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

Final Clinical Study Report for Study AI463110

TITLE OF STUDY: A Comparative Study of Chronic Hepatitis B Subjects Treated with Entecavir Plus Tenofovir Combination Therapy vs Entecavir Monotherapy in Adults Who Are Treatment-naive to Nucleosides and Nucleotides: The BE-LOW Study

INVESTIGATORS/STUDY CENTERS: A total of 64 sites enrolled and randomized subjects

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 12-Apr-2007 **CLINICAL PHASE:** 3b

Study Completion Date: 11-Mar-2011

OBJECTIVES: Primary Objective: To compare the proportion of subjects in each 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 96 of treatment using the Roche COBAS® TaqMan HBV Test for use with the High Pure System (HPS) assay.

Secondary Objectives: To compare the entecavir plus tenofovir (ETV+TDF) combination treatment group with the ETV monotherapy treatment group for the following:

- Proportion of hepatitis B e antigen (HBeAg)-positive subjects who achieved HBV DNA < 50 IU/mL (approximately 300 copies/mL) by PCR at Weeks 48 and 96 using the Roche COBAS TaqMan - HPS assay
- Proportion of HBeAg-negative subjects who achieved HBV DNA < 50 IU/mL (approximately 300 copies/mL) by PCR at Weeks 48 and 96 using the Roche COBAS TaqMan - HPS assay
- Proportion of subjects who achieved HBV DNA < 50 IU/mL (approximately 300 copies/mL) by PCR at Week 48 using the Roche COBAS TaqMan - HPS assay
- Proportion of subjects who achieved HBV DNA < the lower limit of quantitation (LOQ) for the Roche COBAS TaqMan - HPS assay at Weeks 48 and 96 (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 at Weeks 48 and 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 Weeks 48 and 96 using the Roche COBAS TaqMan - HPS assay
- Mean $\log_{10}$ reduction from baseline in HBV DNA by PCR at Weeks 48 and 96 using the Roche COBAS TaqMan - HPS assay

- Proportion of subjects with alanine aminotransferase (ALT) normalization (≤ 1 x upper limit of normal [ULN]) at Weeks 48 and 96
- Proportion of subjects (who were HBeAg-positive at baseline) with loss of HBeAg at Weeks 48 and 96
- Proportion of subjects (who were HBeAg-positive at baseline) with HBe seroconversion (HBeAg loss and presence of hepatitis B e antibody [HBeAb]) at Weeks 48 and 96
- Proportion of subjects with hepatitis B surface antigen (HBsAg) loss and HBsAg serconversion at Weeks 48 and 96
- 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 through Weeks 48 and 96.

METHODOLOGY: This was a 2-arm, randomized, open-label, multicenter study of ETV 0.5 mg plus TDF 300 mg combination therapy given once daily (QD) compared with ETV 0.5 mg monotherapy given QD for 100 weeks in nucleos[t]ide-naive subjects stratified by HBeAg status.

NUMBER OF SUBJECTS (Planned and Analyzed): A total of 384 subjects were planned, 669 were enrolled, and 384 were randomized.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Nucleos[t]ide-naïve subjects with chronic hepatitis B (CHB) infection and compensated liver function.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: ETV 0.5 mg plus TDF 300 mg QD orally. ETV batch nos. 6M15548, 7A30965, 7K24890, 7K24891, 8C37014, 8F36070, 8G40875, 9C4709C, 9D50760, and 9J56930. TDF batch nos. 6K14676, 6M09486, A117179A, A471671D, FBK363, FDJ020A, and FDJ028D.

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: ETV 0.5 mg orally (see batch nos. above).

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 96. Secondary endpoints included the following at Weeks 48 and 96: (1) proportion of subjects who achieve HBV DNA < 50 IU/mL (approximately 300 copies/mL) by PCR; (2) proportion of subjects who achieved HBV DNA < LOQ (LOQ = 29 IU/mL [approximately 169 copies/mL]); (3) proportion of subjects who achieved HBV DNA < LOD (LOD = 10 IU/mL [approximately 58 copies/mL]); (4) proportion of subjects with HBV DNA in relevant categories; (5) mean $\log_{10}$ reduction from baseline in HBV DNA by PCR; (6) proportion of subjects with ALT normalization (≤ 1 x ULN); and (7) proportion of subjects (who were HBeAg positive at baseline) with loss of HBeAg or with HBeAg seroconversion (HBeAg loss and presence of HBeAb).

Safety: Frequency of AEs, SAEs, and discontinuations of study drug due to AEs or laboratory abnormalities.

STATISTICAL CONSIDERATIONS: General: 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. Windows around planned measurement times are constructed based on the midpoint between planned measurement visits unless specified otherwise. Data are summarized at each scheduled visit through the analysis week. Laboratory parameters are summarized using US standard values and units.

Efficacy: HBV DNA by PCR measured using the Roche COBAS TaqMan - HPS assay is reported in IU/mL, with LOQ = 29 IU/mL and LOD = 10 IU/mL. The HBV DNA measurements are transformed to the log10 scale when analyzed as a continuous variable.

Analyses of binary efficacy endpoints during the on-treatment period focused on treated subjects and utilized the analysis of non-completer = failure (NC = F). All treated subjects were included in the denominator, and subjects with missing measurements were counted as non-responders for the specific endpoints. Sensitivity analyses for the primary and secondary efficacy endpoints (HBV DNA < 50 IU/mL by PCR, HBeAg loss and seroconversion, HBsAg loss and seroconversion, and ALT ≤ 1 x ULN) at Weeks 48 and 96 were also conducted on complete cases using the non-completer = missing (NC = M) approach. Sensitivity analyses for the primary and secondary endpoints of HBV DNA < 50 IU/mL by PCR at Week 96 (overall and by HBeAg subgroup) were also conducted on subjects satisfying the per protocol criteria.

Efficacy analyses were stratified by HBeAg status, except when analyses were within HBeAg subgroups. Efficacy results are presented by HBeAg subgroup and overall. Longitudinal presentations include measurements at scheduled on-treatment visit Weeks 4, 12, 24, 36, 48, 60, 72, 84, and 96.

Comparisons of continuous variables used t-tests based on linear regression models with covariates for treatment group and corresponding baseline measurement. Treatment comparisons of binary endpoints were based on the differences between ETV+TDF and ETV, and the 2-sided p-value is presented. The p-value for the comparison within the HBeAg-positive subgroup was based on the 1 degree of freedom chi-square test, while that for the overall (stratified) comparison was based on the Cochran-Mantel-Haenszel (CMH) statistic stratified by HBeAg status.

Confidence intervals (CIs) for the difference in proportions were based on the normal approximation to the binomial distribution, with pooled proportions used in the computation of the standard error of the difference for the stratified analysis.

Safety: Safety analyses include deaths, SAEs, AEs, or events of HBV disease progression, clinical laboratory abnormalities, and special considerations related to safety. Safety data are reported for treated subjects during on-treatment and off-treatment follow-up periods. Subjects in follow up beyond 24 weeks after the end of dosing are included in the safety presentations.

For the on-treatment period, AEs, SAEs, and treatment-emergent laboratory abnormalities, liver function elevation from baseline, and creatinine confirmed increases from baseline are presented cumulatively and also by Year 1 and Year 2.

Deaths and SAEs are reported for enrolled subjects without regard to study periods.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: Disposition data are presented in Table 1 (randomization to end of treatment) and Table 2 (end of dosing to end of study).

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

Subject Disposition	Number of Subjects (%) Treatment Group ETV N=186	ETV+TDF N=198	TOTAL N=384
TREATED	182 (97.8)	197 (99.5)	379 (98.7)
DISCONTINUED PRIOR TO WEEK 48 VISIT	6 (3.2)	12 (6.1)	18 (4.7)
ADVERSE EVENT	1 (0.5)	2 (1.0)	3 (0.8)
LOST TO FOLLOW-UP	5 (2.7)	2 (1.0)	7 (1.8)
OTHER	0	1 (0.5)	1 (0.3)
POOR/NON-COMPLIANCE	0	3 (1.5)	3 (0.8)
PREGNANCY	0	2 (1.0)	2 (0.5)
SUBJECT WITHDREW CONSENT	0	2 (1.0)	2 (0.5)
DISCONTINUED AT OR AFTER WEEK 48 VISIT PRIOR TO WEEK 96	6 (3.2)	11 (5.6)	17 (4.4)
ADVERSE EVENT	1 (0.5)	2 (1.0)	3 (0.8)
DEATH	0	1 (0.5)	1 (0.3)
LACK OF EFFICACY	1 (0.5)	0	1 (0.3)
LOST TO FOLLOW-UP	2 (1.1)	4 (2.0)	6 (1.6)
OTHER	2 (1.1)	0	2 (0.5)
POOR/NON-COMPLIANCE	0	1 (0.5)	1 (0.3)
PREGNANCY	0	2 (1.0)	2 (0.5)
SUBJECT WITHDREW CONSENT	0	1 (0.5)	1 (0.3)
COMPLETED TREATMENT	170 (91.4)	174 (87.9)	344 (89.6)

Table 2: Subject Disposition (End of Dosing to End of Study) - Treated Subjects

Subject Disposition	Number of Subjects (%) Treatment Group ETV N=182	ETV+TDF N=197	TOTAL N=379
ENTERED OFF-TREATMENT FOLLOW-UP	31 (17.0)	32 (16.2)	63 (16.6)
DID NOT ENTER OFF-TREATMENT FOLLOW-UP	151 (83.0)	165 (83.8)	316 (83.4)
DID NOT COMPLETE THE STUDY (OFF-TREATMENT FOLLOW-UP)	11 (6.0)	17 (8.6)	28 (7.4)
ADVERSE EVENT	1 (0.5)	1 (0.5)	2 (0.5)
DEATH	0	1 (0.5)	1 (0.3)
FOLLOWUP NO LONGER REQUIRED PER PROTOCOL	7 (3.8)	6 (3.0)	13 (3.4)
LOST TO FOLLOW-UP	2 (1.1)	6 (3.0)	8 (2.1)
OTHER	0	1 (0.5)	1 (0.3)
PREGNANCY	0	2 (1.0)	2 (0.5)
SUBJECT WITHDREW CONSENT	1 (0.5)	0	1 (0.3)
COMPLETED THE STUDY	20 (11.0)	15 (7.6)	35 (9.2)

Table 3 summarizes baseline demographics and HBV disease characteristics. Subjects in both the ETV monotherapy group and the ETV+TDF combination therapy group had comparable demographic characteristics. The overall mean age was 40 years (range: 17 - 76 years), and the majority of subject were male and Asian or White.

HBV disease characteristics at baseline were comparable between treatment groups, except for ALT; mean ALT for the ETV group was 127 U/L vs. 158 U/L for the ETV+TDF group. The overall mean HBV DNA by PCR was 7.5 $\log_{10}$ IU/mL. Approximately 70% of subjects were HBeAg positive.

Table 3: Demographics and Baseline HBV Disease Characteristics - Treated Subjects

MedDRA Preferred Term	ETV N = 182	ETV+TDF N = 197	Total N = 379
Age (years)			
Mean (SE)	40.2 (1.08)	39.0 (1.01)	39.5 (0.74)
Min, Max	17, 72	17, 76	17, 76
Sex - N (%)			
Male	116 (63.7)	146 (74.1)	262 (69.1)
Female	66 (36.3)	51 (25.9)	117 (30.9)
Race, N (%)			
Asian	84 (46.2)	102 (51.8)	186 (49.1)
Black/African American	10 (5.5)	4 (2.0)	14 (3.7)
Native Hawaiian/Other Pacific Islander	1 (0.5)	1 (0.5)	2 (0.5)
White	83 (45.6)	87 (44.2)	170 (44.9)
Other	4 (2.2)	3 (1.5)	7 (1.8)
HBV DNA by PCR ($\log_{10}$ IU/mL)			
Mean (SE)	7.5 (0.11)	7.5 (0.10)	7.5 (0.07)
Median	7.8	7.7	7.8
Min, Max	3.6, 10.0	2.8, 10.2	2.8, 10.2
Hepatitis B Surface Antigen, N (%)			
Positive	182 (100)	196 (99.5)	378 (99.7)
Negative	0	1 (0.5)	1 (0.3)
Hepatitis B e Antigen, N (%)			
Positive	126 (69.2)	138 (70.1)	264 (69.7)
Negative	56 (30.8)	59 (29.9)	115 (30.3)

Table 3: Demographics and Baseline HBV Disease Characteristics - Treated Subjects

MedDRA Preferred Term	ETV N = 182	ETV+TDF N = 197	Total N = 379
Alanine Aminotransferase (U/L)			
Mean (SE)	127 (7.3)	158 (13.1)	143 (7.7)
Median	99	100	99
Min, Max	8, 642	33, 1583	8, 1583

Efficacy Results: Primary Efficacy Endpoint: At Week 96, in a mixed population (70% HBeAg positive) of nucleos[t]ide-naive CHB subjects, results showed comparable response between the groups (ETV = 139/182 subjects [76%] vs. ETV+TDF= 164/197 subjects [83%]). The treatment difference was 6.9% (95% CI: -1.0, 14.9), with a 2-sided p-value = 0.0882. Results at Week 48 showed a 10% treatment difference estimate, with 70% of subjects in the ETV group and 80% of subjects in the ETV+TDF group achieving HBV DNA < 50 IU/mL.. The stratified analysis was based on the CMH weighted statistical analysis stratified by HBeAg status (Table 3).

Secondary Efficacy Endpoints: Key virologic endpoints are summarized in Table 4 and serologic endpoints are summarized in Table 5. HBV DNA by PCR < 50 IU/mL in treated HBeAg-positive subjects is summarized in Table 6. No emergent resistance to ETV or TDF was detected.

Table 4: Primary and Key Secondary Virologic Endpoints at Weeks 48 and 96 (NC = F) - Treated Subjects

	ETV N = 182	ETV+TDF N = 197	Difference Estimate (95% CI)	ETV N = 182	ETV+TDF N = 197	Difference Estimate (95% CI)
Endpoint		**Week 48**			**Week 96**	
Primary Population Results						
HBV DNA < 50 IU/mL	128/182 (70.3)	158/197 (80.2)	9.9 (1.5, 18.4)	139/182 (76.4)	164/197 (83.2)	6.9 (-1.0, 14.9) p-value = 0.0882
HBV DNA by PCR Change from Baseline (log_{10} IU/mL)						
N	176	180		165	170	
Mean (SE)	-5.57 (0.101)	-5.99 (0.099)	-0.34 (-0.464, -0.212)	-5.77 (0.107)	-5.96 (0.115)	-0.17 (-0.289, -0.056)
SD	1.341	1.333		1.376	1.495	
Median	-5.66	-6.23		-5.86	-6.22	
Min, Max	-8.29, -1.82	-8.19, -1.35		-8.29, -2.15	-8.72, -1.35	
ALT ≤ 1.0 x ULN	151/182 (83.0)	143/197 (72.6)	-10.4 (-18.8, -2.0)	149/182 (81.9)	136/197 (68.0)	-12.8 (-21.5, -4.1)
Key Secondary Population Results by HBeAg Status						
HBeAg +	**N = 126**	**N = 138**		**N = 126**	**N = 138**	
HBV DNA < 50 IU/mL	77/126 (61.1)	103/138 (74.6)	13.5 (2.3, 24.8)	88/126 (69.8)	111/138 (80.4)	10.6 (0.2, 21.0) p-value = 0.0460
ALT ≤ 1.0 x ULN	102/126 (81.0)	97/138 (70.3)		103/126 (81.7)	89/138 (64.5)	
HBeAg Seroconversion	32/126 (25.4)	27/138 (19.6)		49/126 (38.9)	41/138 (29.7)	

Table 4: Primary and Key Secondary Virologic Endpoints at Weeks 48 and 96 (NC = F) - Treated Subjects

	ETV N = 182	ETV+TDF N = 197	Difference Estimate (95% CI)	ETV N = 182	ETV+TDF N = 197	Difference Estimate (95% CI)
Endpoint		**Week 48**			**Week 96**	
HBeAg -	**N = 56**	**N = 59**		**N = 56**	**N = 59**	
HBV DNA < 50 IU/mL	51/56 (91.1)	55/59 (93.2)	2.2 (-7.7, 12.0)	51/56 (91.1)	53/59 (89.8)	-1.2 (-12.0, 9.5)
ALT ≤ 1.0 x ULN	49/56 (87.5)	46/59 (78.0)		46/56 (82.1)	47/59 (79.7)	

Table 5: Serology Endpoints at Weeks 48 and 96 (NC = F) - Treated Subjects

Endpoint	No. HBeAg + Subjects with Response / No. Evaluable (%)	
	ETV N = 182	ETV+TDF N = 197
HBeAg Loss		
Week 48	32/126 (25.4)	27/138 (19.6)
Week 96	50/126 (39.7)	41/138 (29.7)
HBeAg Seroconversion		
Week 48	28/126 (22.2)	25/138 (18.1)
Week 96	41/126 (32.5)	30/138 (21.7)
HBsAg Loss		
Week 48	4/126 (3.2)	2/138 (1.4)
Week 96	5/126 (4.0)	7/138 (5.1)
HBsAg Seroconversion		
Week 48	1/126 (0.8)	1/138 (0.7)
Week 96	2/126 (1.6)	4/138 (2.9)

Table 6: HBV DNA by PCR < 50 IU/mL and Baseline HBV DNA at Weeks 48 and 96 (NC = F) - Treated HBeAg-positive Subjects

HBV DNA at Baseline	Time Point	HBV DNA < 50 IU/mL		
		No. with Response/No. Evaluable (%)		
		ETV N = 126	ETV+TDF N = 138	Difference Estimate (95% CI)
$< 10^8$ IU/mL	Week 48	37/47 (78.7)	43/53 (81.1)	2.4 (-13.3, 18.1)
	Week 98	39/47 (83.0)	44/53 (83.0)	0.0 (-14.7, 14.8)
$\geq 10^8$ IU/mL	Week 48	40/79 (50.6)	60/85 (70.6)	20.0 (5.0, 34.9)
	Week 98	49/79 (62.0)	67/85 (78.8)	16.8 (2.9, 30.7)

Note: If a subject is missing the efficacy assessments for a visit, this is considered a failure and is counted as evaluable.

Safety Results: The safety results reported are summarized in Table 7. Overall, the incidence of AEs, SAEs, and discontinuations of study therapy due to AEs was comparable across the 2 treatment groups.

The 3 deaths reported in the study were all in the ETV+TDF group; 2 deaths had liver-related etiology and 1 subject died from a possible myocardial infarction. There were 4 malignancies in the ETV group (3

hepatocellular carcinoma and 1 gastric cancer in a subject with a prior history of gastric carcinoma in situ) and 1 subject in the ETV+TDF group had breast cancer. ALT flares and events of HBV progression occurred in low numbers and were comparable across treatment groups. Four bone fractures occurred in the study; however, only 1 was considered possibly related to the study drug.

The number of subjects with confirmed creatinine change of > 0.3/0.5 mg/mL from baseline was comparable across the 2 groups, did not require dose adjustments, and subsequently resolved by the time of the subjects' last visits. Tubular reabsorption of phosphate at Week 100 was comparable in both treatment groups in a subset of subjects who were able to participate in Amendment 5 of the protocol.

During the off-treatment follow up, no ALT flares were observed, and 1 subject in the ETV group developed diabetic complications. The incidence of laboratory abnormalities was low and comparable across the 2 treatment groups.

Table 7: Overall Safety - On Treatment and Post-dosing

MedDRA Preferred Term	No. of Subjects (%) ETV N = 182	ETV+TDF N = 197
Deaths	0	3 (1.5)
Serious Adverse Events		
On Treatment	12 (6.6)	14 (7.1)
Off Treatment	1/31 (3.2)	0
Discontinuations Due to Adverse Events (On Treatment)	2 (1.1)	5 (2.5)
Any Adverse Event (On Treatment)	132 (72.5)	131 (66.5)
Most Common Adverse Events (≥ 5% of Subjects)		
Abdominal Pain Upper	13 (7.1)	8 (4.1)
Headache	19 (10.4)	22 (11.2)
Diarrhea	11 (6.0)	13 (6.6)
Fatigue	11 (6.0)	12 (6.1)
Nasopharyngitis	11 (6.0)	18 (9.1)
Cough	7 (3.8)	13 (6.6)
Nausea	7 (3.8)	19 (9.6)
Related Adverse Events	39 (21.4)	49 (24.9)
Grade 3-4 Adverse Events	13 (7.1)	11 (5.6)
Malignancies[1]	4 (2.2)	1 (0.5)
ALT Flares (ALT > 2 x baseline and > 10 x ULN)		
On Treatment	1 (0.5)	2 (1.0)
Off Treatment	0	0
Hepatic Disease Progression[2]	2 (1.1)	1 (0.5)
Serum Creatinine ≥ 0.5 mg/mL from Baseline		
On Treatment	3(1.6)	0
Off Treatment	0	0

[1] On treatment and post-dosing follow up.

[2] Liver-related clinical manifestation of HBV disease progression. No events were reported during post-dosing follow up.

CONCLUSIONS:

- At Week 96, the antiviral efficacy of the combination of ETV+TDF is comparable to that of ETV monotherapy in a mixed population (70% HBeAg positive) of nucleoside-naive CHB subjects.
- In HBeAg-positive nucleoside-naive CHB subjects with high viral load at baseline (HBV DNA $> 10^8$ IU/mL), the combination of 2 highly potent anti-HBV nucleos[t]ide analogs (ETV+TDF) may provide incremental virologic benefit over ETV monotherapy.
- In this study population, the virologic benefit for the combination group was associated with meaningfully lower ALT and HBe-serologic benefits at Week 96; the inconsistency across endpoints raises uncertainty about the reproducibility of the results, and suggests there could be something anomalous about this particular dataset.
- With respect to safety, both regimens (ETV and ETV+TDF) were well tolerated and had comparable safety profiles.

DATE OF REPORT: 14-Nov-2012