

MEMORANDUM

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To: Antiviral Drug Products Advisory Committee Members and Guests

From: Entecavir Review Team

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Subject: Briefing document for NDA 21-797, entecavir 0.5 and 1 mg tablets and NDA 21-798, entecavir oral solution 0.05 mg/mL

1. Executive Summary: Regulatory Issues and Purpose of Meeting

This briefing document provides background information and the FDA perspective on the New Drug Applications (NDAs 21-797 and 21-798) submitted by Bristol-Myers Squibb (BMS) for entecavir (ETV), a nucleoside analogue intended for the treatment of chronic hepatitis B virus (HBV) infection in adults. The information presented in this document represents the preliminary findings and opinions of the primary reviewers from each discipline based on their review of the submitted material. The material included in this briefing document and other material presented by the applicant will be the subject of a meeting of the Antiviral Drug Products Advisory Committee to be held on March 11, 2005.

Entecavir is a guanosine nucleoside analogue with selective activity against HBV; it has no activity against other hepatitis viruses or HIV. The applicant's clinical development program was designed to assess the safety and efficacy of ETV in a variety of distinct patient populations recruited from a global network of investigators. The Advisory Committee will be asked to review and discuss issues related to the strength and completeness of the clinical database, the risk/benefit assessment of the drug in the context of non-clinical data, and the appropriateness for further post-marketing development and pharmacovigilance.

2. Summary of Clinical Development

The applicant has conducted an extensive global development program for ETV in the treatment of chronic HBV. The key clinical studies are summarized in Table 1. At the time these studies were initiated, lamivudine (LVD) was the only approved oral treatment for chronic HBV and was chosen as the appropriate comparator for the Phase 3 studies. The preliminary opinions and discussion to follow are based on review of the 4 designated pivotal trials unless otherwise stated.

Table 1: Summary of Phase 3 and Key Phase 2 Clinical Trials of Entecavir

Study/Sites	Patient Population	Number of Patients Treated on Study	Dose/Duration of Treatment	Primary Efficacy Endpoint
Pivotal Clinical Trials				
AI463022 North America, South America, Asia, Europe	HBeAg positive, nucleoside naïve, ALT > 1.3 x ULN	709	ETV 0.5 mg QD or LVD 100 mg QD for 52 weeks, up to 96 weeks total for partial (virologic) responders	Liver histology at 48 weeks of treatment
AI463027 North America, South America, Asia, Europe	HBeAg negative, nucleoside naïve, ALT > 1.3 x ULN	638	ETV 0.5 mg QD or LVD 100 mg QD for 52 weeks, up to 96 weeks total for partial (virologic) responders	Liver histology at 48 weeks of treatment
AI463014 North America, South America, Asia, Europe	LVD-refractory, HBeAg positive or negative	181 (87 received either ETV 1 mg or LVD 100 mg)	ETV 0.1, 0.5, 1.0 mg QD or LVD 100 mg QD for up to 76 weeks, some low- dose patients received ETV 1.0 mg open label after Week 28	HBV DNA by bDNA at 24 weeks of treatment
AI463026 North America, South America, Asia, Europe	LVD-refractory, HBeAg positive, ALT > 1.3 x ULN	286	ETV 1 mg QD or continued LVD 100 mg QD for 48 weeks, up to 96 weeks total for partial (virologic) responders	Liver histology at 48 weeks of treatment

Study/Sites	Patient Population	Number of Patients Treated on Study	Dose/Duration of Treatment	Primary Efficacy Endpoint
Supportive Clinical Trials				
AI463004 Worldwide	Nucleoside naïve and IFN/LVD-refractory, HBeAg positive or negative	42	ETV 0.05, 0.1, 0.5, or 1 mg QD or placebo for 28 days	HBV DNA by bDNA and PCR assays
AI463005 Worldwide	Nucleoside naïve, HBeAg positive or negative	177	ETV 0.01, 0.1, or 0.5 mg QD or LVD 100 mg QD for 24 weeks, up to 48 weeks in partial responders	HBV DNA by bDNA and PCR assays
AI463007 Worldwide	Rollover study for patients completing AI463004	28	Open label ETV 0.1 mg QD for 24 weeks	HBV DNA by bDNA and PCR assays
AI463015 Worldwide	Liver transplant patients with HBV reinfection despite LVD or HBIG	9	ETV 1 mg for 48 weeks, 48 week extension	HBV DNA by bDNA and PCR assays
AI463038 Worldwide	HIV/HBV coinfecting patients, LVD-refractory	68	ETV 1 mg or placebo added to LVD-containing HAART regimen for 24 weeks, open label ETV 1 mg for additional 24 weeks	HBV DNA by bDNA and PCR assays, HIV PCR
AI463901 Worldwide	Rollover study for patients who have failed monotherapy in Phase 2 or 3 study, HBeAg positive or negative	969 (currently still enrolling)	ETV 1 mg QD plus LVD for 52 weeks, up to 144 weeks for partial responders	HBV DNA by bDNA and PCR assays

Data were submitted from 19 pharmacokinetic studies that provided a good understanding of ETV's absorption, distribution, metabolism, excretion, and interactions with other commonly used drugs. These studies are summarized in Appendix A.

3. Summary of Non-clinical Toxicology and Carcinogenicity

3.1. Overview of General Non-clinical Findings

Entecavir is efficiently phosphorylated to ETV-triphosphate (TP) by cellular nucleoside kinases. By competing directly with the natural deoxyguanosine triphosphate (dGTP),

ETV-TP potently inhibits each of the 3 distinct activities of the HBV viral polymerase: priming, reverse transcription of first-strand DNA synthesis, and the DNA-dependent DNA polymerase activity responsible for second-strand DNA synthesis. Entecavir has little activity against the DNA polymerase of mitochondria.

The pharmacokinetic (PK) characteristics of entecavir in mice, rats, rabbits, dogs, and monkeys are comparable to those in humans indicating the acceptability of these species for the toxicological assessment of ETV.

Species-specific, reversible CNS inflammation was seen in dogs administered doses that achieve ~51 times the exposure to ETV in humans at clinically proposed doses. It was concluded that this is not relevant to human safety. Other target organs in repeat-dose studies in animals were the kidneys, liver, lungs, skeletal muscle and testis. Data from a 1-year study in monkeys indicated that there was no target organ toxicity in monkeys at exposures to ETV ~136 times those in humans.

Long-term dosing of ETV was evaluated in a woodchuck model of chronic HBV. In this study, woodchucks received a daily dose of ETV equivalent to the 1 mg human dose for 2 months and then were maintained with weekly dosing for up to 3 years. Viral suppression was maintained through 3 years of treatment with no evidence of emergence of resistant HBV. The applicant reported survival rates of 40% and 80% for animals treated for 14 and 36 months, respectively, compared to a survival of 4% in historical controls. Of most interest, the occurrence of hepatocellular carcinoma was significantly reduced in the animals treated long-term compared to historical control animals.

3.2. Overview of Carcinogenicity Studies

In a battery of genetic toxicology studies, ETV was an *in vitro* mutagen in mouse lymphocytes and clastogenic *in vitro* in human lymphocytes (without metabolic activation). However, ETV was negative in an Ames assay as well as a mammalian-cell gene mutation assay and a cell transformation assay. It was also negative in two *in vivo* assays, one for the induction of micronuclei and one for the induction of unscheduled DNA synthesis in primary liver cells.

Carcinogenicity studies in Sprague Dawley rats and CD-1 mice were conducted. Increased incidences of tumors were observed in both the studies. The results of these studies were presented to the Executive Carcinogenicity Assessment Committee (ECAC) on June 17, 2003. The key results of these studies are presented in tabular format in Appendix B. The outcomes of the two studies were as follows:

Rat Carcinogenicity Study: The oncogenicity potential of ETV was investigated in male rats at oral gavage dosages of 0.003 (low), 0.02 (mid), 0.2 (high) or 1.4 mg/kg/day (highest) and in females at dose levels of 0.01 (low), 0.06 (mid), 0.4 (high) or 2.6 mg/kg/day (highest) in comparison with untreated controls for a period of 104 weeks.

The no observed effect level (NOEL) for neoplasia was 0.2 mg/kg/day for males and 0.06 mg/kg/day for females. At tumorigenic doses, systemic exposures were 35- and 4-times that in humans (1 mg daily dose) in male and female rats, respectively.

Treatment-Associated Tumors:

1. Hepatocellular adenomas in female rats were significant ($p=0.005$) at the highest dose level. Combined adenomas and carcinomas in the female rats were also significant ($p=0.005$) at the highest dose. In female rats, the combined incidence of adenomas and carcinomas was 1% (controls), 4% (low), 5% (mid), 2% (high) and 18% (highest).
2. Brain gliomas were significant ($p=0.025$) at the highest dose in both male and female rats. In male rats, the incidence was 0% (controls), 2% (low), 2% (mid), 3% (high) and 7% (highest). In female rats, the incidence was 0% (controls), 0% (low), 2% (mid), 0% (high) and 5% (highest).
3. The skin fibromas in female rats were significant ($p=0.025$) at the high and highest doses. In female rats, the incidence was 0% (controls), 0% (low), 2% (mid), 3% (high) and 5% (highest).

Mouse Carcinogenicity Study: The oncogenicity potential of ETV was investigated in mice at oral gavage dosages of 0.004 (low), 0.04 (mid), 0.4 (high) or 4.0 mg/kg/day (highest) in comparison with untreated controls for a period of 104 weeks.

The NOEL for neoplasia was 0.004 mg/kg/day for males, based on pulmonary adenomas; for all other tumors in males and females, the NOEL was 0.4 mg/kg/day. At the tumorigenic dose in male mice, systemic exposure was 3-times that in humans (1 mg daily dose).

Treatment-Associated Tumors:

1. Lung adenomas were significant ($p=0.005$) in male mice (mid, high and highest) and in the female mice at the highest dose ($p=0.005$); lung carcinomas in both male and female mice were significant ($p=0.005$) at the highest dose. Combined lung adenomas and carcinomas were significant ($p=0.005$) in male mice at the mid, high and highest dose levels and in the female at the highest dose level ($p=0.005$). In male mice, the combined incidence of adenomas and carcinomas was 12% (controls), 20% (low), 26% (mid), 40% (high) and 58% (highest). In female mice, the combined incidence of adenomas and carcinomas was 20% (controls), 13% (low), 10% (mid), 35% (high) and 52% (highest).
2. Hepatocellular carcinomas in male mice were significant ($p=0.005$) at the highest dose level. Combined liver adenomas and carcinomas were also significant ($p=0.005$) at the highest dose level in the male mice. In male mice, the combined incidence of adenomas and carcinomas was 11% (controls), 9% (low), 8% (mid), 16% (high) and

25% (highest).

3. Vascular tumors in female mice (hemangiomas of ovaries and uterus and hemangiomas/hemangiosarcomas of spleen) were significant ($p=0.005$) at the highest dose level. In female mice, the incidence of vascular tumors was 16% (controls), 23% (low), 29% (mid), 26% (high) and 64% (highest).

The ECAC found that the carcinogenicity studies in mice and rats were adequately designed and conducted. The committee judged the results of ETV carcinogenicity studies. They concluded that ETV was a carcinogen in rodents. The committee concluded that ETV produced tumors in both species and both genders, and these results suggest a potential cancer hazard to patients.

At the request of the sponsor, the results of the carcinogenicity studies were presented to the full FDA CAC (CAC), a committee that has been designated as the arbiter of disputes between applicants and review divisions regarding the relevance of results in carcinogenicity studies. The CAC met with the applicant and the Review Team on January 7, 2005 and concluded that hepatocellular adenomas and carcinomas in female rats, skin fibromas in female rats and brain gliomas in both male and female rats were relevant. The committee also agreed that in the mouse carcinogenicity study, liver tumors in males and vascular tumors in females as well as lung tumors in both sexes were relevant to human safety evaluation.

4. Summary of Efficacy Data

4.1. Dose Selection

The proposed dose of ETV was selected on the basis of reductions in HBV DNA and safety and tolerability of the drug observed during short and long-term Phase 2 dose-ranging studies. In Study 004, reduction in HBV DNA over a 28-day dosing period and 28-day follow-up was greater in treatment groups receiving 0.5 and 1 mg daily than those receiving lower doses. Similarly, in Study 005, the dose of 0.5 mg resulted in greater decreases in HBV DNA over 22 weeks of dosing compared to either ETV 0.1 mg or LVD 100 mg. In these early Phase 2 studies, safety and tolerability of ETV 0.5 mg appeared to be somewhat better than ETV 1 mg, so the 0.5 mg dose was carried forward into Phase 3 trials for nucleoside-naïve patients (Studies 022 and 027).

The applicant anticipated that LVD-refractory patients would require a higher dose based on *in vitro* data demonstrating that LVD-resistant HBV also had reduced sensitivity to ETV. Dose selection for this population was based on the interim, 24-week results from Study 014. In this study, a dose-response relationship for ETV was observed in HBV DNA reduction and the dose of ETV 1 mg was superior to 0.5 mg or to LVD 100 mg for the proportion of patients achieving HBV DNA < LLOQ by bDNA. In this study, there were no observed differences in safety and tolerability across the treatment arms.

Consequently, ETV 1 mg was carried forward into the Phase 3 study in LVD-refractory patients (Study 026).

Pharmacokinetic and ADME studies of ETV document that the drug is predominately eliminated by the kidneys. Pharmacokinetics in patients with renal insufficiency, including those requiring hemodialysis or continuous ambulatory peritoneal dialysis, were studied in Study AI363011. Based on this study and pharmacokinetic modeling, the sponsor has proposed dose adjustments for patients with moderate or severe renal impairment. Elderly patients demonstrated increased ETV exposure but this could be attributed to decreased renal function and did not warrant a change in dosing based on age alone.

4.2. Summary of Study Designs

Study 014 was a Phase 2, randomized, double-blind, pilot study to evaluate 3 doses of ETV (0.1 mg, 0.5 mg and 1.0 mg) compared to LVD 100 mg in patients with HBV viremia while receiving LVD (“LVD-refractory”). Patients could be HBeAg-positive or negative. Patients were randomized to either continue LVD or receive ETV. Management decisions to discontinue or continue study treatment were made at Week 28 on the basis of the Week 24 assessments. Patients who achieved ≥ 1 log reduction in HBV DNA continued blinded therapy to Week 52. Patients failing to achieve at least 1 log reduction in HBV DNA discontinued study treatment but were eligible for the rollover study (AI463901) or other available therapy. Patients remaining on study treatment were reassessed at Week 48 and management decisions were based on criteria similar to those used in other studies. Patients could continue blinded therapy for up to 76 weeks. Liver biopsy for histology was optional in this study. The primary endpoint was the proportion of patients who achieved HBV DNA levels below the LOQ by the bDNA assay (0.7 MEq/mL) at 24 weeks. This study was intended to be a dose selection study for Study 026. Only the 87 patients receiving ETV 1 mg or LVD 100 mg QD were included in the efficacy analyses and the major safety assessments presented here. The patients receiving doses less than 1 mg daily were included in only selected analyses.

The 3 pivotal Phase 3 studies utilized similar study design and endpoint analyses. Study 022 was a randomized, double-blind comparison of ETV 0.5 mg versus LVD 100 mg in HBeAg-positive, nucleoside-naïve patients. Other key inclusion criteria included: age > 16 years, ALT $> 1.3 \times$ ULN, normal renal function, and compensated liver disease. Previous treatment with IFN was not an exclusion. Continuation of blinded study treatment at the end of 52 weeks was based on results of the Week 48 evaluation. Complete Responders (HBV DNA by bDNA assay < 0.7 MEq/mL and loss of HBeAg) stopped study treatment and were followed for 24 weeks off therapy to assess durability of response. Partial Responders (HBV DNA by bDNA assay < 0.7 MEq/mL but still positive for HBeAg) continued blinded therapy for up to 96 weeks or until complete response was achieved. Non-responders (HBV DNA by bDNA ≥ 0.7 MEq/mL) discontinued study treatment but were eligible for the rollover study or other available therapy. The primary endpoint was histologic improvement on liver biopsy at 48 weeks

defined as ≥ 2 point decrease in Knodell necroinflammatory score with no worsening in fibrosis score. Secondary endpoints included improvement in Ishak fibrosis score, change in HBV DNA by bDNA assay and by PCR assay, normalization of ALT, HBeAg loss, HBeAg/HBeAb seroconversion, and various composite endpoints.

Study 027 was a randomized, double-blind comparison of ETV 0.5 mg versus LVD 100 mg in HBeAg-negative, nucleoside-naïve patients. Study design was similar to Study 022 with similar management decisions occurring at Week 52. Inclusion criteria were similar to those in Study 022 except for HBeAg status. In the study treatment management algorithm, patients achieving < 0.7 MEq/mL HBV DNA by bDNA assay and ALT $< 1.25 \times$ ULN at 48 weeks were considered to have reached the composite efficacy endpoint (Composite Responders) and were eligible to discontinue study treatment and enter the follow-up phase. The primary efficacy endpoint was histologic improvement at 48 weeks defined as ≥ 2 point decrease in Knodell necroinflammatory score with no worsening in fibrosis score. Secondary endpoints were similar except that HBeAg loss and HBeAb seroconversion were not evaluated.

Study 026 was a randomized, double-blind comparison of ETV 1 mg versus LVD 100 mg in HBeAg-positive, LVD-refractory patients with compensated liver function. Patients were randomized to either continue LVD or receive ETV. Continuation of treatment at the end of 52 weeks was based on results of Week 48 evaluation. Criteria for continuation of blinded therapy through 96 weeks were based on Complete, Partial, or Non-response and were similar to Study 022. For this study there were co-primary endpoints at Week 48: histologic improvement on liver biopsy similar to other Phase 3 studies and the proportion of patients with both undetectable HBV DNA by bDNA assay (< 0.7 MEq/mL) and normalization of ALT (defined as $< 1.25 \times$ ULN). Multiple secondary endpoints were evaluated as in the other studies.

All of the Phase 2 and 3 studies used 2 assays to measure changes in HBV DNA: HBV DNA using a branched DNA assay (Chiron/Bayer Quantiplex™ v1.0) with a lower limit of quantitation (LLOQ) of 0.7 MEq/mL and HBV DNA using a PCR assay (Roche COBAS Amplicor HBV Monitor™ v2.0) with an LLOQ of 300 copies/mL. Clinical management decisions were based on real-time reporting of HBV DNA by the bDNA assay results while the PCR assays were conducted at a later time. For study defined endpoint calculations, the applicant used a cut-off HBV DNA value of < 400 copies/mL for the PCR assay. Neither the bDNA assay nor the PCR assay has been approved by the FDA and both are considered investigational. However, there is considerable experience with the use of both assays in clinical trials and clinical practice.

4.3. Patient Demographics

Patients who participated in the clinical trials include a representative sampling of patients with chronic HBV and compensated liver disease. Study participants were recruited from 31 countries in North America, South America, Asia, and Europe. Study demographics and baseline HBV disease characteristics for the 4 pivotal trials are summarized below (only those patients receiving ETV 1 mg or LVD were included from

Study 014). For each study, demographic and baseline disease characteristics were similar across the treatment arms.

Table 2: Patient Demographics

Characteristic	Nucleoside Naïve Studies		LVD-refractory Studies	
	Study 022	Study 027	Study 014	Study 026
Mean Age (years)	35	44	48	39
Gender				
Male	75%	75%	39%	74%
Female	25%	25%	61%	26%
Race				
Asian	57%	39%	37%*	30%
Caucasian	40%	58%	62%	63%
Other**	3%	3%	1%	7%

*In Study 014 “Asian” racial designation includes all Asian/Pacific Islander.

**Other designation includes: Black/African American, native Hawaiian/other Pacific Islander, Hispanic/Latino, Filipino, and others not specified.

Table 3: Baseline HBV Disease Characteristics

Characteristic	Nucleoside Naïve Studies		LVD-refractory Studies	
	Study 022	Study 027	Study 014	Study 026
Mean HBV				
Log bDNA (MEq/mL)	2.59	1.24	2.45	2.50
Log PCR (copies/mL)	9.66	7.58	9.18	9.36
Mean ALT (U/L)	143	142	125	128
Knodell	7.8	7.9	ND	6.5
necroinflammatory score				
Knodell fibrosis score	1.7	1.9	ND	1.7
Ishak fibrosis score	2.3	2.4	ND	2.3
HB e antigen positive	98%	< 1%	97%	68%
HB e antibody positive	3%	99%	4%	28%

ND, not done

4.4. Primary Efficacy Analysis

As noted above, the primary efficacy endpoints for the Phase 3 studies were based on the change in liver histology over the initial 48 week study period when patients received blinded study drug. Histologic improvement was defined as ≥ 2 point decrease in the Knodell necroinflammatory score with no worsening in the fibrosis score. All liver biopsy specimens were evaluated by a single reader who was blinded to treatment group and biopsy order and assigned the histologic scores by both the Knodell and Ishak criteria.

The FDA statistical analysis confirmed the applicant’s analysis of the primary efficacy endpoint. The applicant’s analysis included patients with available baseline biopsy data and counted those with missing or inadequate Week 48 biopsy data as treatment failures. Although the studies were originally designed to show non-inferiority of ETV to LVD, this analysis demonstrated that patients receiving ETV experienced superior overall histologic improvement compared to LVD in all 3 studies (P values ≤ 0.02 in all studies). ETV performed better for each of the individual components of the overall histologic improvement, ≥ 2 point decrease in Knodell necroinflammatory score and no worsening in Knodell fibrosis score.

The FDA statistical reviewer also conducted sensitivity analyses of the primary histologic endpoint that included several methods of imputing missing data. A more conservative analysis included all patients who received study drug and counted patients with missing baseline or Week 48 biopsy as treatment failures. This analysis continued to show superiority of ETV compared to LVD (P values < 0.03 in all studies) in both nucleoside-naïve and LVD refractory patients.

ETV was equivalent (non-inferior) to LVD for the secondary histologic endpoint of improvement in Ishak fibrosis score in the nucleoside-naïve Studies 022 and 027 but was superior in the LVD-refractory patient population in Study 026. Sensitivity analyses were also conducted for the secondary histologic endpoints and supported the conclusion that ETV was no worse than LVD as measured by the Ishak score. Histologic efficacy results are summarized in Table 4 below.

Table 4: Histologic Efficacy Assessments at 48 Weeks in Studies 022, 027, and 026

	Study 022		Study 027		Study 026	
	ETV 0.5 mg (N=354/314)	LVD 100mg (N=355/314)	ETV 0.5 mg (N=325/296)	LVD 100mg (N=313/287)	ETV 1 mg (N=141/124)	LVD 100mg (N=145/116)
Knodell scores						
Overall histologic improvement*	72% [#]	62%	70% [#]	61%	55% [#]	28%
Fibrosis no worse*	89% [#]	82%	84% [#]	79%	87% [#]	70%
Necroinflammatory ≥ 2 point decrease*	74% [#]	64%	73% [#]	64%	55% [#]	32%
FDA histologic improvement**	64% [#]	55%	64% [#]	56%	48% [#]	22%
Ishak scores						
Improvement*	39%	35%	36%	38%	34%	16%
Missing baseline biopsy	11%	12%	9%	8%	12%	21%
Missing or inadequate biopsy at Week 48	6%	13%	10%	12%	10%	12%

N = number receiving study treatment /number with evaluable baseline liver biopsy.

*Primary endpoint: ≥ 2 point decrease in Knodell necroinflammatory score with no worsening of Knodell fibrosis score. Individual components of primary endpoint are also shown. Efficacy calculations based on analysis of patients with available baseline biopsy, with missing Week 48 biopsy = failure.

**FDA sensitivity analysis: Efficacy calculation based on same definition of improvement but analysis of all patients who received study drug, with missing baseline or Week 48 biopsy = failure.

#ETV significantly better than LVD, P values all < 0.03 .

4.5. Secondary Efficacy Analysis

Treatment effects of ETV compared to LVD were also assessed for a number of secondary endpoints using virologic, serologic and biochemical measurements. Although the Phase 3 studies were originally designed using the HBV bDNA assay for treatment management decisions, discussions with the FDA prior to submitting the NDA identified the HBV PCR assay as the assay that provided better discrimination in virologic endpoints.

FDA analyses confirmed the applicant's results for the following secondary endpoints: proportion of patients with HBV DNA below LLOQ by PCR at Week 48, change from baseline in HBV DNA by PCR at Week 48, ALT normalization, and HBeAg seroconversion (loss of e antigen and gain of e antibody).

Table 5: Virologic, Serologic, and Biochemical Efficacy Endpoints for Studies 022, 027, and 026

	Study 022		Study 027		Study 026	
	ETV 0.5 mg	LVD 100 mg	ETV 0.5 mg	LVD 100 mg	ETV 1 mg	LVD 100 mg
HBV DNA PCR < LLOQ*	72% [#]	42%	95% [#]	77%	22% [#]	1%
Log HBV DNA by PCR – mean change from baseline	-7.0 [#]	-5.5	-5.2 [#]	-4.7	-5.1 [#]	-0.5
HBeAg seroconversion**	21%	18%	NA	NA	8%	3%
ALT Normalization (< 1 x ULN)	69% [§]	61%	78% [§]	71%	65% [#]	17%

NA: not applicable

*LLOQ: Lower limit of quantitation calculated as < 400 copies/mL.

**HBeAg seroconversion defined as loss of e antigen with gain of e antibody.

[#]ETV significantly better than LVD, all P values < 0.01 .

[§]ETV significantly better than LVD, P values < 0.05

One of the applicant's secondary endpoints was determining the proportion of patients in each study who met the criteria of Complete Response or Composite Response at Week 48. Each study's treatment management algorithm allowed these patients to discontinue blinded study drug but remain in follow-up. The proportions of patients meeting the response criteria were different in the Phase 3 studies because of the differences in the

study populations. In Study 022 in which HBeAg positive patients were considered Complete Responders if they achieved HBV DNA by bDNA < 0.7 MEq/mL and loss of e antigen, only 21% of ETV patients and 19% of LVD patients reached the Complete Response endpoint. In Study 027 in which HBeAg negative patients were considered Composite Responders if they achieved HBV DNA by bDNA < 0.7 MEq/mL and ALT < 1.25 x ULN, 85% of ETV patients and 78% of LVD patients reached the Composite Response endpoint. In Study 026 in which HBeAg positive, LVD-refractory patients had to meet the same Complete Responder criteria as Study 022, 9% of ETV patients and <1% of LVD patients reached the Complete Response endpoint.

5. Summary of Safety Data

5.1. Exposure

Table 6 summarizes the disposition of patients in the Phase 3 studies and their exposure to study drug as of the most recent safety update to the NDA. These studies continue to follow patients still on blinded therapy or in 24-week, off-treatment follow-up.

Table 6: Disposition and Extent of Exposure of Patients Enrolled in Phase 3 Entecavir Studies

	Study 022		Study 027		Study 026	
	ETV 0.5 mg	LVD 100 mg	ETV 0.5 mg	LVD 100 mg	ETV 1 mg	LVD 100 mg
Randomized	357	358	331	317	147	146
Received study drug	354	355	325	313	141	145
Completed first year of blinded dosing	340 (96%)	321 (90%)	311 (96%)	296 (95%)	133 (94%)	126 (87%)
Continued to second year of dosing (Partial responders)	252 (71%)	190 (54%)	46 (14%)	59 (19%)	91 (65%)	28 (19%)
Entered 24-week follow-up	135 (38%)	132 (37%)	299 (92%)	263 (84%)	22 (16%)	20 (14%)
Mean time on study treatment (weeks)	75.3	64.7	55.5	56.4		

Proportions calculated based on number of patients who received at least one dose of study drug.

5.2. Common Adverse Events, Serious Adverse Events, and Laboratory Abnormalities

FDA review of the safety database for the pivotal trials confirmed the applicant's analysis of common adverse events (AEs), serious adverse events (SAEs), and laboratory abnormalities. All patients who received at least one dose of blinded study medication in the pivotal trials were included in the safety analyses. The review included assessment of proportions of patients who experienced AEs and SAEs according to severity,

relationship to blinded study drug, and action required to manage the event (interruption or discontinuation of study drug). The safety review evaluated clinical events and laboratory abnormalities according to assigned treatment and over 2 study periods (on blinded treatment and off treatment). Organ systems identified as potential targets in the non-clinical animal studies were specifically reviewed. The review evaluated safety in each of the studies individually and also pooled the analyses of nucleoside-naïve patients (Studies 022 and 027) and LVD-refractory patients (Study 014 groups receiving ETV 1 mg or LVD and Study 026). Summary results of the pooled analysis will be presented below. Minor differences between the applicant's results and the FDA's results can be attributed to slightly different methods of defining visit windows and conducting the analyses and do not alter the final conclusions.

AEs were reported frequently in the nucleoside-naïve patients although there were few differences in the pattern of AEs reported by ETV-treated patients compared to LVD-treated patients. On treatment AEs reported in > 5% of patients in either arm in the nucleoside-naïve studies included: headache, upper respiratory infection, nasopharyngitis, cough, pyrexia, abdominal pain, diarrhea, fatigue, arthralgia, dizziness, nausea, influenza, sore throat, rhinorrhea, dyspepsia, increased ALT, increased blood amylase, back pain, and myalgia. Most of the reported events were mild and not considered related to study treatment. The proportions of patients with reported AEs considered by the investigators to be possibly or probably related to blinded study drug were similar in the 2 treatment groups (ETV 37%, LVD 38%). AEs were reported in smaller numbers of nucleoside-naïve patients during the off-treatment follow-up period and very few events were observed in \geq 5% of patients (increased ALT in ETV 3% and LVD 11%, headache in ETV 5% and LVD 6%). During the off-treatment period, only increased ALT occurred more frequently in LVD patients than ETV patients. Other AEs occurred in similar numbers of patients in both groups.

The pattern of commonly reported AEs was very similar in the LVD-refractory patients. On treatment AEs reported in > 5% of patients in either arm in the LVD-refractory studies included: headache, upper respiratory infection, abdominal pain, fatigue, cough, nasopharyngitis, pyrexia, diarrhea, arthralgia, dizziness, nausea, sore throat, dyspepsia, ALT increased, back pain, and myalgia. Most of the events were described as mild and not related to study drug. In this population, increased ALT was reported more frequently in patients receiving LVD (11%) than in those receiving ETV (3%) and fever and sore throat were reported more frequently in ETV patients (9% and 7%, respectively) than in LVD patients (4% and 2%). Reflective of the relatively small proportion of LVD-refractory patients who entered off-treatment follow-up, few patients experienced AEs during the off-treatment period. There were no significant differences in the pattern of off-treatment AEs between the treatment groups.

The number of patients who developed SAEs (death, hospitalization, cancer, congenital anomaly, life-threatening condition, or other medically significant event) while on study was small. Similarly, the number of patients discontinuing their assigned study drug because of an AE or SAE was low, 1% for ETV-treated patients and 4% for LVD-treated patients.

Table 7: Proportions of Patients Reporting Adverse Events or Serious Adverse Events while on Study Drug

	Nucleoside Naïve Studies		LVD-refractory Studies	
	ETV (N=679)	LVD (N=668)	ETV (N=183)	LVD (N=190)
Patients reporting any AE	552 (81%)	551 (82%)	156 (85%)	155 (82%)
Patients with AE possibly or probably related to drug	248 (37%)	251 (38%)	83 (45%)	71 (37%)
Patients with Grade 3 or 4 AE	76 (11%)	96 (14%)	35 (19%)	32 (17%)
Patients with Grade 3 or 4 and related AE	32 (5%)	45 (7%)	15 (8%)	21 (11%)
Patients reporting any SAE	48 (7%)	54 (8%)	19 (10%)	14 (7%)
Patients with SAE possibly or probably related to drug	1 (<1%)	11 (2%)	1 (<1%)	2 (1%)
Patients discontinuing study drug due to any AE or SAE	7 (1%)	20 (3%)	4 (2%)	14 (7%)

Clinical laboratory monitoring for safety included assessments of routine hematology and coagulation studies, serum biochemical studies, and urinalysis at each study visit. Confirmatory review of the applicant’s analysis consisted of evaluation of the numbers of patients who exhibited extreme laboratory values (Grade 3 or 4). As with the clinical AEs, laboratory abnormalities were compared across treatment groups and for both on-treatment and off-treatment periods. Results are presented for pooled nucleoside-naïve patients and pooled LVD-refractory patients during the on-treatment period.

The most commonly observed hematologic/coagulation abnormalities in the nucleoside-naïve patients were prolonged PT and increased INR. During the on-treatment period, prolonged PT was identified in 36% of ETV patients and 32% of LVD patients. Increased INR was observed in 28% of ETV patients and 24% of LVD patients. However, Grade 3 or 4 abnormalities of PT and INR were observed in 2% and 1%, respectively, of ETV patients and < 1% each of LVD patients. Abnormalities in other hematologic parameters were rare and balanced across treatment groups. Among LVD-refractory patients, PT and INR abnormalities were the most commonly observed abnormalities (ETV 34% and 32%, respectively, LVD 36% and 38%). In this population, 4% of ETV patients compared to 11% of LVD patients had low platelet counts at some time on-treatment but Grade 3 or 4 hematologic abnormalities were rare.

There were few significant abnormalities in serum biochemical tests identified in either the nucleoside-naïve or LVD-refractory patient populations. Elevations of pancreatic enzymes, increased creatinine, and abnormalities in electrolytes occurred rarely and with similar prevalence across the treatment groups. The most commonly observed biochemical abnormalities were elevations in liver transaminases. Since increased ALT was one of the screening criteria for all clinical trials, most patients had documented transaminase abnormalities at baseline. In general, mean ALT and AST levels decreased

among nucleoside-naïve patients on treatment in both treatment arms. For example, among ETV patients with ALT values in the nucleoside naïve safety dataset, mean ALT decreased from 141 U/L at baseline to 36 U/L at Week 48. Among LVD patients in the same population, mean ALT decreased from 145 U/L at baseline to 45 U/L at Week 48. In this population, significant numbers of patients experienced Grade 3 or 4 ALT elevations after the baseline value: 21% of ETV patients and 25% of LVD patients. Among LVD-refractory patients, Grade 3 or 4 ALT elevations were also reported in a significant number of patients and were more common in the LVD group: 19% of ETV patients and 31% of LVD patients. Additional information regarding the occurrence of ALT “flares” will be presented in more detail in Section 5.4.1.

5.3. Deaths

There were a total of 15 deaths during treatment with study drugs during all of the reported ETV trials. Across the pivotal trials, 12 deaths were balanced between patients receiving ETV and those receiving LVD (see Table 8). In the nucleoside-naïve studies there were 6 deaths among the 1347 subjects (0.4%) while in the LVD-refractory studies there were 6 deaths in the 373 (2%) patients receiving study drug. Three additional deaths were reported from the Phase 2 supportive studies. None of the deaths were considered by the investigators to be related to study drugs but one death was thought to be possibly related to withdrawal of study drug and resulting hepatic decompensation.

Table 8: Deaths Reported During Treatment in Entecavir Pivotal Trials

Site ID - Patient ID	Gender, Age, Race, Country	Study Days to Death	Study Regimen	Cause of Death
Study AI463022				
15-10127	Male, 78, Caucasian, Argentina	192	3TC 100 mg	Severe dyspnea
115-10657	Male, 64, Caucasian, Italy	395	3TC 100 mg	Diffuse metastases, prior renal carcinoma
136-10204	Female, 58, Caucasian, Brazil	239	3TC 100 mg	Grade 4 hepatic decompensation, hepato-renal syndrome
209-11016	Male, 55, Caucasian, Polish	260	3TC 100 mg	Unknown
Study AI463027				
12-51342	Female, 53, Asian, U.S.	314	ETV 0.5 mg	End stage liver disease, hepatocellular carcinoma
189-50838	Male, 61, Caucasian, Russia	54	ETV 0.5 mg	Multi-organ failure

Site ID - Patient ID	Gender, Age, Race, Country	Study Days to Death	Study Regimen	Cause of Death
Study AI463014				
39-6039	Male, 47, Caucasian, U.S.	551	ETV 0.1 mg	Liver failure Known LDV-resistant virus, liver failure five months after stopping ETV 0.1 mg and on non-study treatment with LVD. Deemed probably related to withdrawal of study drug.
50-6057	Female, 62, Caucasian, Greece	243	ETV 0.1 mg	Septic shock following acute appendicitis/esophageal hemorrhage/ARDS
49-6020	Male, 58, Caucasian, Greece	191	ETV 0.1 mg	Hepatocellular carcinoma
Study AI463026				
81-80299	Male, 59, Caucasian, Brazil	307	LVD 100 mg	Septic shock, underlying newly diagnosed liver nodule of high grade dysplasia.
101-80042	Male, 46, Caucasian, Turkey	557	LVD 100 mg	Liver failure, hepatitis B flare 18 weeks after discontinuing blinded treatment after transaminase elevations, no subsequent alternative treatment
134-80058	Female, 54, Asian, Thailand	680	ETV 1.0 mg	CNS complications of splenic lymphoma, GI bleed

5.4. Events of Special Interest

5.4.1. ALT “Flares” and Hepatic Adverse Events

Acute exacerbations of hepatitis, sometimes called “flares,” represent an important safety issue in the treatment of chronic HBV infection. Flares have been described during treatment with all of the approved drugs and after discontinuation of drugs that have activity against HBV. During the ETV development program, the applicant tracked hepatitis flares using a standardized definition, the occurrence of ALT value at least twice the baseline value and 10 x the ULN. Safety data was also reviewed to evaluate the occurrence of these ALT flares in combination with other clinical hepatic events or other laboratory abnormalities consistent with worsening liver function. During the clinical trials, ALT flares were separated into those occurring during treatment and those occurring after discontinuation of study drugs.

ALT flares occurred infrequently in nucleoside-naïve patients during the on-treatment period: 15 ETV patients (2%) and 27 LVD patients (4%). Flares appeared clustered in the first 12 weeks on study drugs and again in the later stages of the on-study

period. The flares occurring during the first 12 weeks on study were often accompanied by decreases in HBV DNA and did not necessitate discontinuing study drug (9 ETV patients and 11 LVD patients). Flares occurring later in treatment (2 ETV and 12 LVD) were often accompanied by increases in HBV DNA and more often prompted study drug discontinuation. One LVD patient had both an early and a late flare, the second prompting drug discontinuation. Among the nucleoside-naïve patients, 1 ETV patient and 3 LVD patients discontinued study drug due to flares and one LVD patient developed hepatic decompensation with hepatorenal syndrome and died. During the off-treatment follow-up, 15/414 (4%) ETV patients and 30/377 (8%) LVD patients with off-treatment data experienced ALT flares.

ALT flares were documented more often among patients in the LVD-refractory trials (including Study 026 patients and the Study 014 patients who received ETV 1 mg or LVD). In this population, 4 ETV patients (2%) and 19 LVD patients (10%) experienced ALT flares while receiving study drug. Six LVD patients discontinued study drug because of ALT flares. During the off-treatment follow-up, 4/56 ETV patients (7%) and 4/31 LVD patients (13%) with follow-up data experienced ALT flares.

Clinical AEs related to the hepatobiliary system or to hepatic (laboratory) investigations reported as AEs were also tabulated. Among the nucleoside-naïve patients, 57 ETV patients (8%) and 87 LVD (13%) patients reported a clinical or laboratory AE related to the hepatobiliary system while receiving study treatment. Most of these events represented increases in ALT, AST, or bilirubin. The most common clinical AE reported was “hepatic pain” reported in five patients in each treatment group. A total of 13 nucleoside-naïve patients experienced non-malignant hepatobiliary SAEs while on study treatment: 3 ETV patients and 10 LVD patients. These events included: increased ALT, portal vein thrombosis, and cholelithiasis in ETV patients and increased ALT, AST, and/or bilirubin (7), cholecystitis (2), and hepatic failure in LVD patients. Hepatic malignancies were considered SAEs but will be discussed separately.

Among LVD-refractory patients, 22 ETV patients (12%) and 32 LVD patients (17%) experienced a hepatobiliary clinical or laboratory AE during the treatment period. The most commonly reported events were clinically significant abnormalities of ALT, AST, and bilirubin. The most common clinical AEs reported were cholelithiasis (1 ETV patient and 2 LVD patients) and “liver lesion” (2 ETV patients). Four patients experienced non-malignant, hepatobiliary SAEs while on study treatment: acute cholecystitis/ cholelithiasis and severe hepatitis in ETV patients and cholecystitis and hepatic flare in LVD patients.

5.4.2. Malignancies

Evaluation of malignancies was of special interest during the review process because chronic HBV is known to be a strong risk factor for development of hepatocellular carcinoma (HCC) and because the results of the rodent carcinogenicity studies

suggested that ETV might itself be a potential carcinogen. Early pre-clinical studies using a woodchuck model suggested that administration of ETV to HBV-infected woodchucks decreased the occurrence of HCC in animals that were maintained on the drug long-term.

The applicant's initial evaluation of malignancies for the NDA included data from 10 Phase 2 and 3 studies through a cut-off date of May 28, 2004. This analysis includes data from 1392 patients initially treated with ETV, 899 patients treated with LVD, and 108 patients who initially received placebo. Of the patients initially randomized to receive placebo, 105 subsequently received ETV and are included with that group for a total of 1497 patients receiving ETV.

As of the cut-off date reported in the NDA, a total of 27 malignancies had been identified in 26 patients (17 ETV patients and 9 LVD patients). No malignancies were diagnosed among the 108 patients who originally received placebo in early clinical trials. In addition, there were 5 patients (3 ETV and 2 LVD) who were reported to have lesions that were categorized as pre-malignant or unclassifiable. These patients and their diagnoses are summarized in Appendix C.

The Medical Officers reviewed all narrative summaries and Case Report Forms of patients with reported malignancies and it was concluded that none of the case descriptions were unusual or reported the occurrence of rare tumor types. Some of the reported malignancies occurred in patients who were relatively young for a tumor type but not outside the reported range (eg., breast cancer in a 30 year old woman, HCC in a 26 year old man). Some malignancies were identified after a relatively brief exposure to ETV or LVD, suggesting that study drug use had little impact on the development of the cancer in those cases. Others were identified after the patient received study drug for over a year. Even this is a relatively short reporting period for assessing carcinogenic potential.

Little information is available regarding prior medical history or risk factors for malignancy for patients enrolled in the ETV clinical trials. Six of the patients reported to have malignancies were known to have had previous malignancies. Patient AI463015-16-2010 had a history of HCC prior to transplant and then was diagnosed with renal cancer 779 days after beginning ETV. Patient AI463022-115-10657 had a history of nephrectomy for renal cell carcinoma prior to study and then developed multiple metastatic lesions in the brain, bones, and lungs (no biopsy diagnosis) after 358 days on LVD. Patient AI463022-80-10451 had a history of gastric cancer prior to study enrollment and developed recurrence of her gastric cancer and metastases after 277 days on LVD. Additionally, 3 patients who reported basal cell or squamous cell carcinoma of the skin during study observation had a previous history of skin cancer.

The applicant calculated the rate of malignancies over time for patients receiving ETV or LVD in the clinical trials. They note that the overall rate of malignant neoplasms was 8.5 per 1000 patient years of observation for patients receiving ETV

and 7.8 per 1000 patient years for patients receiving LVD. This compares to rates of 9.7 per 1000 patient years for all cancers in patients with chronic HBV and 3.8 per 1000 patients years in patients without evidence of HBV calculated from a U.S. cohort study commissioned by BMS. For HCC, the most commonly reported malignancy, the rate was 3.5 per 1000 patient years for ETV patients and 3.4 per 1000 patient years for LVD patients. These rates compare to rates of 4.6 per 1000 patient years in patients with chronic HBV and 0.02 per 1000 patient years in the non-HBV comparator group calculated from the U.S. cohort study.

Addition of new cases reported in a recent Safety Update containing data through August 17, 2004, brings the total number of patients with identified malignancies in the ETV development program to 37. Of these patients 28 were in the randomized populations: 19/1497 ETV patients (1.3%) and 9/899 LVD patients (1%). Nine patients were in special study populations not previously analyzed (decompensated, HIV/HBV co-infected, or receiving dual therapy): 3 receiving ETV alone, 2 receiving adefovir (ADV) alone, and 4 receiving combination therapy with ETV+LVD. There was less information available on these patients for review but summary data is included in the table in Appendix A.

6. Resistance

Entecavir has demonstrated activity against HBV replication *in vitro* with IC₅₀ values ranging from 0.36 nM to 3.6 nM. The active intracellular moiety of ETV, ETV-triphosphate, is a competitive inhibitor of dGTP and functions as a non-obligate chain terminator. Cell culture studies have shown that viruses with the LVD resistance-associated amino acid substitutions rtM204V/I and rtL180M in the HBV polymerase display cross-resistance to ETV, having approximately 5- to 30-fold reduced susceptibility *in vitro*. Resistance analyses from early Phase II studies provided evidence that substitutions at positions rtT184, rtS202, and/or rtM250 are associated with ETV resistance, but developed only when LVD resistance mutations were present. The addition of substitutions at rtT184, rtS202, and/or rtM250 together with the LVD-resistance mutations, rtL180M and rtM204V, in recombinant viruses resulted in 38- to 2,000-fold reduced susceptibility to ETV *in vitro*.

The efficacy of ETV was examined in both nucleoside-naïve and LVD-refractory patient populations. In nucleoside-naïve Studies 022 (HBeAg positive subjects) and 027 (HBeAg negative subjects), 83% (541/653) of patients on 0.5 mg QD ETV treatment were suppressed with HBV DNA < 400 copies/mL as quantified by the COBAS Amplicor HBV Monitor PCR assay at week 48 compared to 59% (363/619) of patients on 100 mg QD LVD treatment. Genotypic and phenotypic analyses of paired clinical isolates obtained at study entry and Week 48 were performed to monitor baseline and emerging amino acid substitutions and to determine their impact on virologic response to ETV. In these studies, no ETV-associated resistant substitutions (T184S/A/I, S202G, M250L) emerged in any isolate on ETV therapy by 48 weeks. Two subjects experienced virologic rebound on ETV treatment but had no detectable amino acid changes emerge on treatment and no change in phenotypic susceptibility to ETV, ADV or LVD.

Studies 014 and 026 examined the efficacy of ETV 1 mg QD compared to LVD 100 mg QD in patients with LVD-refractory HBV with prior LVD experience. In these studies, LVD-resistant substitutions rtL180M and rtM204V/I were detected in > 80% of baseline isolates from both the ETV and LVD arms and these substitutions were maintained during the study, presumably because of the selective advantage in the presence of LVD and ETV. In Studies 014 and 026, 21% (36/174) of patients on ETV were suppressed to below 400 copies/mL HBV DNA by PCR assay at week 48 compared to 1% of patients on LVD.

Genotypic analyses determined that LVD-resistance substitutions L80V, L180M, M204V or I emerged in the HBV of 17% (7/42) of patients on ETV by Week 48 in Study 014. These substitutions often arose in the context of mixtures at these sites at baseline and other LVD-resistance mutations at baseline. Despite the emergence of LVD-resistance substitutions, the viral load in 4 of 7 patients was suppressed below 300 copies/mL (LLOQ) and the other 3 subjects experienced > 2 log₁₀ reductions in viral load at the time the isolate developed the LVD-resistant mutations. ETV-associated resistance substitutions at T184 developed on 1 mg ETV therapy in 5 (12%) patients after week 48 in Study 014 and coincided with rebounds in viral load. In Study 026, substitutions at RT residues rtI169, rtT184, rtS202 and/or rtM250 emerged on therapy in 9% (12/134) of ETV subjects with Week 48 data. In all cases, the ETV-resistant substitutions emerged when pre-existing LVD-resistant changes were present.

The supportive Study 015 examined the antiviral activity of open label ETV 1 mg QD in 9 orthotopic liver transplant (OLT) recipients who were > 100 days post-transplant and had recurrent HBV infection despite prophylaxis with anti-HBV agents. In this study, virologic rebound occurred in 6 out of 8 patients - one in the first year therapy, one in the second year, and four in the third year while 2 patients maintained HBV DNA suppression with no rebound out to 127 and 131 weeks of therapy. Seven of the eight patients showed the development of ETV-resistance substitutions at S202G or I (n=5), T184S/I/A/L/F (n=4) or M250V (n=1), and these substitutions were linked to LVD-resistant changes L180M and M204V.

The substitutions at rtI169, rtT184, rtS202 and/or rtM250 were associated with phenotypic ETV resistance. The median fold change from reference of ETV susceptibility was 38 (range 12-2139) for the ETV failure isolates (> 400 copies/mL HBV DNA) that developed ETV-resistance substitutions at 48 weeks in Study 026 (n = 15) and 83 (range 12-10022) for all ETV failure isolates from Studies 026 and 015 \geq 48 weeks (n = 22).

Overall, the following conclusions can be summarized from the resistance data collected in Studies 022, 027, 014, 026, and 015.

- Greater proportions of nucleoside-naïve subjects (83%) with chronic HBV infection achieved HBV DNA levels < 400 copies/mL on ETV treatment compared to LVD-refractory subjects (21%).
- Genotypic or phenotypic evidence of resistance to ETV in nucleoside-naïve patients chronically infected with HBV (n = 430) has not been observed up to 48 weeks of 0.5 mg QD ETV treatment in Studies 022 and 027, including 2 subjects in Study 022 who experienced a confirmed virologic rebound.

- 7.4% (14/190) of LVD-refractory subjects treated with 1 mg ETV had evidence of emerging ETV-resistance substitutions by week 48.
- ETV-associated resistance substitutions at rtI169, rtT184, rtS202, and/or rtM250 emerged concomitant with LVD-resistant mutations at rtL180 and/or rtM204 and were associated with virologic rebound upon prolonged ETV therapy.
- Overall, 4 ETV treated subjects exhibited a confirmed rebound in their HBV DNA levels of $\geq 1 \log_{10}$ by week 48:
 - 2 isolates from Study 022 with no evidence of ETV-resistant substitutions or other genotypic changes
 - One isolate from Study 015 that developed an rtT184A
 - One isolate from Study 026 that developed an rtT184A/S
- LVD-resistance substitutions L80V, L180M, M204V or I can emerge in the HBV of patients on 1 mg ETV by Week 48. These substitutions often arise in the context of mixtures at these sites at baseline and other LVD-resistant mutations at baseline.
- Even when LVD-resistant mutations emerged in HBV on ETV therapy, ETV can suppress HBV DNA levels to below detection limits.
- $> 2 \log_{10}$ reductions in viral load and viral load suppression below 400 copies/mL HBV DNA can occur in subjects with LVD-resistance in their HBV at baseline when treated with 1 mg ETV.
- Cross-resistance to ETV was not observed with ADV-resistant HBV.
- HBV developing ETV resistance-associated substitutions in addition to LVD-associated resistance substitutions remained resistant to LVD.

Studies evaluating treatment responses to ETV and monitoring resistance to ETV beyond 48 weeks of dosing are ongoing.

7. Issues for Committee Discussion

7.1. Risk/benefit Assessment

Several issues must be considered in determining the overall risk/benefit of ETV in the treatment of chronic HBV and how it might fit into the current treatment armamentarium. Chronic HBV remains a major contributor to the global rates of cirrhosis, HCC, and mortality. ETV achieves reliable drug exposure in patients, has few significant drug-drug interactions, and dosing can be reasonably adjusted in patients with impaired renal function using the oral solution formulation. We conclude from the pivotal clinical trials and supportive studies that ETV effectively reduces the HBV viral burden and leads to improvement in liver histology and normalization of liver transaminases in patients receiving the drug for 48 weeks. It achieved these endpoints in a greater proportion of patients than did LVD in both nucleoside-naïve patients and LVD-refractory patients. The general tolerability and safety profile of ETV was similar to that of LVD over the observed dosing and post-dosing periods. Assessment of the drug in dosing beyond 48 weeks is ongoing.

These positive findings from the ETV studies must be weighed against findings that are less clearly understood. While resistance to ETV has not yet emerged in nucleoside-naïve patients during the observation period, patients with prior resistance to LVD appear to be at risk for development of reduced susceptibility to ETV. This may have a significant impact on long-term dosing as the clinical trials continue.

Even more uncertainty emerges in the assessment of the potential risk that ETV may be a carcinogen given the results of the rodent studies. This issue is complicated by the oncogenic properties of HBV itself and by accumulating animal and human data suggesting that HBV treatment may prevent or delay the occurrence of HCC. LVD has been studied in similar carcinogenicity studies and has been found to have no carcinogenic effects even at high doses. Carcinogenicity studies with ADV were limited by an inability to deliver high doses of the drug to rodents because of significant renal toxicity. It is possible that the dose-related pulmonary tumors identified in mice receiving ETV are species specific. However, multiple other tumors were identified in both mice and rats receiving high doses of ETV, raising the possibility that the drug may have broader carcinogenic effects. It is always difficult to extrapolate animal carcinogenicity data to human risk and so we are unable to determine the magnitude of the risk to humans from currently available data. To our knowledge, there has not been a public discussion of an acceptable level of carcinogenicity risk in relationship to chronic HBV treatment.

Issues for discussion:

The risk/benefit assessment of ETV in the context of the available clinical safety and efficacy data and non-clinical carcinogenicity data.

7.2. Pediatric Development

Although HBV vaccination has been universally recommended for infants in the U.S. and many other countries, there remains a substantial population of pediatric patients affected by chronic HBV. These patients are at high risk for development of HCC over their lifetimes. At present, interferon- α and LVD are approved for treatment of chronic HBV in pediatric patients. The Review Team asked BMS to delay its pediatric development program after the results of the rodent carcinogenicity studies were reported. We proposed that pediatric drug development could proceed if a full assessment of the potential risks and benefits of the drug in the adult population determined that ETV might provide significant benefit for pediatric patients.

Issues for discussion:

- 1. Potential risks and benefits of proceeding with development of ETV for the treatment of chronic HBV in pediatric patients.*
- 2. Additional information needed about either ETV or the pediatric population in order to proceed.*

7.3. Post-marketing Commitments

The applicant has proposed a post-marketing pharmacovigilance plan with the objectives of providing longer-term safety data. The events of most interest include: death, malignancy (HCC and other), hepatitis flares occurring on-treatment and post-dosing, and need for liver transplantation. Currently enrolling rollover studies will be continued with Studies 050 and 901 extending dosing for up to 3 years and Study 049 extending post-treatment observation for up to 5 years. These studies will capture many of the patients completing other Phase 2 and 3 studies. The applicant will also provide periodic safety updates summarizing AEs and SAEs of special interest from both the on-going clinical development program and from spontaneous post-marketing reporting.

In order to provide additional assurance that ETV does not pose an increased risk of malignancy, the applicant has proposed conducting a randomized, prospective, post-marketing observational study. The protocol synopsis proposes to enroll approximately 12,500 patients with chronic HBV who are eligible for treatment and randomize them to receive either ETV or other standard nucleoside/nucleotide therapy. This large, simple study will track overall mortality, liver transplantation, and malignancy (HCC and non-HCC) for 5 years after the last patient is enrolled. We have encouraged the applicant to further develop a full protocol for review but recognize that there are inherent limitations in a study of this type. In spite of its length, the study may not be able to identify a cancer risk with a long latency and, other than HCC, no specific tumor type can be targeted for surveillance. Different proportions of patients from specific geographic areas or at different stages of disease may not be balanced across the treatment arms and patients may change treatments during the observation period increasing the difficulty interpreting results. However, we accept that the applicant's proposal represents a good faith effort to identify 5 to 8-year cancer risk.

Issues for discussion:

Appropriateness of the applicant's proposed pharmacovigilance plan to address clinically relevant issues.

Appendix A: Summary of Entecavir Clinical Pharmacology

The clinical pharmacology and pharmacokinetic profile of ETV have been defined in healthy subjects and HBV-infected patients. These studies show ETV demonstrates the following clinical pharmacology characteristics:

- An integrated summary of ETV single and multiple dose pharmacokinetic parameters following administration of the proposed therapeutic doses (0.5 mg and 1 mg) in the fasted state are presented in the following table.

Dose (mg)	Day	C _{max} (ng/mL)	T _{max} ^a (hr)	AUC ^b (ng•h/mL)	t _{1/2} (hr)	CL/F (mL/min)	CL _r (mL/min)
0.5	1	N =158 4.09 (30.1)	N =158 0.75 (0.5, 2.0)	N =158 9.77 (27.2)	N =23 83.24 (40.4)	NA	NA
	14	N =12 5.22 (35.0)	N =12 0.88 (0.5, 1.0)	N =12 16.21 (14.7)	N =12 113.25 (25.0)	N =12 520.74 (94.7)	N =12 368.20 (60.0)
1	1	N =172 8.72 (29.2)	N =172 0.75 (0.25, 3.0)	N =172 19.00 (24.0)	N =107 95.61 (44.1)	N =49 557.48 (108.9)	N =49 379.65 (98.5)
	14	N =11 9.83 (27.1)	N =11 0.75 (0.5, 1.5)	N =11 31.15 (17.2)	N =11 108.68 (39.0)	N =11 543.23 (102.8)	N =11 409.83 (109.8)

Data presented as geometric mean (CV%) unless otherwise specified.

NA Not available

^a Data presented as median (minimum, maximum).

^b AUC is AUC(0-T) on Day 1 and AUC(TAU) on Days 7 & 14

- ETV plasma concentrations are similar following administration of the tablet or oral solution.
- Following the administration of ETV at the clinically relevant doses of 0.5 or 1 mg, the systemic exposure demonstrated approximately 2-fold accumulation. ETV has an apparent terminal half life of approximately 130 hours and an effective half life for accumulation of approximately 24 hours. Trough concentrations indicated that steady state was attained by approximately 9 to 10 days following once-daily dosing.
- ETV exposure decreased by approximately 20 % following a high-fat or light meal compared to fasted conditions. The proposed label recommends ETV be administered on an empty stomach (at least 2 hours before and at least 2 hours after a meal).
- The protein binding of ETV in human serum is low (approximately 13%), and ETV uniformly distributes between plasma and red blood cells in whole human blood.

- Following administration of a 1 mg dose of [¹⁴C]-ETV, 75% of the total radioactivity (TRA) administered was recovered in the urine and 6% was recovered in the feces. Approximately 70% of the administered ETV dose was excreted as unchanged drug in urine over 14 days of collection, suggesting an estimated bioavailability $\geq 70\%$.
- Renal excretion of unchanged drug is the primary route of ETV elimination, while biliary excretion plays a minor role. Values for renal clearance of ETV were greater than the glomerular filtration rate, indicating that the excretion of ETV by the kidneys occurs via a combination of glomerular filtration and net tubular secretion.
- ETV is not a substrate for P-glycoprotein.
- Several *in vitro* studies indicate that ETV is not a substrate, inhibitor, or inducer of the CYP450 enzyme system. The only metabolites detected in human plasma, urine, and feces were minor amounts of phase 2 metabolites, namely, glucuronide and sulfate conjugates. No oxidative metabolites of ETV were detected indicating that CYP450 does not play a role in the metabolic clearance of ETV *in vivo*.
- There were no significant pharmacokinetic interactions between ETV and LVD, ADV, or tenofovir in Phase 1 drug interaction studies. In addition, an *in vitro* study showed that co-administration of stavudine, didanosine, abacavir, zidovudine, LVD, or tenofovir with ETV had no effect on anti-HBV and/or anti-HIV-1 activity of any of the compounds.
- In subjects with selected degrees of renal impairment, as renal function declined mean apparent total body clearance and renal clearance of ETV decreased. This decrease in clearance resulted in a longer half life and greater exposure to ETV, as compared to subjects with normal renal function. Additionally, hemodialysis removed about 13% of the ETV dose, while continuous ambulatory peritoneal dialysis (CAPD) removed $< 1\%$ over 7 days in subjects with severe renal impairment. Based on these findings, dosage reduction of ETV is warranted in the presence of renal impairment. Modeling and simulation of multiple-dose administration of the proposed dosage recommendations in patients with varying degrees of renal function was performed. Based on the safety margin defined by the Phase 1 program, a target range of exposure was defined as two times the geometric mean steady state AUC value in subjects with normal renal function (maximum) and the lowest predicted value for subjects with normal renal function (minimum). Specific dosage recommendations for patients with renal impairment are currently under review.
- Hepatic impairment had a negligible impact on ETV exposure, and no dose modification based on the presence of hepatic impairment is necessary.
- Differences in ETV PK between Asian and non-Asian populations were observed. C_{max} and AUC following multiple 0.5 mg dosing of ETV were approximately 50% and 20% higher in healthy Asian subjects versus healthy non-Asian subjects. Weight-normalized CL/F values were comparable between the Japanese and non-Asian study populations, suggesting the ethnic differences in exposure between Asian and non-Asian populations

may be attributable to differences in body weight, but small sample sizes across these study populations preclude definition of an effect of race on ETV pharmacokinetics.

- ETV exposure was approximately 29% higher in elderly compared to young subjects, a disparity attributable to differences in renal function.
- No significant gender-related differences in ETV pharmacokinetics were observed.
- Differences in ETV exposure were observed between healthy subjects and in HBV-infected subjects. In comparison to healthy subjects, ETV AUC was approximately 30% and 71% higher after multiple daily dosing of 0.5 mg and 1 mg, respectively. In HBV subjects post-orthotopic liver transplant (OLT), mean C_{\max} was increased by approximately 42% and the mean AUC was increased by approximately 116% compared to healthy subjects following 14 days of oral 1 mg ETV. This increase in C_{\max} and AUC in OLT patients was consistent with the degree of renal impairment in these subjects.
- No dose- or concentration-dependent relationships between QT interval (with Bazett's or Fridericia's correction) or change in QTc were observed following ETV doses up to 20 mg for up to 14 days or as a single dose of 40 mg in healthy volunteers. In contrast, a slight concentration-dependent effect on PR interval was observed following ETV doses of up to 20 mg for 14 days (slope = 0.124). These findings were based on a retrospective analysis of 5 controlled Phase 1 studies. The slight prolongation in PR in this retrospective analysis is not expected to be clinically significant.

Appendix B: Summary of Key Animal Carcinogenicity Findings

Table B1: Rat Carcinogenicity Findings

Male Group	1	2	3	4	5	6
Dose (mg/kg/day)	0	0	0.003	0.02	0.2	1.4
MHD	-	-	<1	0.3	5	35
Brain - Glioma	0	0	1	1	2	4*
Female Group	1	2	3	4	5	6
Dose (mg/kg/day)	0	0	0.01	0.06	0.4	2.6
MHD	-	-	<1	<1	4	24
Brain - Glioma	0	0	0	1	0	3*
Liver - Adenoma	0	1	2	3	1	8**
Liver - Carcinoma	0	0	0	0	0	3
Liver - Adeno + Carc Combined	0	1	2	3	1	11**
Skin - Fibroma	0	0	0	1	2	3*

MHD = Multiple of the human dose

* p = 0.025 **p = 0.005

Table B2: Mouse Carcinogenicity Findings

Male Group	1	2	3	4	5	6
Dose (mg/kg/day)	0	0	0.004	0.04	0.4	4
MHD	-	-	1	3	14	42
Lung Adenoma	4	4	8	11*	17*	20*
Lung Carcinoma	3	3	4	4	7	15*
Lung Adeno + Carc Combined	7	7	12	15*	24*	35*
Liver Carcinoma	1	0	1	3	2	8*
Female Group	1	2	3	4	5	6
Dose (mg/kg/day)	0	0	0.004	0.04	0.4	4
MHD	-	-	1	3	11	40
Lung Adenoma	9	6	5	4	16	15*
Lung Carcinoma	3	5	3	2	5	16*
Lung Adeno + Carc Combined	12	11	8	6	21	31*
Ovary -hemangiomas	3	3	6	7	5	19
Uterus - hemangiomas	4	3	4	4	5	8
Whole Body - hemangiomas	10	13	13	12	11	26*
Whole Body - hemangiosarcomas	2	1	2	3	2	4
Whole Body - hemangiomas and hemangiosarcomas	12	14	15	15	13	30*

MHD = Multiple of the human dose, * P = 0.005

Appendix C: Summary of Malignancies Reported during Clinical Trials of ETV

Table C1: Malignant Neoplasms or Suspicious Lesions Reported in NDA

Patient ID (Study#-Site#- Subject#)	Age/Sex/Race	Study Drug (Days of Exposure)	Type of Malignancy	Additional Comments
Hepatic Malignancies				
AI463004-12-010	63/M/White	ETV 0.1 mg (28)	Hepatocellular carcinoma	History of cirrhosis
AI463012-4-7030	26/M/Asian	ETV 0.5 mg (308)	Hepatocellular carcinoma	
AI463014-27-6105	64/F/White	ETV 0.5 mg (233)	Hepatocellular carcinoma	
AI463014-49-6020	58/M/White	ETV 0.5 mg (107)	Hepatocellular carcinoma	
AI4630022-8-10672	62/M/Asian	ETV 0.5 mg (352)	Hepatocellular carcinoma	Baseline cirrhosis with KnoFibSc=4
AI463026-102-80125	42/M/White	LVD 100 mg (217)	Hepatocellular carcinoma	
AI463027-12-51342	53/F/Asian	ETV 0.5 mg (291)	Hepatocellular carcinoma	History of Stage 3 fibrosis on pre-study biopsy
AI463027-101-50558	46/M/White	ETV 0.5 mg (309)	Hepatocellular carcinoma	History of significant ethanol intake (pre-study)
AI463027-40-50662	42/M/Asian	LVD 100 mg (40)	Hepatocellular carcinoma	History of bridging fibrosis on pre-study biopsy
AI463027-88-50369	55/M/Asian	LVD 100 mg (22)	Hepatocellular carcinoma	
AI463027-122-50927	43/M/White	LVD 100 mg (365/425)	Hepatocellular carcinoma	Baseline biopsy with KnoFibSc=3 and cirrhosis at Week 48

Patient ID (Study#-Site#-Subject#)	Age/Sex/Race	Study Drug (Days of Exposure)	Type of Malignancy	Additional Comments
Non-hepatic Malignancies				
AI463014-10-6073*	65/M/White	ETV 0.1 mg (102,412)	Basal cell carcinoma	
AI463014-19-6182 (AI463901-12-6182)	67/M/White	ETV 0.5 mg (366) (671)	Squamous cell carcinoma, skin (Basal cell carcinoma)	History of skin cancer
AI463014-25-6236	61/M/White	ETV 0.5 mg (313)	Prostate cancer	History of benign prostatic hypertrophy
AI463014-14-6254	80/M/White	LVD 100 mg (287)	Basal cell carcinoma	History of skin cancer (pre-study)
AI463015-16-2010	46/M/White	ETV 1.0 mg (779)	Renal cell carcinoma	Prior liver transplant for HCC (pre-study)
AI463022-53-10168	67/M/Black	ETV 0.5 mg (480)	Prostate cancer	
AI463022-80-10451	41/F/Asian	LVD 100 mg (277)	Recurrent gastric adenocarcinoma	History of gastric adenocarcinoma (pre-study)
AI463022-115-10657	64/M/White	LVD 100 mg (357)	Cerebral metastases of unknown primary	History of renal cell carcinoma (pre-study)
AI463026-67-80149	62/M/White	ETV 1.0 mg (185)	Basal cell carcinoma	History of skin cancer (pre-study)
AI463027-5-50742	72/M/Asian	ETV 0.5 mg (322)	Gastric adenocarcinoma	History of gastric ulcer and gastritis
AI463027-58-51369	30/F/White	LVD 100 mg (325)	Breast (ductal) adenocarcinoma	
AI463027-99-50677	70/F/White	ETV 0.5 mg (56) (314)	Breast cancer (invasive ductal and lobular carcinoma) Basal cell carcinoma	
AI463027-113-51000	39/F/White	ETV 0.5 mg (363/370)	Uterine adenocarcinoma	
AI463027-193-50490	66/F/White	LVD 100 mg (325)	Breast carcinoma in situ	
Pre-malignant or Unclassified Lesions				
AI463022-175-10643	20/F/Other	ETV 0.5 mg (242)	Breast dysplasia	
AI463027-102-50091	33/F/White	LVD 100 mg (138)	Actinic keratosis	
AI463026-81-80299	59/M/White	LVD 100 mg (193)	Hepatic neoplasm	Described as "liver nodule," biopsy showed high grade dysplasia but patient died before definitive diagnosis
AI463014-1-6005	38/M/Black	ETV (393)	Neoplasm	Described as "R leg small raised lesion"
AI463014-25-6237	64/M/White	ETV (402)	Neoplasm	Described as "polyploid lesion on back"

*Patient had 2 separate basal cell carcinomas in different locations.

Table C2: Additional Malignant Neoplasms Reported in IND Safety Update

Patient ID (Study#-Site#- Subject#)	Age/Sex/Race	Study Drug (Days of Exposure)	Type of Malignancy	Additional Comments
Hepatic Malignancies				
AI463048-43-40005	45/M/Asian	ADV 10 mg (272)	Hepatocellular carcinoma	History of cirrhosis
AI463048-43-40043	51/M/Asian	ETV 1 mg (168)	Hepatocellular carcinoma	History of cirrhosis, increased AFP at screening
AI463048-42-40006	59/F/Asian	ADV 10 mg (240)	Hepatocellular carcinoma	History of cirrhosis, increased AFP at screening, suspicious liver lesion by imaging at screening
AI463048-43-40003	56/M/Asian	ETV 1 mg (161)	Hepatocellular carcinoma	History of cirrhosis, increased AFP prior to screening, history of resected liver mass, liver lesion present by imaging at screening
Non-hepatic Malignancies				
AI463022-163-10765	52/M/White	ETV 0.5 mg (180)	Prostate cancer	
AI463022-192-10443	61/M/White	ETV 0.5 mg (660)	Esophageal cancer	
AI463026-134-80058	54/F/Asian	ETV 1 mg (110)	Metastatic splenic lymphoma	
AI463901-24-6229	46/M/White	ETV 1 mg + LVD 100 mg (589)	Gastric cancer	Chronic gastritis and H. pylori infection Previously on Study 014 – LVD x 357 days
AI463901-179-80339	46/F/White	ETV 1 mg + LVD 100 mg (180)	Multiple myeloma	Previously on Study 026 – LVD x 366 days
AI463901-30-6047	42/M/White	ETV 1 mg + LVD 100 mg (207)	CTCL/recurrent mycosis fungoides	History of CTCL for 13 years prior to study Previously on Study 014 – ETV 0.1 mg x 224 days
AI463038-29-30055	43/M/White	ETV 1 mg (175)	Testicular cancer (seminoma)	