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 AI463109

TITLE OF STUDY: Study of the Antiviral Activity of Entecavir in Patients Receiving Liver Transplant Due to Chronic Hepatitis B Virus Infection

INVESTIGATORS/STUDY CENTERS: Twenty-seven sites enrolled and treated subjects (US - 8, Brazil, France, Italy, and Korea - 3 each, Australia, Spain, and Taiwan- 2 each, and Argentina - 1)

PUBLICATIONS: None

STUDY PERIOD: Study Initiation Date: 03-Apr-2007 **CLINICAL PHASE:** 3b

Study Completion Date: 10-Mar-2011

OBJECTIVES: The primary objective was to determine the proportion of patients who experienced virological recurrence of hepatitis B virus (HBV) at 72 weeks post-orthotopic liver transplantation (OLT) as measured by HBV deoxyribonucleic acid (DNA) by polymerase chain reaction (PCR) ≥ 50 IU/mL (approximately ≥ 300 copies/mL).

Key secondary objectives include the following:

- Loss of hepatitis B e antigen (HBeAg) and HBe seroconversion for baseline HBeAg-positive subjects was to be assessed as counts and proportions
- Loss of hepatitis B surface antigen (HBsAg) and HBs seroconversion at 72 weeks post-OLT was to be assessed as counts and proportions.
- Safety, as measured by the incidence of adverse events (AEs), key clinical laboratory abnormalities, and discontinuation due to AEs.

METHODOLOGY: This was a single-arm, non-randomized study to evaluate entecavir (ETV) in subjects receiving liver transplants due to chronic HBV (CHB) infection with HBV DNA < 172 IU/mL (approximately < 1,000 copies/mL)] at the time of transplant. Subjects were to start ETV on the day of OLT and continue for 72 weeks. At the Week 72 visit (end of study dosing), further treatment with commercially available anti-HBV therapies (which may have included marketed ETV) was at the discretion of the investigator, and could have included provision of ETV through the Bristol-Myers Squibb Company Post-Study Drug Progam for those subjects who met eligibility criteria.

This study was designed to assess the use of ETV in the setting of current standard-of-care post-transplant management. It was not designed to assess whether ETV monotherapy could replace the combination of hepatitis B immune globulin (HBIg) plus a nucleoside/tide antiviral.

NUMBER OF SUBJECTS (Planned and Analyzed): Planned: 70; treated and analyzed: 65.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION: Male and female adults (≥ 16 years of age) receiving OLT due to end-stage liver disease due to CHB with HBV DNA < 172 IU/mL (approximately < 1000 copies/mL) at the time of liver transplant. Subjects were to have HBV DNA < 172 IU/mL (approximately < 1,000 copies/mL) by PCR prior to OLT. Among these subjects, at least 50 were to have HBV DNA by PCR of < 50 IU/mL (approximately 300 copies/mL) at the time of OLT and no more than 20 subjects were to have HBV DNA by PCR of ≥ 50 IU/mL and < 172 IU/mL (approximately 300 copies/mL and 1000 copies/mL) at the time of OLT.

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: ETV 1 mg/day orally for 72 weeks. ETV 0.5 mg tablet (batch nos. 6C19110, 7K27641, 7K27643, 6L12151, 6L19208, 8B41858, 8D35491, 8G41163, 9C55583), ETV 1.0 mg tablet (batch nos. 0A58914, 7B26016, 7B26025, 6C19113, 6C19114, 6G19493, 8A41608, 8D35489, 8D35492, 8H37668, 9B47708, 9B47709, 9D54826, 9J56965), and ETV 0.05 mg/mL oral solution (batch no. 7C32615).

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, DURATION OF TREATMENT, BATCH NUMBERS: Not applicable

CRITERIA FOR EVALUATION:

Efficacy: Primary endpoint: The proportion of subjects who experienced virological recurrence of HBV DNA at 72 weeks post-OLT.

Secondary endpoints assessed at 72 weeks post-OLT were loss of HBeAg and HBe seroconversion for baseline HBeAg-positive subjects, loss of HBsAg, HBs seroconversion, and HBsAg recurrence for subjects who had experienced loss of HBsAg on treatment, and distribution of alanine aminotransferase (ALT) levels.

Safety: Safety endpoints were the number and percentage of subjects with AEs, serious adverse events (SAEs), key clinical laboratory abnormalities, and discontinuations due to AEs.

STATISTICAL CONSIDERATIONS: Sample size: The primary endpoint was the proportion of subjects who experienced virological recurrence of HBV DNA by PCR assay ≥ 50 IU/mL (approximately ≥ 300 copies/mL) at 72 weeks post-OLT. Approximately 70 enrolled and treated subjects would have resulted in 60 subjects remaining on therapy after 1 month of transplant. With the 60 evaluable subjects, it could be stated with 95% confidence that the virological recurrence rate for the treatment of ETV was < 20%, if there were ≤ 5 subjects with virological recurrence at 72 weeks post-OLT.

Method: The principal analyses of binary efficacy endpoints during the on-treatment period were based on evaluable subjects (ie, evaluable subjects included treated subjects who received at least 1 month of ETV therapy), and utilized the analysis of last observation carried forward (LOCF) for subjects with no measurement in the specified visit window. Supportive analyses for binary efficacy endpoints of HBV DNA ≥ 50 IU/mL, HBeAg loss and seroconversion, HBsAg loss, HBs seroconversion, and HBsAg recurrence at Week 72 based on treated subjects were also performed using the method of noncompleter = missing, where subjects who discontinued early or were missing the measurement were excluded from the specific analysis. The distribution of ALT levels as a continuous variable was summarized.

The distribution of total bilirubin and PT was summarized. The numbers of rejection episodes and re-transplants were reported. The numbers and proportions of subjects with AEs, laboratory abnormalities, and discontinuation due to AEs were tabulated.

SUMMARY OF RESULTS:

Disposition and Baseline/Demographic Characteristics: Subject disposition on treatment is summarized in Table 1. Ten of 65 subjects treated discontinued prior to the Week 72 visit. Four subjects discontinued with < 1 month of ETV treatment (2 deaths - 1 subject who required retransplantion was discontinued by the investigator who had not realized that the subject could have continued in the study and 1 subject no longer met study criteria. This subject was enrolled and treated, but was discontinued for not meeting HBV viral load inclusion criteria). Of the remaining 6 subjects who received ETV treatment for ≥ 4 weeks, 3 discontinued early due to death, 2 for non-compliance, and 1 for other reasons. Fifty-five subjects (85%) completed the study.

The mean age of the study population was 49 years, and the majority of subjects were male. The majority of subjects were either White (39%) or Asian (37%). The majority of subjects were HBeAg negative; only 7 subjects had HBeAg-positive disease. Demographics and HBV baseline disease characteristics are summarized in Table 2.

The majority of subjects received grafts from cadaveric donors, and cold ischemia time was < 20 hours for a majority of these grafts. Of the 26 subjects with evidence of tumors in the removed liver, 24 were HCC, 1 was a dysplastic nodule, and 1 was a focal lesion; 19 of these subjects had HCC reported in the past medical history. Source of donor liver, cold ischemia time, and the presence of HCC are predictive factors for the success of OLT.

Table 1: Subject Disposition (Treatment to End of Study Therapy) - Treated Subjects

	Number of Subjects (%)
	Treatment Group
Subject Disposition	ETV N=65
TREATED	65(100.0)
DISCONTINUED PRIOR TO WEEK 72 VISIT	10 (15.4)
DEATH	4 (6.2)
OTHER	2 (3.1)
POOR/NON-COMPLIANCE	2 (3.1)
SUBJECT NO LONGER MEETS STUDY CRITERIA	2 (3.1)
DISCONTINUED AT OR AFTER WEEK 72 VISIT	0
COMPLETED TREATMENT	55 (84.6)

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

Characteristics	Treatment Group ETV N=65
Age (years)	
N	65
MEAN (SE)	49.3 (1.32)
MEDIAN	51.0
MIN, MAX	23, 68
Sex - N (%)	
MALE	53 (81.5)
FEMALE	12 (18.5)
Race - N (%)	
ASIAN	24 (36.9)
BLACK/AFRICAN AMERICAN	7 (10.8)
NATIVE HAWAIIAN/OTHER PACIFIC ISLANDER	1 (1.5)
WHITE	25 (38.5)
OTHER	8 (12.3)
Region - N (%)	
ASIA	16 (24.6)
EUROPE	21 (32.3)
NORTH AMERICA	14 (21.5)
SOUTH AMERICA	14 (21.5)
HBV DNA by PCR (log10 IU/mL)	
N	65
MEAN (SE)	0.9 (0.06)
MEDIAN	0.8
Q1, Q3	0.8, 0.8
MIN, MAX	0.8, 3.7
Hep B E Antigen	
POSITIVE	7 (10.8)
NEGATIVE	58 (89.2)

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

Characteristics	Treatment Group ETV N=65
YMDD Mutation	
PRESENT	8 (12.3)
ABSENT	22 (33.8)
INSUFFICIENT HBV DNA	34 (52.3)
MISSING	1 (1.5)
Evidence of Tumors in Removed Liver	
YES	26 (40.0)
NO	32 (49.2)
MISSING	7 (10.8)

Efficacy Results: Sixty-one subjects met criteria for the evaluable cohort (received at least 1 month of ETV treatment). In the evaluable cohort, ETV treatment was effective in preventing HBV DNA recurrence when used together with variable regimens of HBIg; none of the 61 evaluable subjects had any HBV DNA values ≥ 50 IU/mL. Recurrence of HBsAg occurred in only 2 of 61 subjects, and was not associated with detectable HBV DNA. The overall population demonstrated an improvement in their ALT from a mean baseline ALT of 158.7 U/L (range = 10 - 1,485 U/L) to a mean ALT of 26.9 U/L (range = 7 - 136 U/L) at end of treatment.

The primary and key efficacy endpoints (last observation carried forward analyses) are summarized in Table 3.

Table 3: Primary and Key Secondary Endpoints Through Week 72 - Evaluable Subjects (LOCF)

Endpoint	ETV (N = 61)	95% CI
Primary Endpoint:		
HBV DNA by PCR ≥ 50 IU/mL	0/61	0.0, 5.9
Key Secondary Endpoints:		
HBsAg Loss	59/61 (96.7%)	88.7. 99.6
HBsAg Seroconversion[1]	49/61 (80.3%)	68.2, 89.4
HBsAg Recurrence	2/61 (3.3%)	0.4, 11.3
HBeAg Loss[2]	7/7 (100%)	59.0, 100.0
Seroconversion[2]	0/7	0.0, 41.0

[1] Received concomitant HBIg therapy.

[2] Evaluable HBeAg-positive subjects.

Safety Results: On-treatment, the majority of subjects (95%) had a reported AE, with more than half of these subjects experiencing SAEs (Table 4). The most frequent individual SAEs were acute renal failure and hepatic artery thrombosis, each occurring in 3 subjects (5%). The 3 cases of hepatic artery thrombosis all occurred within the first month post-OLT. These events are considered to be expected complications in the post-transplant population, either as a result of pre-existing CHB co-morbidity or as post-operative complications of OLT. The observed event rates for both SAEs are within the expected range based on liver transplant literaure (up to 12% for acute renal failure and 0% - 42% for hepatic artery thrombosis). No deaths were considered drug related by the investigators, and there was no discontinuation of study drug due to an AE. Six ALT flares were observed on treatment, and all occurred within 2 weeks of OLT; none was associated with an increase in HBV DNA or rejection of the transplanted liver, and all resolved within 1 month without complications. One malignancy was reported, a recurrence of HCC that occurred at 8 months post-liver transplant. Fifteen subjects (23%) had events classified within the ETV program as representing “HBV disease progression” (14 had ascites and 1 subject each had bacterial peritonitis, HCC, and hepatic encephalopathy). Since these events occurred within 30 days of liver transplantation, they were more likely due to post-operative complications rather than as a result of HBV disease. Eighteen of the 65 treated subjects had episodes of liver rejection, and in the evaluable cohort, a majority were managed

medically with only 1 subject requiring retransplantation. The observed rate of liver rejection in this study was consistent with the reported rates of rejection among HBsAg-positve subjects who received concomitant HBIg therapy (25%) versus those without HBIg therapy (70%).

On treatment, 40 subjects (62%) and 25 subjects (39%) had a confirmed creatinine increase from baseline ≥ 0.3 or ≥ 0.5 mg/dL, respectively. All of these subjects had received calcineurin inhibitors as part of their immunosuppresion regimen.

Treatment-emergent hematologic abnormalities that increased to Grade 3 or 4 were observed in < 10% of subjects.

Table 4: Adverse Events (All Treated Subjects) - On Treatment

MedDRA Preferred Term	No. of Subjects (%) (N = 65)
Deaths	4 (6.2)
Serious Adverse Events	36 (55.4)
Discontinuations Due to Adverse Events	0
Any Adverse Event	62 (95.4)
Related Adverse Events	11 (16.9)
Most Common Adverse Events (≥ 20% of Subjects)	
Hypertension	22 (33.8)
Diarrhea	19 (29.2)
Abdominal Pain	17 (26.2)
Hyperglycemia	15 (23.1)
Ascites	14 (21.5)
Headache	13 (20.0)
Insomnia	13 (20.0)
Grade 2 - 4 Related Adverse Events	8 (12.3)
Grade 3 - 4 Adverse Events	30 (46.2)
Malignancies	1 (1.5)
ALT Flares (ALT > 2 x baseline and > 10 x ULN)	6 (9.2)

CONCLUSIONS:

- Treatment with ETV (in combination with a variety of investigator-selected HBIg regimens) prevented recurrence of HBV viral replication in subjects who received liver transplant due to CHB
- The frequency of liver rejection and HCC recurrence was consistent with the literature
- ETV was well tolerated in this population. The frequency and nature of safety events reported were consistent with the expected safety events for the population under study.

DATE OF REPORT: 14-Oct-2011