RHO\BMS\Entecavir\Studies\AI463-111\data EXTRACT DATE: 27-JUL-2012
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Table 2: Key Demographics and Baseline HBV Disease Characteristics - Treated Subjects

Characteristics	Treatment Group ETV+ADV N=138	ETV* N=140	ADV+LVD N=137	TOTAL N=415
Age (years)				
N	138	140	137	415
MEAN (SE)	45.3 (0.97)	43.5 (0.92)	43.7 (1.08)	44.1 (0.57)
MEDIAN	46.0	43.5	43.0	45.0
MIN, MAX	18, 69	19, 71	16, 74	16, 74
Sex - N (%)				
MALE	91 (65.9)	88 (62.9)	97 (70.8)	276 (66.5)
FEMALE	47 (34.1)	52 (37.1)	40 (29.2)	139 (33.5)
Region - N (%)				
ASIA	130 (94.2)	131 (93.6)	126 (92.0)	387 (93.3)
EUROPE	7 (5.1)	9 (6.4)	11 (8.0)	27 (6.5)
NORTH AMERICA	1 (0.7)	0	0	1 (0.2)
HBV DNA by PCR (log10 IU/mL)				
MEAN (SE)	7.4 (0.08)	7.4 (0.09)	7.5 (0.09)	7.4 (0.05)
MEDIAN	7.6	7.5	7.6	7.6
IN, MAX	4.2, 9.5	3.0, 9.7	3.2, 10.0	3.0, 10.0
Hep B E Antigen				
POSITIVE	138 (100.0)	139 (99.3)	135 (98.5)	412 (99.3)
NEGATIVE	0	1 (0.7)	2 (1.5)	3 (0.7)
Hep B E Antibody				
POSITIVE	0	1 (0.7)	2 (1.5)	3 (0.7)
NEGATIVE	138 (100.0)	139 (99.3)	135 (98.5)	412 (99.3)
ALT (U/L)				
MEAN (SE)	71 (6.3)	69 (5.1)	78 (11.5)	72 (4.6)
MEDIAN	49	50	45	47
MIN, MAX	10, 480	12, 367	14, 1300	10, 1300

Table 2: Key Demographics and Baseline HBV Disease Characteristics - Treated Subjects

Characteristics	Treatment Group ETV+ADV N=138	ETV* N=140	ADV+LVD N=137	TOTAL N=415
LVD-R Substitution** - N (%)				
PRESENT	136 (98.6)	137 (97.9)	134 (97.8)	407 (98.1)
ABSENT	2 (1.4)	3 (2.1)	3 (2.2)	8 (1.9)
HBV Subtype				
A	6 (4.3)	10 (7.1)	11 (8.0)	27 (6.5)
B	3 (2.2)	7 (5.0)	6 (4.4)	16 (3.9)
C	124 (89.9)	119 (85.0)	113 (82.5)	356 (85.8)
D	3 (2.2)	3 (2.1)	5 (3.6)	11 (2.7)
H	1 (0.7)	1 (0.7)	0	2 (0.5)
MISSING	1 (0.7)	0	2 (1.5)	3 (0.7)

*= 33 subjects added TDF after Week 48.
** LVD resistance substitution at reverse transcripton codon 204 (M240V/I/S) by INNOLiPA HBV DR line-probe assay.

Efficacy Results: Primary Endpoint - At Week 48, the proportions of subjects who achieved HBV DNA < 50 IU/mL (non-completer = failure [NC = F]) were 25% (35/138), 20% (27/137), and 16% (23/140) in the ETV+ADV, ADV+LVD, and ETV monotherapy groups, respectively. The difference estimates did not meet statistical significance when comparing either ETV+ADV vs LVD+ADV combination therapies (p = 0.2619), or ETV+ADV combination therapy vs ETV monotherapy (p = 0.1336) (primary endpoint in Table 3).

Other key secondary endpoints at Week 48 had the following results for the ETV+ADV, ADV+LVD, and ETV monotherapy groups, respectively: mean change from baseline in HBV DNA by PCR of -4.65, -4.11, and -3.35 $\log_{10}$ IU/mL, respectively; ALT normalization for those with ALT > ULN at baseline of 76% (59/78), 77% (53/69), and 78% (64/82), respectively; HBeAg loss of 7% (10/138), 6% (8/135), and 7% (9/139), respectively; and HBeAg seronconversion of 5% (7/138), 4% (5/135), and 3% (4/139), respectively. At Week 48, 1 subject in the ADV+LVD group achieved HBeAg loss without seroconversion and 1 subject in the ETV+ADV group had full HBeAg seroconversion (HBeAg loss and acquisition of HBeAb).

At Week 96, the ETV+ADV combination regimen had superior virologic efficacy compared with the ADV+LVD combination regimen, with HBV DNA < 50 IU/mL (NC = F) in 44% (60/138) vs 29% (39/137) (p = 0.0095) of subjects, respectively, and in 39% (55/140) of the ETV group.

Results for the secondary efficacy endpoints at Week 96 were as follows for the 2 comparative groups ETV+ADV and ADV+LVD combination therapies, respectively: the mean reductions from baseline in HBV DNA were -5.06 and -4.49 $\log_{10}$ IU/mL, respectively (-4.17 $\log_{10}$ IU/mL for ETV); ALT normalization occurred in 77% and 80%, respectively (75% for ETV); HBeAg loss occurred in 12% (17/138) and 14% (19/137), respectively (11% or 15/140 in ETV); and HBeAg seroconversion in 7% (10/138) and 5% (7/137), respectively (4% or 5/140 for ETV). No subjects had HBsAg loss or -seroconversion in the NC = F analysis. Overall, 2 subjects (AI463111-108-38195 and AI463111-140-38508 in the ETV+ADV and ADV+LVD combination therapy groups, respectively) achieved HBsAg loss at Week 48. One of the 2 subjects achieved HBsAg seroconversion at that time point. Both subjects were HBsAg positive and HBsAb negative on Week 96 analysis.

The Year 1 cumulative probabilities of emergent resistance (assessed by new, on-treatment substitutions to either ETV or ADV) were 0.8%, 2.3%, and 3.8% for the ETV+ADV, ADV+LVD, and the ETV monotherapy groups, respectively. The Year 2 cumulative probabilities of emergent resistance to either ETV or ADV/TDF were 1.5%, 3.8%, and 10.7% for the ETV+ADV, ADV+LVD, and ETV groups, respectively. In Year 2, there were no identified cases of treatment-emergent resistance among the subset of 33 subjects in the ETV monotherapy group that had added TDF at Week 48.

Table 3: Efficacy Endpoints at Week 96 (Non-completer = Failure) - Treated Subjects

Efficacy Parameter (No. with Response/ No. Evaluable)	ETV+ADV (N = 138)	ETV[a] (N = 140)	ADV+LVD (N = 137)	Difference Estimate (95% CI) (ETV+ADV vs ADV+LVD)
Primary Endpoint at Week 48:				
HBV DNA by PCR < 50 IU/mL	35/138 (25.4%)	23/140 (16.4%)	27/137 (19.7%)	5.7 (-4.2, 15.5)[b] p = 0.2619
Secondary Endpoints at Week 96:				
HBV DNA by PCR < 50 IU/mL	60/138 (43.5%)	55/140 (39.3%)	39/137 (28.5%)	15.0 (3.7, 26.4) p = 0.0095
HBV DNA by PCR < LOQ (29 IU/mL)	53/138 (38.4%)	51/140 (36.4%)	35/137 (25.5%)	12.9 (1.8, 23.9)
HBV DNA by PCR < LOD (10 IU/mL)	46/138 (33.3%)	38/140 (27.1%)	28/137 (20.4%)	12.9 (2.4, 23.4)
HBV DNA by PCR Change from Baseline (log_{10} IU/mL)				
N	131	128	129	
Mean (SE)	-5.06 (0.090)	-4.17 (0.163)	-4.49 (0.116)	
SD	1.033	1.840	1.323	
Median	-5.07	-3.81	-4.43	
Min, Max	-7.52, -2.59	-8.22, -0.05	-7.71, -0.10	-0.59 (-0.912, -0.268)
ALT ≤ 1.0 x ULN[c]	60/78 (76.9%)	61/82 (74.4%)	55/69 (79.7%)	-2.8 (-16.2, 10.6)
HBeAg Loss[d]	17/138 (12.3%)	15/140 (10.7%)	19/137 (13.9%)	-1.5 (-9.5, 6.4)
HBeAg Seroconversion	10/138 (7.2%)	5/140 (3.6%)	7/137 (5.1%)	2.1 (-3.6, 7.8)
HBsAg Loss	0/138	0/140	0/137	N/A
HBsAg Seroconversion	0/138	0/140	0/137	N/A
Other Endpoints:				
HBV DNA by PCR < 1,000 IU/mL	92/138 (66.7%)	68/140 (48.6%)	64/137 (46.7%)	20.0 (8.2, 31.7)

[a] Thirty-three subjects added TDF after Week 48.

[b] Confidence interval and p-value adjusted according to Hochberg procedure.

[c] For subjects with ALT > 1 x ULN at baseline.

[d] For subjects who were HBeAg positive at baseline.

Safety Results: On-treatment AEs are summarized in Table 4. In general, the incidence of AEs, SAEs, and discontinuations of study therapy due to AEs was comparable in all 3 treatment groups. Two deaths were reported (both due to hepatocellular carcinoma - 1 subject in the ETV+ADV group subject and 1 subject in the ETV+TDF group). The incidence of related AEs was comparable in the 2 combination therapy groups, and numerically lower than the incidence in the ETV group, with the difference accounted for primarily by more related ALT elevations in ETV. In general, rates of laboratory abnormalities were comparable across groups.

Table 4: Adverse Events - Cumulative On Treatment

	No. of Subjects (%)		
MedDRA Preferred Term	**ETV+ADV N = 138**	**ETV[a] N = 140**	**ADV+LVD N = 137**
Deaths	1 (0.7)	1 (0.7)[b]	0
Serious Adverse Events	14 (10.1)	21 (15.0)	13 (9.5)
Discontinuations Due to Adverse Events	1 (0.7)	3 (2.1)	2 (0.5)
Any Adverse Event	105 (76.1)	112 (80.0)	100 (73.0)
Most Common Adverse Events (≥ 5% of Subjects)			
Upper Respiratory Tract Infection	23 (16.7)	28 (20.0)	19 (13.9)
Nasopharyngitis	17 (12.3)	17 (12.1)	8 (5.8)
Dyspepsia	10 (7.2)	6 (4.3)	8 (5.8)
Abdominal Discomfort	8 (5.8)	3 (2.1)	7 (5.1)
Alanine Aminotransferase Increased	8 (5.8)	8 (5.7)	5 (3.6)
Headache	8 (5.8)	5 (3.6)	13 (9.5)
Nausea	6 (4.3)	8 (5.7)	4 (2.9)
Abdominal Pain Upper	5 (3.6)	10 (7.1)	6 (4.4)
Aspartate Aminotransferase Increased	5 (3.6)	7 (5.0)	1 (0.7)
Fatigue	4 (2.9)	4 (2.9)	8 (5.8)
Cough	2 (1.4)	5 (3.6)	7 (5.1)
Hypertension	2 (1.4)	7 (5.0)	3 (2.2)
Hepatic Steatosis	4 (2.9)	8 (5.7)	9 (6.6)
Related Adverse Events	8 (5.8)	23 (16.4)	10 (7.3)
Grade 2 - 4 Related Adverse Events	2 (1.4)	12 (8.6)	2 (1.5)
Grade 3 - 4 Related Adverse Events	0	1 (0.7)	0

Table 4: Adverse Events - Cumulative On Treatment

MedDRA Preferred Term	No. of Subjects (%)		
	ETV+ADV N = 138	**ETV[a] N = 140**	**ADV+LVD N = 137**
Bone-related Adverse Events[c]	7 (5.1)	6 (4.3)	2 (1.5)
Malignancies[c]	5 (3.6)	6 (4.3)	2 (1.5)
ALT Flares On Treatment (ALT > 2 x baseline and > 10 x ULN)	3 (2.2)	2 (1.4)	2 (1.5)
Hepatic Disease Progression[c,d]	8 (5.8)	8 (5.7)	4 (2.9)

[a] Thirty-three subjects added tenofovir (TDF) after Week 48.
b The subject received ETV+TDF, and died on Day 865.

[c] Includes on treatment and post-dosing follow-up.
[d] Liver-related clinical manifestation of HBV disease progression.

CONCLUSIONS:

- Week 48 Efficacy:
  - For the primary assessment at Week 48, there was no statistically significant difference in the virologic efficacy of ETV+ADV as compared with either of the 2 reference groups (ADV+LVD or ETV monotherapy), as assessed by the proportions of subjects with HBV DNA < 50 IU/mL. The virolgic response rates ranged from 16% to 25% in this difficult-to-treat HBeAg-positive population with high HBV DNA and confirmed LVDr at baseline.
- In secondary virologic analyses, the overall distribution of HBV DNA was shifted lower in the ETV+ADV combination group relative to either of the other 2 treatment groups, suggesting that some benefit from this combination might be observed with longer treatment.
- Week 96 Efficacy:
  - At Week 96, the combination regimen of ETV+ADV demonstrated superior virologic efficacy relative to the ADV+LVD reference (absolute difference in rates of 15 percentage points, but both groups achieved virologic suppression in a minority of subjects.
  - Serologic response rates through Week 96 were low, likely reflecting the inherent immunologic characteristics of this heavily pre-treated population.
- Resistance: At Week 96, the 2 combination treatment groups had lower resistance rates than the ETV treatment group, with that difference considered clinically relevant.
- Safety: All 3 treatment regimens (ETV+ADV combination therapy, ADV+LVD combination therapy, and ETV were well tolerated and had comparable safety profiles through Week 96.

DATE OF REPORT: 14-Nov-2012